# Post-Spaceflight Orthostatic Hypotension Occurs Mostly in Women and is Predicted by Low Vascular Resistance

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Abbreviated Title: Orthostatic Responses in Women and Men Astronauts

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**ABSTRACT**

About 20% of astronauts suffer post-spaceflight presyncope, but the underlying etiology remains elusive. We studied responses to standing in 36 astronauts before and after spaceflight (5–16 days). Individuals were separated into presyncopal women, presyncopal men, and non-presyncopal men based on their ability to stand for 10 min postflight. Preflight, presyncopal women and presyncopal men had low vascular resistance, with the women having the lowest. Postflight, women experienced significantly higher rates of presyncope ($P<0.01$) and significantly greater losses of plasma volume than the men ($P<0.05$). Both presyncopal women and men had lower standing arterial pressure ($P\leq0.001$) and vascular resistance ($P<0.05$), smaller increases in norepinephrine ($P\leq0.058$) and greater increases in epinephrine ($P\leq0.058$) than non-presyncopal men. Both presyncopal groups had a strong dependence ($P\leq0.05$) on plasma volume to maintain standing stroke volume. These findings suggest that postflight presyncope is ascribed to a combination of inherently low resistance responses, a strong dependence on volume status, and spaceflight-induced hypoadrenergic responses. In contrast, high vascular resistance and spaceflight-induced hyperadrenergic responses prevent presyncope.

**KEYWORDS**: microgravity, gender, hypoadrenergia, plasma volume

**INTRODUCTION**

Virtually all astronauts suffer from post-spaceflight orthostatic intolerance. About 20% of all astronauts returning from 10-14 days of spaceflight experience orthostatic intolerance severe enough to cause presyncope (27). In a previous paper (10), we noted that women seemed to have a greater propensity toward postflight orthostatic hypotension and presyncope than men. Specific mechanisms contributing to individual susceptibility still are not completely understood, but appear to be multifactorial. Postflight orthostatic intolerance certainly is aggravated by loss of plasma volume. However, while all astronauts suffer losses of plasma volume, not all astronauts become presyncopal on landing day, and we showed no differences in plasma volume losses between those who did and those who did not become presyncopal (10). Rather than by plasma volume, presyncopal astronauts are defined primarily by their smaller increases in plasma norepinephrine levels (10) and total peripheral resistance (3,10) with standing than non-presyncopal astronauts. There also is evidence of indicators of postflight orthostatic hypotension that may be discernable preflight. As a group, those who will become presyncopal after flight have lower supine and standing peripheral vascular resistance and arterial pressure than those who will not (10). To date, no study has performed a systematic analysis of hemodynamic, volume, and neuroendocrine variables in a large enough sample of astronauts to definitively assess the relative contributions of gender, plasma volume, autonomic function, and preflight predisposition to susceptibility to postflight orthostatic hypotension.

The purpose of the present study was four-fold. First, we sought to extend previous observations in a larger sample of astronauts and test the hypothesis that women are more susceptible to post-spaceflight orthostatic hypotension than men. Having shown that to be true, our second goal was to compare and contrast supine and standing hemodynamic and neuroendocrine variables in the three classifications of astronauts: presyncopal women, presyncopal men, and non-presyncopal men. These comparisons were made both before and after flight. The third purpose was to examine the relationships between plasma volume and hemodynamic responses to tilt in the three groups. The fourth purpose was to characterize the Guytonian relationships between vascular resistance, cardiac output, and arterial pressure in the two groups of presyncopal astronauts, and test the hypothesis that these basic relationships differ between presyncopal and non-presyncopal groups.

## METHODS

The data presented include both retrospective analyses of previously published data (10) and new findings. Subjects were recruited from the Astronaut Corps at Johnson Space Center (6 women, 30 men). Protocols were approved by the Johnson Space Center Institutional Review Board and all subjects gave their written informed consent. Studies were conducted between 10 and 90 days prior to Shuttle spaceflight, on landing day (1-3 h after landing), and three days after landing. The duration of spaceflight ranged from 5 to 16 days. On each test day, subjects had abstained from caffeine, alcohol, and any vasoactive medications for the preceding 12 h; were at least 2 h postprandial; and had not exercised maximally in 24 h. The subjects were instrumented for electrocardiogram, manual (sphygmomanometer) or automated blood pressure (Dinamap, Johnson & Johnson, Arlington, TX), and beat-to-beat blood pressure (Finapres, Ohmeda, Tewksburi, MA). Two-dimensional echocardiography and continuous wave Doppler ultrasound (Biosound, Indianapolis, IN) were used to determine aortic cross-sectional diameter and flow, respectively. An intravenous catheter was inserted into an antecubital vein. After a 20 minute supine rest period, plasma volume was determined by using carbon monoxide rebreathing (6,25,33). A blood sample was drawn for baseline plasma norepinephrine and epinephrine levels. Baseline hemodynamic measurements continued while the subjects remained supine for five additional minutes. Subjects were then placed in the upright position by using one of two methods: 1) using an automated tilt table, or 2) three investigators who lifted the subject by supporting both shoulders while the subjects' feet were swept off the bed. The finger with the continuous arterial pressure device was held at heart level either by an armboard attached to the bed (tilt protocol) or a system of velcro straps (stand protocol). Five of the six women, and 24 of the 30 men underwent stand tests. The remaining subjects underwent tilt tests. Subjects remained standing for 10 minutes or until presyncopal symptoms intervened. A final blood sample for plasma norepinephrine and epinephrine was drawn at the end of the test. When subjects became presyncopal, the blood sample was drawn immediately. Arterial pressure, heart rate, and respiration were recorded on analog, audio, and digital tape for later analyses. Echocardiographic images were recorded on video tape. Analog signals were also recorded on paper. Prior to landing, the subjects followed the standard oral fluid loading procedure (equivalent to isotonic saline at a rate of 15 cc/kg within two hours). Between landing and the time of the data collection, they consumed $272 \pm 51$ cc's fluid with a range from 0 to 1000 cc's.

*Analyses*

The following variables were compared during the minute prior to standing and the last minute of standing: heart rate, arterial pressure, stroke volume, cardiac output (stroke volume x heart rate), and total peripheral resistance (mean arterial pressure/cardiac output). Analyses of all analog signals were made off-line by using standard data acquisition and analyses packages. Plasma norepinephrine and epinephrine levels were determined by radioimmunoassay (19). Plasma volume, stroke volume, cardiac output, and total peripheral resistance were each divided by the subject's body surface area to create an indexed parameter used for all statistical analyses. For discussion purposes, all non-indexed terms were used.

*Statistics*

All results are presented as means ± SE. All data were tested for normalcy and equal variance using the Kolmogorov-Smirnov test and the Levene Median test, respectively. For analyses, astronauts were separated both by gender and occurrence of presyncope (those who could not maintain 10 minutes of upright posture on landing day). Since only one woman out of six was not presyncopal on landing day, she was not compared with the other three groups although her data are represented in Figure 1. Thus, the effects of interest were group (presyncopal women, presyncopal men, and non-presyncopal men) and day (preflight, landing day, and three days after landing). A two-way analysis of variance or two-way analysis of variance on ranks (for non-parametric data) was used. Student's paired or unpaired t-tests and Signed Rank or Rank Sum tests (for non-parametric data) were performed to document differences among groups in variables when there were significant day or group effects. Least squares regression analyses were performed on standing stroke index versus plasma volume. A Fisher Exact test was used to compare the incidence of presyncope on landing day between men and women. Comparisons were considered significant if $P \leq 0.05$.

**RESULTS**

*Incidences of presyncope*

As a group, the women astronauts suffered postflight presyncope at a significantly higher rate ($P < 0.01$) than the men (Fig. 1). Five of six women studied (83%), but only six of 30 men studied (20%), fell in the presyncopal group (Fig. 1, *top*). Presyncopal symptoms (lightheadedness or a sudden drop in systolic blood pressure below 70 mmHg) occurred between two and nine minutes after standing. There were no vasovagal incidents, and no subject lost consciousness. Many astronauts, 18 of the 30 men, and one of the six women, were pilots of military high performance jet aircraft and thus might have a higher tolerance to gravitational forces, due to genetic and/or training factors. All other astronauts were mission specialists, mostly scientists who were not military pilots before entering the astronaut corps and would not necessarily be expected to have enhanced tolerance to gravitational forces. To avoid a possible artifact, all pilots were removed from the data set and comparisons were repeated using only the mission specialists. There were still three times more women (80%) as men (25%) who became presyncopal on landing day (Fig. 1, *bottom*, $P = 0.1$, between groups). Men and women astronauts did not differ in age ($40.8 \pm 1.0$ vs. $41.5 \pm 1.3$ yrs, $P = 0.80$), but did differ in body surface area ($1.98 \pm 0.03$ vs. $1.64 \pm 0.05$ kg/m$^2$, $P < 0.001$). Presyncopal and non-presyncopal men did not differ in age ($38.6 \pm 1.3$ vs. $41.4 \pm 1.2$ yrs, $P = 0.27$) or body surface area ($2.00 \pm 0.06$ vs. $1.96 \pm 0.04$ kg/m$^2$, $P = 0.58$).

*Plasma volume*

Table 1 depicts plasma volume measurements in presyncopal women, presyncopal men, and non-presyncopal men. On landing day, all three groups had significant reductions in plasma volume from preflight. The losses incurred with spaceflight were significantly greater in the presyncopal women (20%) than either group of men (7%). Three days after landing, plasma volumes were recovered. Of note, the single non-presyncopal woman lost only 1% of her plasma volume.

*Comparisons among presyncopal women, presyncopal men, and non-presyncopal men before flight*

No astronaut in this study became presyncopal during preflight testing. Figure 2 (*left panel*) shows preflight supine and standing measurements in presyncopal women, presyncopal men and non-presyncopal men. Women had significantly lower supine and standing arterial pressures and total peripheral resistances, higher supine heart rates, and higher supine and standing cardiac indices than non-presyncopal men. Women also had significantly lower supine and standing arterial pressures and tended to have higher heart rates and lower vascular resistances than those of the presyncopal men. Presyncopal men had significantly higher standing cardiac indices and tended to have lower ($P = 0.08$) standing vascular resistance than non-presyncopal men. Thus, hemodynamically, the presyncopal men fell between the non-presyncopal men and the women in most variables. There were no significant intergroup differences in stroke index or plasma norepinephrine (Fig. 3A, *top*) and epinephrine (Fig. 3A, *bottom*) responses. Therefore, before flight, both presyncopal groups showed a propensity toward higher cardiac output and lower vascular resistance, but did not have low sympathetic responses.

*Comparisons between presyncopal women, presyncopal men, and non-presyncopal men on landing day*

The middle panel in Figure 2 presents supine and standing measurements on landing day. Both presyncopal women and presyncopal men had significantly lower standing arterial pressures than non-presyncopal men, with presyncopal men having the lowest pressures. Women also had significantly higher standing heart rates and supine cardiac indices than the non-presyncopal men. But presyncope on landing day was most clearly defined by low vascular resistance. Both presyncopal groups had significantly lower standing resistances than the non-presyncopal men.

The underlying cause of the low resistance is suggested in Figure 3. On landing day, both presyncopal women and men had lower norepinephrine responses to standing than the non-presyncopal men (3B, *top*). The women's responses also were less than those of the presyncopal men. Both presyncopal groups had greater epinephrine release with standing than the non-presyncopal men (3B, *bottom*). Thus on landing day, the inherently low resistance of presyncopal subjects is exacerbated by low sympathetic responses, while non-presyncopal subjects are able to recruit a supra-normal sympathetic response.

*Comparisons between presyncopal women, presyncopal men, and non-presyncopal men three days postflight*

All but four subjects (one non-presyncopal man, two presyncopal men, and one presyncopal woman) maintained 10 minutes of upright posture three days after landing. Mean responses of all subjects three days after landing are shown in Figure 2 (*right panel*). Mean arterial pressures were again significantly lower in the women than men.

Standing heart rates were significantly higher in the presyncopal men than either the women or non-presyncopal men. Standing stroke indices were significantly higher in the women, possibly due to their high plasma volumes. Cardiac index showed similar patterns to preflight, with the women and presyncopal men having higher values than the non-presyncopal men. Total peripheral resistance also was similar to preflight, with the non-presyncopal men having the highest and the women having the lowest resistances. There were no intergroup differences in either norepinephrine or epinephrine responses to standing (Fig. 3C).

*Hemodynamic relationships*

Figure 4 depicts the relationships between plasma volume and standing stroke index. Women (4A) had a highly significant positive correlation ($P < 0.001$), indicating a strong dependence on plasma volume to maintain standing stroke volume. Presyncopal men (4B) also had a positive significant correlation ($P = 0.05$), although less significant than the women. The non-presyncopal men (4C) had no correlation between plasma volume and standing stroke index ($P = 0.24$).

The relationships between changes in cardiac index and changes in mean arterial pressure with upright posture on all test days are shown in Figure 5. Preflight (5A), all subjects compensated for falling cardiac indices and maintained arterial pressures adequately, although all but two presyncopal subjects lost pressure while standing. On landing day (5B), the women and men presyncopal astronauts had much greater falls in pressure than preflight, as cardiac index fell. Three days after landing (5C), pressures were again maintained.

When pressure is not maintained during falls in cardiac output, inadequate resistance responses are suggested. Figure 6 depicts the relationships between cardiac index and total peripheral resistance (supine and standing) in all three groups on all test days. Preflight (6A), all three groups fell on the same curve; resistance increased exponentially as cardiac index decreased. However, the presyncopal women and men operated only on the lower two-thirds of the curve. That is, their resistance did not increase to the same degree as that of the non-presyncopal men with the same falls in cardiac index. On landing day (6B), the resistance of both presyncopal women and men had values that fell completely off the curve, indicating a loss of the normal inverse relationship between cardiac output and vascular resistance. This placed them in a very vulnerable position. Three days after landing (6C), the relationships were again similar to preflight, with both presyncopal groups remaining on the lower portion of the curve.

**DISCUSSION**

We compared and contrasted hemodynamic and neuroendocrine variables in three groups of astronauts before and after spaceflight: presyncopal women, presyncopal men and non-presyncopal men. We now know that the group of astronauts most susceptible to postflight orthostatic hypotension and presyncope has at least four major defining characteristics. First, the subjects are primarily, although not exclusively, female. Second, presyncopal astronauts are characterized by low peripheral vascular resistance, both before and after flight, whether they are men or women. Third, although plasma volume loss by itself does not separate presyncopal and non-presyncopal astronauts, compensatory adjustments to losses of plasma volume do separate them. Presyncopal astronauts are highly dependent on a normal hydration status for hemodynamic stability.

The fourth finding from this study is the corroboration and extension of an earlier report that autonomic changes associated with spaceflight, manifested as hypoadrenergic responsiveness, seem to differentially affect the subset of susceptible astronauts in a way that causes them to become presyncopal after, but not before, spaceflight. Each of these topics will be discussed in the following paragraphs.

*Presyncopal women astronauts*

In a previous study (10), we suggested that women astronauts appeared to have a greater incidence of postflight orthostatic hypotension and presyncope than men. In the present study, five of the six women became presyncopal on landing day (Fig. 1), making them significantly more susceptible than the men. This is not an unexpected finding. Several studies have reported that orthostatic intolerance is greater in women than in men (5,24,34). Although the women did not experience presyncope during upright posture before flight, they had significantly lower supine and standing arterial pressures than those of the men. The cardiovascular and autonomic changes they experienced during flight made almost all of them presyncopal on landing day. Their preflight hemodynamic profile seems to predict this postflight susceptibility. The presyncopal women maintained the highest heart rates, stroke volumes and cardiac outputs, and the lowest vascular resistances of the three groups. Therefore, they seem to rely more on cardiac, rather than resistance responses, to maintain upright pressures (Fig. 2). This pattern also is not an unexpected finding in women and is well documented in the literature. Women have greater heart rate responses than men during mental stress (4), standing (16,31), infusions of pressor agents (1), and cold pressor tests (14). It also is known that women have smaller increases in vascular resistance than men in response to lower body negative pressure (7,34), standing (8), cold pressor and facial cooling tests (20) and mental stress (26). As mentioned above, this does not normally represent a functional inadequacy. However, when coupled with other factors, these low resistance responses could result in a failure to maintain standing pressure. The presyncopal women experienced plasma volume losses after flight that were almost three times greater than the men (Table 1). The only woman who did not lose plasma volume was the single non-presyncopal woman. Yet, the women are very dependent on plasma volume (Fig. 4), having a significant direct correlation between plasma volume and standing stroke volume. Thus, this puts them at an extreme disadvantage. After spaceflight, the preflight female hemodynamic strategy was no longer effective in maintaining pressure. Stroke volumes and cardiac outputs fell lower than they had preflight, and were not compensated for with greater increases in resistance, probably a result of the extremely low sympathetic response (Fig. 3), which had not been a problem before flight. While the women had increases in heart rate that were greater than preflight (Fig. 2), they were not as high as might be expected, possibly due to the low sympathetic response as well. These postflight conditions precipitated a collapse of pressure, and the high epinephrine release on landing day suggests a stress response was mounted as a result.

There could be several factors that contribute to the women's low vascular resistance. Probably the most important factor is the presence of estrogen (all women in the present study were premenopausal). The effects of estrogen on vascular function and nitric oxide physiology are well documented. Several studies in humans demonstrate an augmentation of endothelium-dependent vasodilation with estrogen (2,13,17,22,32) that is mediated by nitric oxide (17,32). A very early study demonstrated that venous compliance increases during infusions of 17β-estradiol (15), which would be expected to decrease venous return as well as vascular resistance.

Another factor that might make the women in the present study more susceptible is their smaller body and muscle mass (18,28,34). The influence of muscle mass on orthostatic tolerance is controversial: some data indicate that greater muscle mass may be associated with greater orthostatic tolerance (23) while others have not found that association (21). This difference in size is probably not the primary reason for the intergroup differences in hemodynamic variables or orthostatic tolerance in the current study for two reasons. First, hemodynamic variables were standardized for body surface area. Second, the body surface areas of the presyncopal men were not different from those of the non-presyncopal men.

These data show that presyncopal women astronauts have arterial pressure control mechanisms that normally operate on the low end of normal, but do not ordinarily cause symptoms. However, insertion into an extraordinary environment causes cardiovascular and autonomic changes that challenge those mechanisms to the point of failure. Thus, a majority of the women suffer presyncope.

*Presyncopal men astronauts*

Even though the women, as a group, are more susceptible than the men, postflight orthostatic hypotension is not exclusively a female problem. Twenty percent of the men in the present study were presyncopal on landing day (Fig. 1). Unlike the women, these men showed no evidence of hypotension preflight (Fig. 2). However, like the women, their preflight hemodynamic responses to standing rely more on cardiac and less on resistance responses to maintain arterial pressures. These men are severely affected by spaceflight, having the lowest standing arterial pressures and lowest total peripheral resistances on landing day of any of the groups.

Similarly to the women, the susceptible men also have a significant direct correlation between plasma volume and standing stroke volume, suggesting that they too are dependent on a normal hydration status to maintain hemodynamic stability. Also, like the women, they experience lower norepinephrine release on landing day (Fig. 3), indicating lower sympathetic responsiveness than preflight. The high epinephrine levels postflight suggest a physiologic stress response.

Thus, postflight orthostatic hypotension affects a small subset of male astronauts as well as a majority of female astronauts. The possible mechanisms of this are less clear than those between the women and men. Susceptible and non-susceptible males are not different in age, body surface area, or exercise routine. However, presyncopal men, like the women, have resistance responses that normally operate toward the lower end of the curve, putting them at a slight disadvantage. For reasons still not understood, and also like the women, their sympathetic nervous system becomes less responsive after spaceflight, leaving them vulnerable to hypotension. It may be possible that these men are part of a subgroup of normal individuals who have subtle differences in autonomic function that have no functional consequence preflight, but become severe and cause symptoms to manifest themselves after flight. This possibility is discussed below.

*Non-presyncopal men astronauts*

The non-presyncopal astronauts have three factors that seem to protect them from post-spaceflight orthostatic hypotension. The first is evident in their preflight responses to upright posture. They have significantly higher total peripheral resistance responses than either of the other groups (Fig. 2). Their peripheral resistance, when related to falls in cardiac index with standing, is on the highest portion of the response relation (Fig. 6). This allows them to maintain stable arterial pressures according to standard Guytonian hemodynamic equations. Second, the non-presyncopal men maintain standing stroke volume irrespective of plasma volume changes, unlike either of the presyncopal groups (Fig. 4). Third, and probably most importantly, this group is able to mount hyperadrenergic responses to standing on landing day, as evidenced by the amount of norepinephrine released (Fig. 3). This ability is most likely the primary factor that allows them to increase resistance and maintain pressures. This idea is supported by data from Whitson et al. (35) and Pawelczyk et al. (29), both of whom showed hyperadrenergic responses in non-presyncopal astronauts on landing day.

We have no ready explanation as to why these men differ from the others. However, it seems clear that upright arterial pressure cannot be maintained in the absence of adequate vascular responses, regardless of the cardiac response. As mentioned earlier, we found no demographic differences between the presyncopal and non-presyncopal men. Perhaps genetic components may offer future insights.

*Hemodynamic relationships in presyncopal and non-presyncopal astronauts*

We reported previously that there were no differences in plasma volume losses between presyncopal and non-presyncopal groups (10). This new examination of the data reveals that, even though that remains true in the men, a better maintenance of plasma volume would certainly be of benefit. Presyncopal astronauts, lacking appropriate sympathetic neuronal responses on landing day, are more dependent on plasma volume to maintain standing stroke volume (Fig. 4). Thus, losses of plasma volume represent a greater threat to orthostatic tolerance in these individuals. The women are at the greatest risk since they lose significantly more volume than the men and have the strongest dependence on plasma volume. This obviously contributes to their greater incidence of presyncope. Dependence on volume status suggests that susceptible astronauts have less ability to maintain venous return in the upright posture. In these subjects it is possible that low vascular responsiveness is not only a problem in the arterial circulation, but also in the venous circulation. Since preflight norepinephrine release does not differ among the groups, the adrenergic receptors, vascular smooth muscle, or local factors may be responsible for the low resistance in susceptible persons.

In Figure 5 we show the relationships between cardiac output and mean arterial pressure. Prior to flight, all but two presyncopal astronauts have falls in mean arterial pressure with standing. On landing day, every one of the presyncopal subjects succumbs to falling arterial pressure as cardiac output falls. The explanation for this comes from standard Guytonian equations. If cardiac output falls and vascular resistance does not increase appropriately, arterial pressure necessarily has to fall. Figure 6 depicts the most definitive characteristic of presyncopal astronauts, whether male or female. They have smaller increases in vascular resistance as cardiac output falls. Preflight, they operate only on the lower two thirds of the response relation for the entire group of astronauts, even though their release of norepinephrine is similar to that of the non-presyncopal astronauts. On landing day, their inherently low resistance is further aggravated by lower norepinephrine release when their resistance responses fall off the curve completely, and certainly explain their hypotension. It is interesting to note that the resistances of the non-presyncopal astronauts on landing day are not higher than they were preflight, even though their norepinephrine release is much greater (Fig. 3). This suggests a spaceflight-induced reduction in vascular responsiveness that requires an enhanced sympathetic response to maintain pressure. As mentioned above, non-presyncopal astronauts are unique in their ability to effect enhanced responses postflight. This idea is supported by preliminary data from this laboratory (J. V. Meck, personal communication). Non-presyncopal astronauts actually show a reduced diastolic pressor response to intravenous phenylephrine injections on landing day, suggesting a down-regulation of $\alpha_1$-adrenergic receptors. Presyncopal astronauts show the opposite trend. Thus, there is more evidence of differential adjustments to spaceflight in presyncopal and non-presyncopal astronauts.

*Autonomic changes associated with spaceflight*

One factor that dramatically separates presyncopal and non-presyncopal astronauts is the ability, or lack of ability, to release supra-normal amounts of norepinephrine on landing day. The women were entirely unable to do this; in fact, their response from supine to standing on landing day was only about 25% of the preflight response ($P = 0.01$). The presyncopal men also lacked this ability. Their landing day norepinephrine response was about 66% of that preflight ($P = 0.09$). In contrast, the non-presyncopal men released about 155% of their preflight response ($P < 0.05$).

This seeming adrenergic dysfunction reported here in a subset of astronauts extends previous findings from this laboratory (10). Preliminary data from a concurrent study shed some light on this finding. Intravenous injections of tyramine, an indirect sympathomimetic, cause equal or greater release of norepinephrine on landing day than preflight in both presyncopal and non-presyncopal astronauts (11). This supports the idea that norepinephrine synthesis is not impaired by spaceflight and can be released pharmacologically. Therefore, inadequate release must be caused by decreased baroreceptor afferent signal, central dysregulation, or inadequate release mechanisms.

These are not the only reports of autonomic dysfunction after spaceflight. Previously, we reported that carotid baroreceptor-cardiac reflex responses are reduced on landing day and that the reductions are related to greater difficulty maintaining standing arterial pressure (9,12).

Taken together, the foregoing observations describe a syndrome of autonomic dysfunction on landing day that manifests itself in several different ways, results in severe orthostatic hypotension, and resolves spontaneously without intervention.

Astronauts with presyncope on landing day resemble patients with autonomic dysfunction of central origin who also have normal supine and low standing norepinephrine levels (30,37). These patients combat debilitating syncope on a daily basis and also are particularly vulnerable when their plasma volume is low (36).

*Recovery*

Virtually every figure in this manuscript shows that, only three days after landing, responses to upright posture have returned toward preflight levels. The occurrence of hypotension and presyncope is very rare at this time point. The differences among groups are just as evident as they were preflight. This indicates that the cardiovascular changes associated with short-duration spaceflight are not permanent, but reverse spontaneously without treatment. A more clear understanding of the mechanisms of the reversible changes in astronauts may lead to a better understanding of the irreversible changes associated with many disease states.

*Limitations*

One limitation to this study is that stand tests were performed to assess orthostatic tolerance for data collected before 1997. Therefore comparisons between individuals necessarily required stand versus tilt comparisons. Because tilt tests are thought to be more provocative than stand tests, we compared stand (n=131) and tilt tests (n=25) in a larger group of astronauts. There was no significant difference ($P > 0.1$) in the incidence of presyncope with the two methods. In addition, as mentioned above, most of the women in the present study underwent stand testing. Therefore, we believe that the increased incidence of presyncope in the women was not caused by the difference in methods.

*Summary*

We studied the relationship between gender and presyncope in astronauts. Five of six women became presyncopal on landing day. There was a definitive preflight predisposition in women to low blood pressure, low vascular resistance, and high cardiac output. In presyncopal men, there was a preflight predisposition to high cardiac output without low blood pressure. Both groups were hemodynamically dependent on a normovolemic state. In addition, presyncopal astronauts suffered autonomic changes that resulted in hypoadrenergic responses on landing day. In contrast, non-presyncopal astronauts exhibited high vascular resistance before spaceflight, no hemodynamic dependence on volume state, and autonomic changes that resulted in hyperadrenergic responses on landing day. These data offer the possibility of development of individualized countermeasures for the orthostatic hypotension experienced after spaceflight.

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**FIGURE LEGENDS**

Figure 1. Incidence of presyncope (*gray slice*) during standing immediately following spaceflight in all subjects (*top*) and mission specialists alone (*bottom*). On landing day, women astronauts became presyncopal during standing at a rate that was greater ($P \leq 0.01$) than four times that of men. Even when only the mission specialists were compared, women still became presyncopal during standing at a rate greater than three times that of men. Presyncope is defined as the failure to complete ten minutes of standing without symptoms.

Figure 2. Hemodynamic measurements in presyncopal women (*n=5*, ●), presyncopal men (*n=6*, Δ), and non-presyncopal men (*n=24*, ○) when tested preflight (*left panel*), on landing day (*middle panel*), and three days post-spaceflight (*right panel*). On every testing occasion, men and women destined to become presyncopal on landing day exhibited higher cardiac index and lower resistance responses to standing than those of men not destined to become presyncopal on landing day. Values represent means ± SE. $^{\dagger}P = 0.06$, $^{*}P \leq 0.05$, $^{**}P \leq 0.01$, $^{***}P \leq 0.001$

Figure 3. Plasma norepinephrine (*top*) and epinephrine (*bottom*) responses in presyncopal women (*n=4, black bars*), presyncopal men (*n=6, light gray bars*), and non-presyncopal men (*n=22, dark gray bars*) when tested preflight (*A*), on landing day (B), and three days post-spaceflight (*C*). Plasma catecholamine responses to standing were not different among groups preflight. On landing day, however, presyncopal women and men had lower norepinephrine responses and higher epinephrine responses to standing than the

non-presyncopal men. Three days postflight, the plasma catecholamine responses in all groups returned to preflight values. Values represent means ± SE. †P = 0.058, *P ≤ 0.05, **P ≤ 0.01

Figure 4. The relationship between plasma volume and standing stroke index in presyncopal women (*A, n=5,* ●), presyncopal men (*B, n=6,* Δ), and non-presyncopal men (*C, n=24,* ○). Presyncopal women and men, but not non-presyncopal men, were dependent on plasma volume to maintain standing stroke index. Values represent individual data points from testing preflight and on landing day.

Figure 5. The relationship between standing minus supine cardiac index and standing minus supine mean arterial pressure in presyncopal women (*n=5*, ●), presyncopal men (*n=6*, Δ), and non-presyncopal men (*n=24*, ○) when tested preflight (*A*), on landing day (*B*), and three days post-spaceflight (*C*). Preflight, all groups compensated for falling cardiac index by maintaining arterial pressure. On landing day, however, presyncopal men and women had greater falls in arterial pressure in response to falls in cardiac index. Three days postflight, all groups demonstrated a relationship similar to preflight. Values represent individual data points.

Figure 6. The relationship between cardiac index and total peripheral resistance in presyncopal women (*n=5*, ●), presyncopal men (*n=6*, Δ), and non-presyncopal men (*n=24*, ○) when tested preflight (*A*), on landing day (*B*), and three days post-spaceflight (*C*). Preflight, all groups combined exhibited an inverse relationship between cardiac

index and resistance although the presyncopal groups operated on the lower portion of that relationship. On landing day, the presyncopal groups had resistance responses that fell below the curve. Three days postflight, the relationships in all groups were restored to preflight levels. Values represent individual data points for total peripheral resistance and cardiac index in both supine and standing positions.

Table 1. *Supine Measurements of Plasma Volume (l/kg/m²)*

| | Preflight | Landing Day | Three Days Postflight | % Spaceflight-Induced Loss |
|---|---|---|---|---|
| Presyncopal Women (*n* =5) | 1.81 ± 0.17 | 1.44 ± 0.08*,‡ | 2.02 ± 0.11 (*n* =4) | 19.5 ± 0.04§ |
| Presyncopal Men (*n* =6) | 1.67 ± 0.12 | 1.55 ± 0.12* | 1.66 ± 0.12 | 7.1 ± 0.03 |
| Non-Presyncopal Men (*n* =24) | 1.73 ± 0.04 | 1.60 ± 0.05**,‡ | 1.81 ± 0.05 | 7.1 ± 0.03 |

Values are means ± SE; *n*, No. of subjects. *$P \leq 0.05$, **$P \leq 0.01$, vs. preflight. ‡$P \leq 0.01$, vs. three days postflight. §$P < 0.05$ vs. presyncopal men and non-presyncopal men.

Figure 1

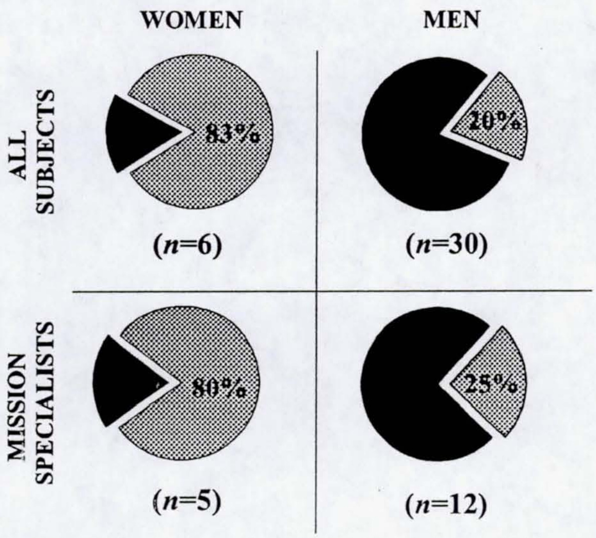

WOMEN
MEN
ALL SUBJECTS
83%
20%
(n=6)
(n=30)
MISSION SPECIALISTS
80%
25%
(n=5)
(n=12)

Figure 2

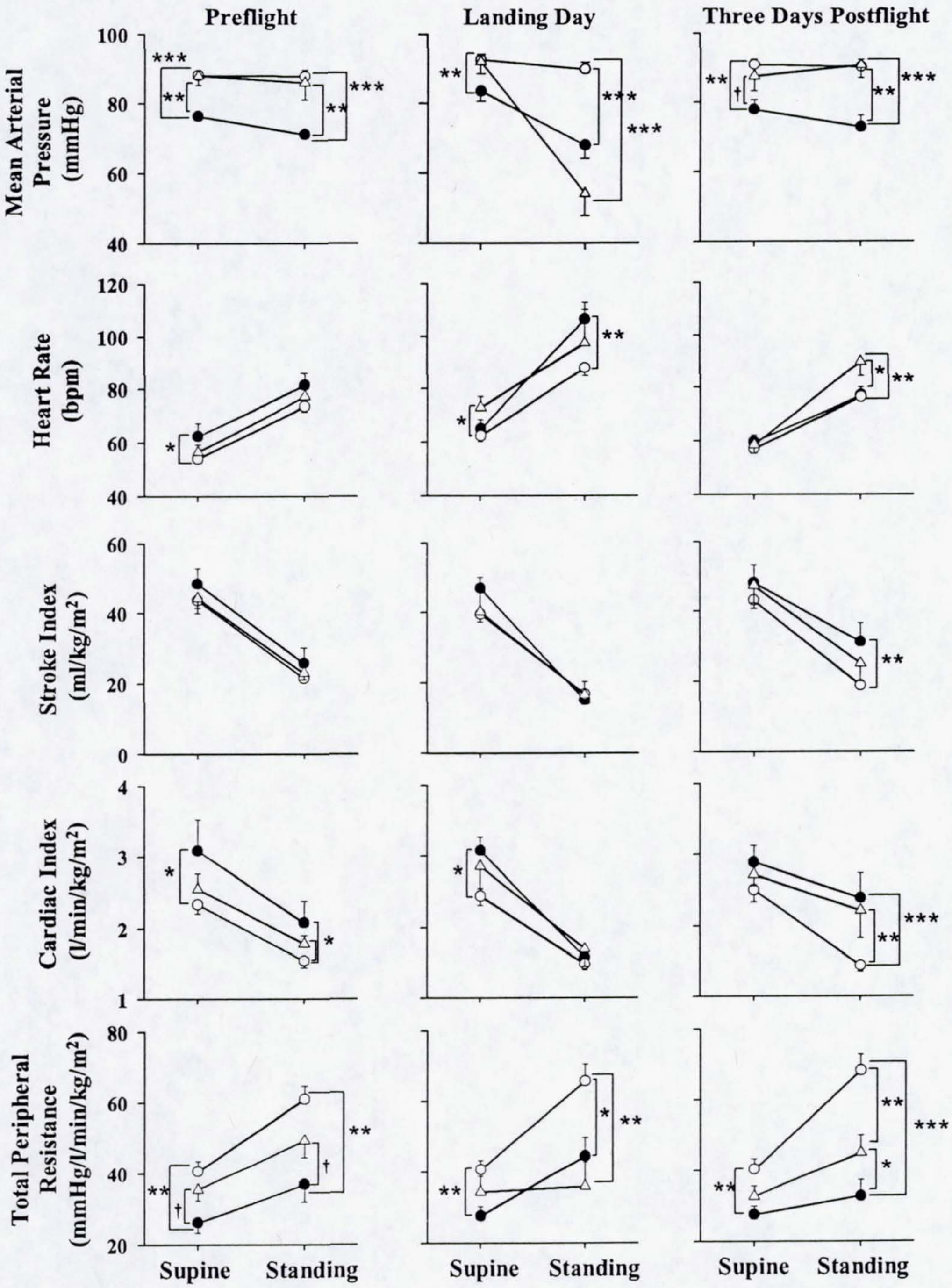

Preflight
Landing Day
Three Days Postflight
Mean Arterial Pressure (mmHg)
Heart Rate (bpm)
Stroke Index (ml/kg/m²)
Cardiac Index (l/min/kg/m²)
Total Peripheral Resistance (mmHg/l/min/kg/m²)
Supine
Standing

Figure 3

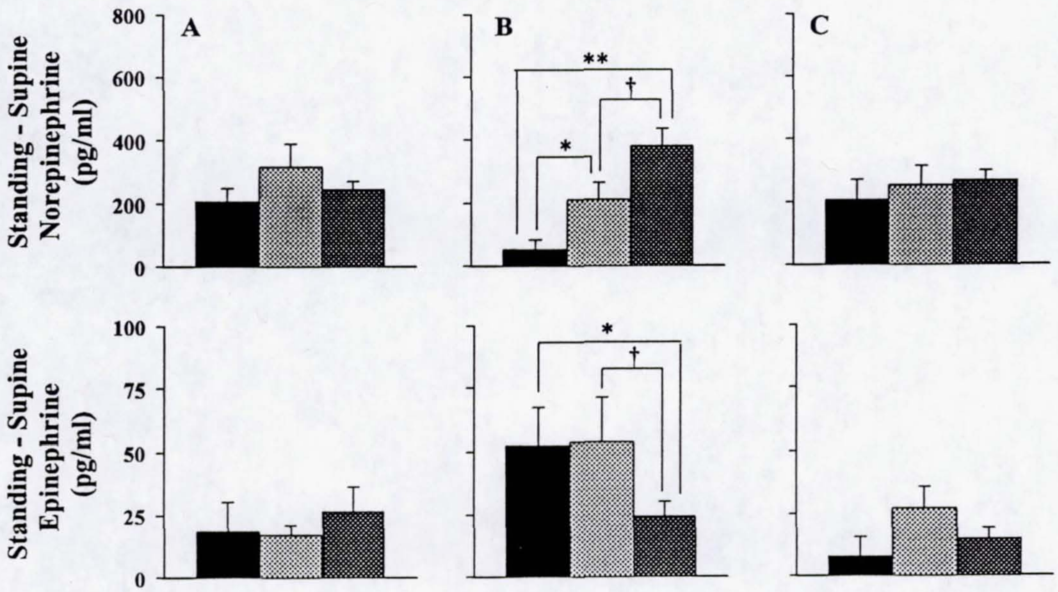

Standing - Supine
Norepinephrine
(pg/ml)
800
600
400
200
0
A
B
C
**
†
*
Standing - Supine
Epinephrine
(pg/ml)
100
75
50
25
0
*
†

Figure 4

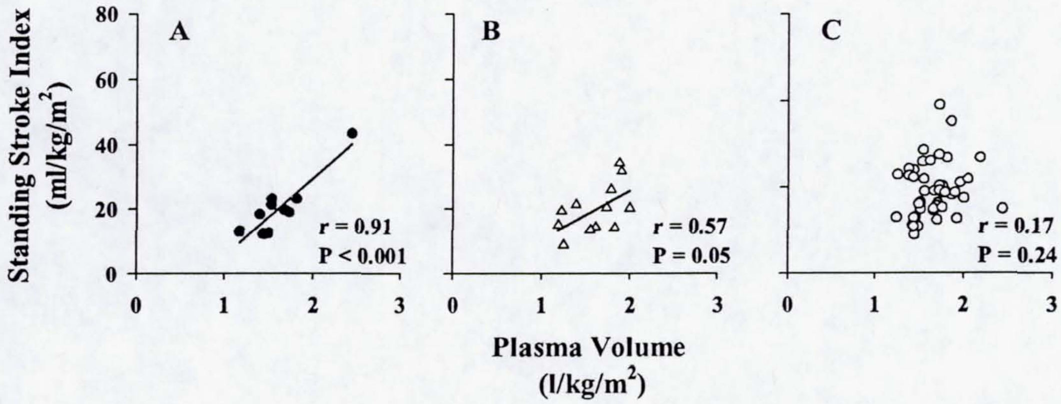

Standing Stroke Index
(ml/kg/m²)
80
60
40
20
0
A
r = 0.91
P < 0.001
B
r = 0.57
P = 0.05
C
r = 0.17
P = 0.24
0
1
2
3
Plasma Volume
(l/kg/m²)

Figure 5

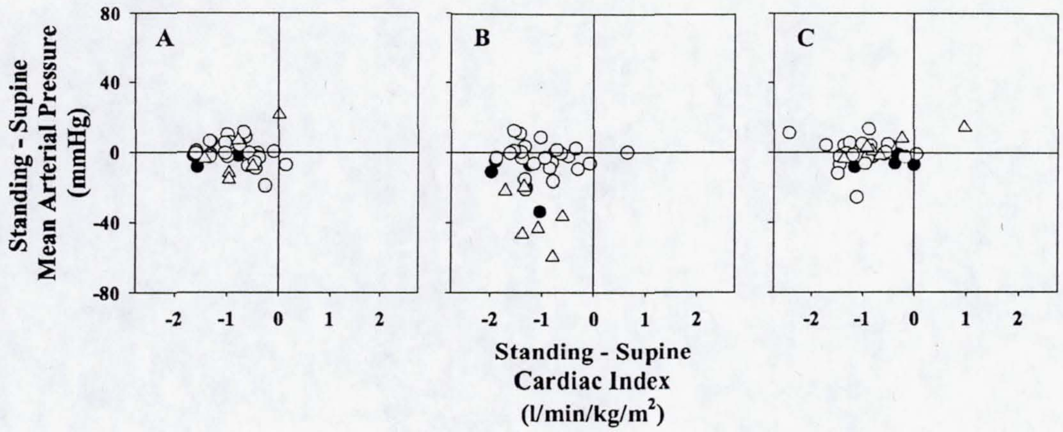
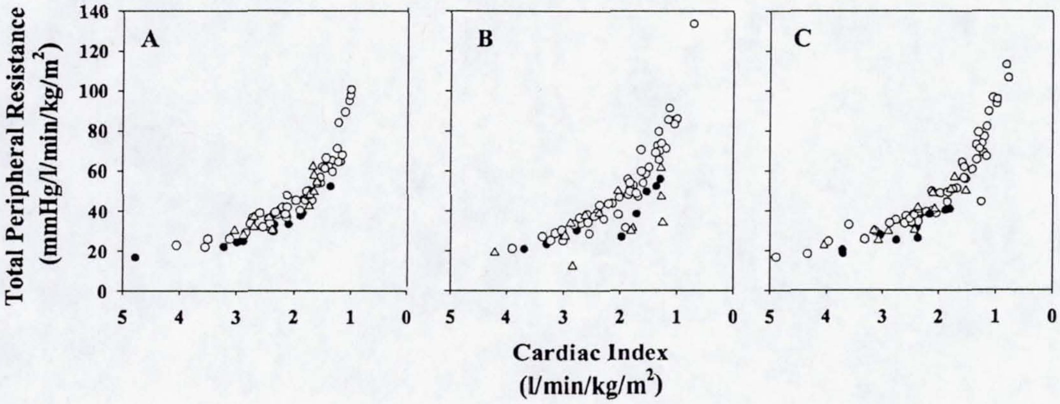

Standing - Supine
Mean Arterial Pressure
(mmHg)
80
40
0
-40
-80
A
B
C
-2 -1 0 1 2
Standing - Supine
Cardiac Index
(l/min/kg/m2)

Figure 6


Total Peripheral Resistance
(mmHg/l/min/kg/m²)
A
B
C
140
120
100
80
60
40
20
0
5
4
3
2
1
0
Cardiac Index
(l/min/kg/m²)