Impairment of Cerebral Blood Flow Regulation in Astronauts With Orthostatic Intolerance After Flight

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Background and Purpose—We investigated cerebral blood flow regulation in astronauts before and after flights. We hypothesized that autoregulation would be different before flight and after flight between nonfinishers and the finishers of a stand test.

Methods—Twenty-seven astronauts from shuttle missions lasting 8 to 16 days underwent a 10-minute stand test: 10 days before flight, 1 to 2 hours and 3 days after landing. Mean blood flow velocity of the middle cerebral artery (MCA) was measured using transcranial Doppler; Mean arterial pressure was measured using a Finapres (Ohmeda, Englewood, CO) and was adjusted to the level of the MCA (BP_MCA). Cross-spectral power, gain, phase, and coherence were determined for the relation between BP_MCA and the cerebrovascular resistance index mean blood flow velocity/BP_MCA.

Results—BP_MCA was reduced with stand (P<0.001). Differences between finishers and nonfinishers (P=0.011) and over test days (P=0.004) were observed. Cerebrovascular conductance was affected by stand (P<0.001), by group (P<0.001) with a group by stand, and test day interaction (P<0.01). Preflight data suggest that the nonfinishers were operating at a higher cerebral vasodilation than finishers for a given BP_MCA, and on landing day the nonfinishers had a greater decrease in mean blood flow velocity as a function of BP_MCA with standing compared to finishers and preflight. There was a significant interaction effect of gender over the test days and from supine to stand (P=0.035).

Conclusions—Our results indicate that the cause of presyncope in astronauts may be related to a mismatch of cerebral blood flow with blood pressure. Astronaut gender may also play a role in susceptibility to orthostatic intolerance after flight. (Stroke. 2011;42:1844-1850.)

Key Words: cerebral blood flow ■ cerebral hemodynamics ■ microgravity ■ gender ■ transcranial Doppler

After space flight, there is a wide range of susceptibility to orthostatic intolerance. It is possible that cerebral autoregulation, which ensures that cerebrovascular conductance is changed to maintain a relatively constant level of perfusion in case of fluctuations in blood pressure,1 could be compromised by the effects of weightlessness.

Investigation of cerebral autoregulation after head-down bed rest (HDBR) studies has revealed conflicting results. After 4 days of HDBR, Arbeille et al2 found no change in dynamic cerebral regulation during head-up tilt. Conversely, Zhang et al3 found an earlier and greater decline in cerebral blood flow during lower body negative pressure after HDBR and speculated that impairment of cerebral autoregulation may contribute to orthostatic intolerance after bed rest. Pavy Le-Trao4 showed no major impairment of cerebral autoregulation with HDBR; however, there was a slower response in vasodilation to a sudden decline in blood pressure in participants who had orthostatic intolerance. In the only reported study of astronauts, Iwasaki et al5 reported improved cerebral autoregulation on landing day; however, all 6 astronauts who participated in the study did not have presyncopal symptoms after their 16-day space flight.

In this study we investigated for the first time to our knowledge the possible importance of cerebral autoregulation on orthostatic intolerance after space flight in a sample that contained presyncopal astronauts on landing day. We hypothesized that autoregulation would be negatively affected by space flight in those astronauts who did not complete a 10-minute stand test (nonfinishers) when compared to those who did (finishers). Although some studies have examined cerebral autoregulation after space flight, we believe that this is the first time that it has been evaluated in astronauts who were, or were not, able to complete a stand test after space flight.

Materials and Methods
This protocol was approved by the Johnson Space Center Human Research Policy and Procedures Committee. Data before and after
flights were recorded from astronauts who took part in shuttle missions lasting 8 to 16 days. Data were collected 10 days before launch (baseline, before flight), on landing day (1 to 2 hours after landing), and 3 days after landing (after flight).6

Cerebral blood flow in the M1 segment of the middle cerebral artery (MCA) was measured using transcranial Doppler ultrasound and blood pressure via noninvasive finger photoplethysmography. The dynamic autoregulatory gain was determined using the noninvasive transfer function method.7 Astronauts were classified as finishers (completed the 10-minute stand test) or as nonfinishers (presyncopal during the stand test). Detailed data collection and analysis procedures can be found in the Supplement (http://stroke.ahajournals.org).

Statistics
A repeated-measures analysis of variance with factors of test day (before flight, landing day, 3 days after flight), stand test (supine, stand), and group (finishers/nonfinishers or male/female) was used with group nested within participants. The JMP-IN statistical package (SAS Institute) was used.

Results
Of the 27 astronauts (20 male, 7 female) who were analyzed in this study, 19 (17 male) were classified as finishers and 8 (5 female) were classified as nonfinishers. Mean arterial pressure at the level of the MCA (BP$_{MCA}$) was significantly reduced by the stand test ($P<0.001$). This was combined with differences between finishers and nonfinishers ($P=0.011$) and over test days ($P=0.004$). On landing day, finishers had a higher BP$_{MCA}$ than those before flight and the nonfinishers (Figure 1). Three days after landing, the finishers had returned to preflight values whereas the nonfinishers had elevated supine BP$_{MCA}$.

Mean cerebral blood flow velocity (MFV) was affected by test day ($P<0.001$) and by the stand test ($P<0.01$). Preflight nonfinishers had higher MFV than finishers. Compared to the preflight group, the supine MFV of the finisher group was elevated on landing day, whereas in the nonfinisher group MFV was unchanged. Unlike preflight MFV, on landing day both finishers and nonfinishers had a reduction in MFV with standing. Only the nonfinishers had MFV reduced lower than preflight values. Three days after landing, both supine and stand MFV were not different from preflight values for the finishers but were significantly elevated in the nonfinishers.

Cerebrovascular conductance was affected by stand ($P<0.001$) and by group ($P<0.001$), and it was different between finishers and nonfinishers during stand and over test days ($P<0.01$). Before flight, conductance increased with the stand test; however, nonfinishers had higher conductance than finishers (Figure 1, bottom). On landing day, supine conductance was unchanged from preflight values, but the response to standing was different. On standing, conductance did not change in the finishers and decreased in the nonfinishers to a value lower than that before flight. Three days after flight, supine conductance was again higher in the nonfinishers compared to the finishers, but it did not increase on standing.

There were significant gender effects with BP$_{MCA}$ ($P=0.035$), MFV ($P=0.044$), and conductance ($P=0.041$), which are represented in Figure 1. Female astronauts had an increase in supine BP$_{MCA}$ 3 days after flight and in overall MFV 3 days after flight compared to preflight values. In

![Figure 1. Blood pressure at the level of the middle cerebral artery of the brain (BP$_{MCA}$), mean cerebral blood flow velocity (MFV), and cerebrovascular conductance as a function stand in astronauts categorized by orthostatic tolerance in finishers or nonfinishers (left) or by gender (right), $P<0.05$. Differences for *supine, †finishers, and ‡preflight.](http://stroke.ahajournals.org)
general, the largest change in conductance occurred in females 3 days after flight, when cerebral conductance was greater than preflight.

The effects of space flight on blood pressure at head level and cerebral blood flow velocity can be seen readily in the beat-by-beat tracing of a nonfinisher astronaut (Figure 2). Although the blood pressures in the supine and early standing conditions were similar, MFV was drastically lower. In the expanded view of presyncope, beat-by-beat differences can be seen in signals from preflight to 2 hours after landing.

To further explore impairment of autoregulation on landing day, we plotted the average MFV against average BP_MCA (Figure 3) in each of the groups. The large decline of MFV on landing day in the nonfinishers is visible, and this decrease occurred within the same blood pressure range seen before flight in both finishers and nonfinishers. A standardized autoregulation curve1 with arbitrary upper and lower limits was superimposed over the preflight data with the supine and standing data on the plateau of the curve (Figure 3, dashed lines). The curve was adjusted to the landing day results through a simple increase in the slope (slope, curved arrow, Figure 3) of the plateau region. The data from 3 days after flight also could be represented by a simple upward shift (plateau, vertical arrow, Figure 3) of the preflight autoregulation curve. The same pattern of increased slope of the plateau on landing day and upward shift of the curve 3 days after flight also could be observed in the group of nonfinishers but with larger changes in slope on landing day and upward shift (plateau) 3 days after flight.

Before flight, the change in MFV as a function of BP_MCA (slope of solid lines, Figure 4) was not different between males ($0.16 \pm 0.22$ cm$^{-1}$ mm Hg$^{-1}$) and females ($0.01 \pm 0.51$ cm$^{-1}$ mm Hg$^{-1}$; $P = 0.76$); however, it was greater in females on landing day ($1.10 \pm 0.35$ cm$^{-1}$ mm Hg$^{-1}$) when compared to preflight values ($P = 0.048$) and compared to males on landing day ($0.19 \pm 0.21$ cm$^{-1}$ mm Hg$^{-1}$; $P = 0.06$).

**BP_MCA and Cerebrovascular Resistance Index**

**Autospectral Data**

Differences in BP_MCA low-frequency (LF) (0.07–0.20 Hz) power were observed between finishers and nonfinishers during the stand tests (Figure 5). On average, nonfinishers had elevated ($P < 0.001$) LF power ($3.07 \pm 0.31$ mm Hg$^2$ Hz$^{-1}$) compared to finishers ($1.49 \pm 0.18$ mm Hg$^2$ Hz$^{-1}$). There was also a significant overall difference between the finishers and nonfinishers with respect to the stand test (interaction, $P < 0.001$).

There was a significant effect of test day on the cerebrovascular resistance index (CVRi) very-low-frequency (VLF) power between the finishers and nonfinishers ($P = 0.04$); the nonfinishers had significantly higher CVRi VLF power 3 days after flight (Figure 5).

**BP_MCA and CVRi Cross-Spectral Data Gain and Phase**

In the VLF region, there was a significant 3-way interaction (day, stand, presyncope; $P = 0.0037$). The finisher group was characterized by constant autoregulation gain in the VLF region over all test conditions (Figure 6). Preflight, the nonfinisher group had a greater supine VLF gain than did the finisher group, which decreased on standing. On landing day, the supine VLF gain of the nonfinisher group was not different from that of the finishers; however, during the stand portion the gain was greater than that of the finishers.

Significant main effects were observed for the gain in the LF region of cerebral autoregulation. Overall, supine gain was higher than stand gain ($0.043 \pm 0.002$ CVRU mm Hg$^{-1}$, $0.032 \pm 0.002$ CVRU mm Hg$^{-1}$, respectively; $P = 0.0004$). An interaction was found between test day and astronaut presyncope ($P = 0.005$). Astronauts who could finish the 10-minute stand test had a significant reduction in their LF gain from preflight to landing and 3 days after landing; however, the nonfinishers had a significant increase in LF gain on landing day that was greater than the finisher group.

In the VLF range, females had an overall larger gain ($0.039 \pm 0.004$ CVRU mm Hg$^{-1}$) than males ($0.022 \pm 0.002$ CVRU mm Hg$^{-1}$; $P = 0.03$). Preflight, females had a larger supine VLF gain than males; on landing day, females had a higher VLF gain while standing compared to males (Figure 6). Males had a reduction in LF gain from preflight to landing and 3 days after landing. Males had lower LF gain than female astronauts on landing day and 3 days after landing.

**Figure 2. Left.** Beat-by-beat mean cerebral blood flow velocity in the M1 segment of the middle cerebral artery (MFV-MCA) and blood pressure at the level of the MCA of the brain (BP_MCA) for a landing day nonfinisher. These graphs represent landing day (solid lines) data from 1 minute before standing to 1 minute after return to supine, and the corresponding timed data for preflight (dashed lines).

**Right.** Continuous preflight and landing day cerebral blood flow velocity of the MCA (MCA velocity) and BP_MCA for the timed region when the nonfinisher astronaut had presyncopal symptoms on landing day.

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Both male and female astronauts had a significant main effect of a decrease in LF gain from supine to stand $^{(P=0.036)}$; however, visual inspection of the data (Figure 6) would suggest that this was not the case on landing day.

**Figure 6.** Both male and female astronauts had a significant main effect of a decrease in LF gain from supine to stand ($P=0.036$); however, visual inspection of the data (Figure 6) would suggest that this was not the case on landing day.

**Discussion**

For the first time to our knowledge, we present cerebral autoregulation analyses for astronauts with and without orthostatic intolerance after flight. Our results confirm previous space flight data by Iwasaki et al., who showed that astronauts who do not exhibit orthostatic intolerance after flight have normal cerebral autoregulation on landing day; however, there was a severe impairment of cerebral blood flow velocity regulation in astronauts with orthostatic intolerance after flight.

Preflight, nonfinishers were operating at a higher resting cerebral blood flow velocity and similar mean supine blood pressure compared to finishers (Figure 1). On landing day, nonfinishers exhibited a large decrease in MFV associated

**Figure 3.** Mean cerebral blood flow velocity (MFV) as a function of blood pressure at the level of the middle cerebral artery of the brain ($BP_{MCA}$) in astronauts who finished (finishers) or could not finish (nonfinishers) the stand test. Supine data (closed symbols) are connected by a solid line to stand data (open symbols). Circles indicate preflight; triangles, landing day; and squares, 3 days after landing. Error bars are ± standard error of mean. For cerebral autoregulation curves, the region between supine and stand in the preflight data were considered to be within the plateau region of the standard autoregulation curve. Theoretical upper (right) and lower limits (left) of the autoregulation curves are represented by the dashed lines. S indicates change in slope of the plateau region from preflight to landing; R indicates rightward shift in the lower limit of autoregulation from preflight to landing; P, upward shift of the autoregulation curve from preflight to 3 days after flight.

**Figure 4.** Mean cerebral blood flow velocity (MFV) as a function of blood pressure at the level of the brain ($BP_{MCA}$) in male and female astronauts. Supine data (closed symbols) are connected by a solid line to stand data (open symbols). Circles indicate preflight; triangles, landing day; and squares, 3 days after landing. Error bars are ± standard error of mean.

with the same decline in $BP_{MCA}$ with standing as exhibited preflight. These results suggest that the cause of presyncope in astronauts may be linked with the loss of cardiovascular control of blood pressure and also may be related to a change in ability to autoregulate cerebral blood flow within the preflight blood pressure range.

**Cerebral Autoregulation**

Our analyses provide new information on cerebrovascular control during orthostatic hypotension after space flight. Preflight data (Figure 1) suggest that autoregulation characteristics of nonfinishers and finishers were different. MFV and conductance were much higher in the nonfinisher group in both the supine and standing positions. This could indicate that the nonfinishers were operating at a higher cerebral vasodilation for a given blood pressure. Although preflight $BP_{MCA}$ decreased from supine to stand, both finishers and nonfinishers had an increase in conductance, an appropriate response of a functional cerebral autoregulation system, and did not become presyncopal.

Finishers had neither an increase nor a decrease in conductance with standing as exhibited preflight. These results suggest that the cause of presyncope in astronauts may be linked with the loss of cardiovascular control of blood pressure and also may be related to a change in ability to autoregulate cerebral blood flow within the preflight blood pressure range.
1) after flight and that autoregulation was operating at a new set point. The lack of increase in conductance with the decline in $BP_{MCA}$ with standing also suggests some impairment in autoregulatory function before flight, although this was not serious enough to precipitate symptoms of presyncope.

In the nonfinishers, the decrease of landing day MFV with standing (Figure 1) was much greater than that of the finishers and those preflight. These data indicate that the nonfinishers were more severely challenged in terms of cerebral blood flow during stand than the finishers. This would indicate a severe impairment of cerebral autoregulation and may have precipitated presyncope in these astronauts. This can be seen in the sample landing day data from a nonfinisher (Figure 2); prolonged cerebral hypoperfusion attributable to loss of vasodilatory response (reduced blood flow) may be an important factor in the development of presyncope. A decrease

Figure 5. Autospectra for mean arterial pressure at the level of the middle cerebral artery ($BP_{MCA}$) and the cerebrovascular resistance index (CVRi) as a function of stand in astronauts categorized by orthostatic tolerance in finishers or nonfinishers (left) or by gender (right). VLF indicates very-low-frequency (0.03–0.07 Hz); LF, low-frequency (0.07–0.20 Hz). Values are mean±standard error. $P<0.05$. Differences for *supine to stand and #finishers and nonfinishers. Horizontal bar denotes a main effect collapsed over supine/stand.

Figure 6. Transfer function gain for the relationship mean arterial pressure at the level of the middle cerebral artery ($BP_{MCA}$) and cerebrovascular resistance index (CVRi) as a function of stand tests performed before flight, on landing day, and 3 days after landing in astronauts by orthostatic tolerance in finishers or nonfinishers (left) or by gender (right). VLF indicates very-low-frequency (0.03–0.07 Hz); LF, low-frequency (0.07–0.20 Hz). Values are mean±standard error. $P<0.05$. Differences for *supine to stand and #finishers and nonfinishers. Horizontal bar denotes a main effect collapsed over supine/stand.
in MCA conductance could be related to an increase in vascular stiffness, as seen in cerebral vessels after hind limb suspension in rats, or it could be that the cerebral vessels were close to maximal dilation and the decrease in MFV was directly attributable to the decline in blood pressure during standing.

Although it has been suggested that vasoconstriction, rather than vasodilation, could occur during presyncope because of increased sympathetic cerebral vasoconstriction,1,2,13 this mechanism may not play a role in the presyncope of the astronauts because this group has been shown to have a less effective sympathetic response to standing.6,13 An increase of cerebral blood volume, caused by vasodilation, could result in intracranial pressure elevation, which is positively correlated with cerebral blood flow velocity latency.14 Using our data, however, we are unable to speculate on this. The current data on cardiac output and blood pressure in these astronauts indicate hypovolemia and, therefore, a decrease in cerebral volume during standing. However, with respect to space flight, it has been speculated that the headward fluid shift causes vasodilation in the cerebral vessels, which may cause similar velocity latency14 on landing day.

When plotted as a function of $BP_{MCA}^*$, the large decline of MFV on landing day in the nonfinishers is visible, as is the fact that this decrease occurred within the same blood pressure range seen before flight in both finishers and nonfinishers (Figure 3). This representation of data suggests a possible explanation of the change in autoregulation with space flight that is common between both finishers and nonfinishers, only with greater effect in the nonfinisher group; however, the steepness of the plateau region on landing day suggests a severe impairment or loss of autoregulation in this group.

Further evidence in the difference in the 2 groups is provided by the analysis of dynamic autoregulation. Overall, there was less variation in vascular resistance (lower CVRi autospectral power) in the nonfinisher group despite a greater variation in blood pressure (higher $BP_{MCA}^*$ autospectral power; Figure 4). This may indicate an overall reduced autoregulation capacity in the nonfinisher group.

Preflight, only the nonfinisher group had a decrease in dynamic autoregulation gain when going from supine to standing. In general, one can interpret a higher $BP_{MCA}^*$→CVRi gain as an indication of a more effective filtering of blood pressure oscillations.5 When going rapidly from supine to stand, there is a sudden decrease in blood pressure at the level of vessels involved with the cerebral autoregulation and an effective autoregulation system should not be affected or at least should not have a decrease in gain.

In the finisher group, supine dynamic autoregulation gain was reduced on landing day and 3 days later (Figure 4). On landing day, supine blood pressure was higher than preflight values (Figure 1), yet MFV remained unchanged. These data would indicate that with the increased blood pressure, the system was within the limits of autoregulation. On landing day, supine blood pressure was higher in the finisher group compared to preflight values. It is possible that this may produce less defined, or passive, resting dynamic autoregulation with a wider variation of participant autoregulation curves.

Conversely, the nonfinisher group had an overall increase in dynamic autoregulatory gain on landing day (Figure 6), with no change in supine or standing blood pressure compared to preflight values. Although the increase in gain suggests improved autoregulation, greater decrease in MFV and a large decrease in cerebral conductance with standing compared to preflight (Figure 1) values suggest that on landing day these astronauts were unable to autoregulate cerebral blood flow with a normal decrease in $BP_{MCA}^*$. This could indicate that the lower limit of autoregulation had shifted to the right (Figure 3, right), or that the changes in cerebrovascular resistance were ineffectual in maintaining normal cerebral perfusion. The incidence of presyncope was eliminated by day 3, most likely through changes in blood pressure regulation. The increase in blood pressure may have augmented blood flow to a region of effective autoregulation.

Gender

Our results indicate that female astronauts have different autoregulation characteristics, and on landing day females had reduced autoregulation compared to males. Astronaut gender may also play a role in susceptibility to orthostatic intolerance after flight. In this data set, 5 of 8 nonfinishers were female, whereas 17 of 19 finishers were male. A compilation of statistics (25 female, 140 male) on incidence of presyncope after short-duration space flight (5–16 days) showed a similar effect, with presyncope occurring in 28% of the females and in 7% of the males.

The majority of cerebral autoregulation characteristics are similar between males and females; however, there are a few characteristics that are different and that may predispose females to orthostatic intolerance. These include differences in cerebral blood flow velocity and cerebrovascular reactivity. In our study, we did observe higher cerebral blood flow velocity in females 3 days after flight, but not during preflight or on landing day (Figure 1). However, preflight VLF gain was double that of males (Figure 6) and reduced on landing day. This may indicate a reduction in autoregulation on landing day compared to that of males. Pavy Le-Trao4 showed no major impairment of cerebral autoregulation with HDBR in females; however, there was a slower response in vasodilation to a sudden decline in blood pressure in participants who were orthostatic-intolerant.

Limitations

Changes in velocity can only be equated to changes in flow if changes in the diameter of the MCA are minimal. Measurements of MCA caliber were not performed in the present study; however, previous invasive studies have shown minimal change in the M1 segment MCA diameter under a variety of conditions known to affect cerebral perfusion. Changes in blood CO2 are known to influence the set point for autoregulation level. Unfortunately, CO2 was not measured in the astronauts during the stand test, so its effect on the outcome of the present study is not known. Breathing rate was controlled in all tests at 15 breaths per minute; however, ventilatory effects on CO2 cannot be ruled out because no
attempt was made to monitor tidal volume. There may be other factors besides CO₂ that may contribute to the shift in the cerebral autoregulatory set point. This possibility cannot be ruled out in the present study either, because spaceflight may influence ≥1 of the factors that determine the level at which autoregulation tries to maintain cerebral blood flow and, hence, an individual’s susceptibility to orthostatic intolerance after flight.

Conclusions
Cerebrovascular regulation was found to be different between astronauts who were able to remain standing (finishers) or not (nonfinishers) without assistance for 10 minutes on landing day and across gender. On landing day, nonfinishers had a decrease in conductance with standing, whereas the finishers did not. This was accompanied by an increase in VLF gain with stand and overall LF gain on landing day, which suggest that the autoregulation system was under greater stress in the face of declining blood pressure. Because the decrease in blood pressure during the time of these measurements was within the range of preflight and finisher values, these data indicate that a mismatch of cerebral blood flow and blood pressure control may be related to presyncope after flight. Astronaut gender may also play a role in susceptibility to orthostatic intolerance after flight.

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Impairment of cerebral blood flow regulation in astronauts with post-flight orthostatic intolerance

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Supplemental Methods
Astronauts were familiarized with the study protocol and data collection procedures 30 days pre-flight. Of the 40 original astronaut participants, 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; six could not be analyzed for cerebral autoregulation since on all the test days either continuous blood pressure or cerebral blood flow velocity data were not available. Therefore, only 27 astronauts whose mean age was 38.7 ± 5.2 yr, were used in our analysis.

The research protocol and cardiovascular data for these astronauts have already been presented 1; however, the make-up of the astronauts used in this paper will not match exactly those presented previously due to the requirement for complete and continuous data for blood pressure and cerebral blood flow velocity and no requirement for plasma catecholamines. Briefly, all data were collected continuously, following a 10-minute supine set-up period. Data were analyzed from 256 consecutive beats immediately following set-up and 30 seconds after the astronaut was assisted to standing. From these segments the dynamic autoregulatory gain was determined using the non-invasive transfer function method 2 along with the average cerebral blood flow velocity (MFV), blood pressure at brain level (BP_{MCA}) and cerebrovascular conductance (MFV/ BP_{MCA}).

**Detailed methods**

On each test day the participant had abstained from caffeine, alcohol, and any medications for the preceding 12 hours; was at least 2 hours postprandial; and had not exercised heavily in 24 hours. Upon arrival, the astronaut was placed in the supine position. Over the first 10-minutes the participant was instrumented for the study. This was followed by 5-min of supine data collection during which the participant paced their breathing with an auditory signal at 15 breaths per minute. The participant was then placed in the left lateral position for 7
minutes to perform echocardiography and carbon monoxide rebreathing to determine plasma volume for another NASA project being conducted simultaneously and the concentration of carbon monoxide used in the blood volume measurement was very small and of short duration. There was no significant difference between two minute pre and two minutes post rebreathe segments pre-flight, landing day, or 3 days post flight in either the finisher group (Pre vs post: 45.5±2.1 vs 49.7±2.6, 47.7±1.4 vs 50.0±1.7, 51.5±2.6 vs 51.4±2.8 cm·s⁻¹) or in the non-finisher group (Pre vs post: 50.5±5.7 vs 54.3±5.8, 49.7±6.7 vs 48.1±4.4, 57.8±6.4 vs 62.4±5.5 cm·s⁻¹).

Following the carbon monoxide rebreathe procedure, the participant was returned to the supine position and, after two minutes, was assisted to the standing position by three investigators. To minimize blood pressure changes due to the effort of standing, the participant was lifted from behind both shoulders while their feet were swept off the bed. The participant remained unassisted in the standing position for up to 10 min and was returned to the supine position. During the first five minutes of the stand test, each participant was again requested to follow an auditory signal to pace their breathing at 15 breaths per minute. If the participant became presyncopal during the stand, they were returned immediately to the supine position. Participants were deemed to be presyncopal if the participant indicated symptoms such as dizziness or nausea, or if we observed any of the following: i) a sudden decrease in HR of more than 15 beats per minute; ii) a decrease in systolic BP of more than 25 mm Hg per minute; iii) a decrease in diastolic BP of more than 15 mm Hg per min; iv) a decrease in MFV of more than 15 cm/s per minute; or, v) loss of diastolic flow.

Data Collection

Mean blood flow velocity (MFV) of the middle cerebral artery (MCA) was measured through either the right or left temporal window with 2-MHz pulsed transcranial Doppler
ultrasound (Medasonics, Fremont, CA). The temporal window determined to produce the best signal during pre-flight testing was used on all test days. Blood pressure was measured using the non-invasive Finapres (Ohmeda, Inglewood, CO). The finger with the continuous arterial pressure device was held at heart level by a system of Velcro straps. Each participant was also instrumented for an electrocardiogram.

The analog signals from these devices were recorded simultaneously at 12 kHz per channel using an eight-channel digital tape recorder (TEAC RD–111T, Montebello, CA). Beat-by-beat analysis of these data was performed off-line. The mean arterial blood pressure was adjusted to the level of the MCA (BP\textsubscript{MCA}) by applying a hydrostatic correction. The pressure and velocity envelope tracing, respectively, between the initial increases in blood pressure or velocity after successive ECG R-waves described a single beat for both blood pressure and cerebral blood flow velocity. BP\textsubscript{MCA} and MFV for each beat were calculated as the arithmetic average of the pressure and velocity waveforms respectively. The Doppler and blood pressure tracings were manually reviewed for anomalies and movement artifact. Any unusable blood flow velocity or blood pressure data (raw data from beats in which the mean could not be reliably calculated, either due to noise or lack of signal) were removed and the time series adjusted by interpolating new values from the two valid points surrounding the excluded segment. If more than 5% of any 256 beat segments were interpolated, the results were deemed invalid. The cerebrovascular resistance index (CVRi) was determined beat-by-beat as the ratio: BP\textsubscript{MCA}/MFV. From these data BP\textsubscript{MCA} and CVRi time series were constructed for each participant on each of the test days.
Dynamic Autoregulation Analysis:

In this study, care was taken to ensure that data used for cerebrovascular analysis was from segments that were closest to being steady state. Baseline analysis was performed on data collected after the participant was supine for at least ten minutes and before the carbon monoxide (CO) rebreathe test for blood volume. During the stand portion of the test, analysis was not performed until at least one minute had passed, allowing for heart rate and blood pressure to stabilize. This was at least three minutes after the CO-rebreathe protocol and at least eight minutes after the inhalation of CO for the blood volume test.

The dynamic autoregulatory gain was determined using the non-invasive transfer function method. Autospectra of the MFV and CVRi were calculated and the mean spectral power was determined within two distinct frequency regions (very low frequency, VLF: from 0 to 0.07 Hz; low frequency, LF: from 0.07 to 0.2 Hz) found to represent the region of cerebral autoregulation. Cross-spectral power, transfer function gain and phase, and coherence were determined within the same frequency regions for the relation between BP_{MCA} → CVRi.

The BP_{MCA} → CVRi transfer function relies on the inherent physical link between the two measured variables BP_{MCA} and MFV to calculate CVRi. The transfer function analysis of BP_{MCA} → CVRi provides an intuitively attractive means of assessing cerebrovascular autoregulation, inasmuch as improved autoregulation is denoted by increased gain and reduced phase lag. In our study, therefore, cross-spectral power, transfer function gain and phase, and coherence were determined within the same frequency regions for the relation between BP_{MCA} → CVRi. Gain and phase relations were obtained only from those regions of the spectra where coherence was greater than 0.5.
References


Abstract

Impairment of Cerebral Blood Flow Regulation in Astronauts With Orthostatic Intolerance After Flight

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Abstract

飛行後に起立不耐症をきたす宇宙飛行士の脳血流調節障害
Impairment of Cerebral Blood Flow Regulation in Astronauts With Orthostatic Intolerance After Flight

背景および目的：我々は、飛行前後の宇宙飛行士の脳血流調節について検討した。起立試験を完成できた者とできなかった者では、飛行前後の自己調節能に違いがあるという仮説を立てた。

方法：8 ～ 16 日間のシャトルミッションを行う宇宙飛行士 27例に対し、飛行の 10日前と着陸の 1 ～ 2時間後および5日後に10分間の起立試験を実施した。心拍数、脈波ドプラ検査により、大脳動脈（MCA）の平均血流速度を測定した。Finapres（連続血圧・血行動態測定装置：Ohmeda, Englewood, CO）を用いて平圧動脈圧を測定し、MCAレベルに補正した（BP_MCA）。クロスパワースペクトル、ゲイン、位相、コヒーレンスを測定し、BP_MCAと脳血管抵抗の指標である平均血流速度／BP_MCAの関係を検討した。

結果：起立によりBP_MCAは低下した（p < 0.001）。試験完了者と非完了者では差がみられた（p = 0.001）。脳血管コンダクタンスは、起立（p < 0.001）および被験者群（p < 0.001）の影響を受けており、被験者群×起立および被験者群×試験日間の交互作用がみられた（p < 0.01）。飛行前のデータから、非完了者は完了者に比べて、ミッション前の任意のBP_MCAにおける脳血管拡張が大きいことが示唆された。また着陸日の起立試験では、非完了者は完了者および飛行前に比べて、BP_MCAの間数である平均血流速度の低下が大きかった。性別と試験日、性別と仰卧位から立位への変化の間には、有意な交互作用効果が認められた（p = 0.035）。

結論：本研究結果は、宇宙飛行士にみられる失神前状態の原因は、脳血流と血圧のミスマッチに関係があると考えられるこを示している。飛行後に起立不耐症を起こすか否かは、宇宙飛行士の性別によっても異なる可能性がある。

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