

HYPOVOLEMIA INDUCED ORTHOSTATIC HYPOTENSION IN PRESYNCOPIAL
ASTRONAUTS AND NORMAL SUBJECTS RELATES TO HYPOADRENERGIC
RESPONSIVENESS

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ABSTRACT

Circulating blood volume is reduced during spaceflight, making astronauts hemodynamically compromised. After landing, astronauts separate into two groups. One group compensates for the hypovolemia with a hyper-sympathetic response during upright tilt testing and can complete a tilt test with few symptoms. The other group is unable to mount a hyper-sympathetic response and experiences orthostatic hypotension and presyncope during upright tilt tests. We tested the hypothesis that hypovolemia alone, in the absence of spaceflight, also would cause subjects to separate into presyncopal and non-presyncopal groups according to their sympathetic responses during tilt. We studied 20 subjects, including 10 veteran astronauts, on three occasions. On Days 1 (normovolemia) and 3 (hypovolemia), plasma volume, tilt tolerance and supine and standing plasma norepinephrine levels were measured. Forty hours prior to Day 3, subjects were given intravenous furosemide, followed by 36 hours of a 10MEq Na diet. Statistical comparisons were made between normovolemia and hypovolemia responses. This protocol reproduced landing day tilt test outcomes with 100% fidelity in the astronauts. Similarly to patterns reported after flight, non-presyncopal subjects had greater norepinephrine responses to tilt during hypovolemia compared to normovolemia (580 ± 79 vs. 298 ± 37 pg/ml, $P<0.05$), but presyncopal subjects had no increase (180 ± 44 vs. 145 ± 32 pg/ml, $P=NS$). This model can be used to predict astronauts who will become presyncopal on landing day, so that prospective, individualized countermeasures can be developed. Within patient populations, it can be used to study the interaction of volemic state and the sympathetic nervous system.

INTRODUCTION

The study of human physiological changes during spaceflight often leads to findings that can be relevant to clinical populations. Spaceflight challenges the human body with physiological stresses that must be overcome for survival. Sometimes these stresses unmask symptoms that would not manifest under normal conditions. A major physiological change that all astronauts experience and must overcome is a reduction in circulating blood volume of about 9% (2, 3, 10). This results from a diuresis initiated by the cephalad fluid shifts upon entry into microgravity. While not of much hemodynamic importance during microgravity, this fluid loss is a prime example of a physiological change for which other systems must compensate if astronauts are to function normally after landing. During postflight testing of orthostatic tolerance, only those who can mount an extra-ordinary sympathetic response are able to maintain upright blood pressures during stand or tilt tests. A substantial percentage of astronauts cannot mount such a response and experience severe orthostatic hypotension and presyncope or syncope. We have documented this repeatedly over the last 15 years (2, 3, 10, 13). The ability to predict, before flight, who those astronauts will be on landing day would be a major breakthrough for the development of appropriate countermeasures. To date, the only predictor of postflight orthostatic hypotension and presyncope has been the outcome from a prior flight (7). Preflight identification has been made difficult by the fact that, prior to flight, large sympathetic responses are not needed to maintain upright posture, and incidents of presyncope are very rare in these normal healthy astronauts. We theorized that, since loss of blood volume is a large driver of postflight orthostatic hypotension, it may be possible to reproduce the landing day presyncope by reproducing the landing day hypovolemia. In a ground-based study, we used a regimen of an

intravenous dose of furosemide plus a low salt diet to induce hypovolemia. We tested the hypothesis that the incidence of presyncope during upright tilt testing would be the same during hypovolemia as on landing day, and that the underlying cause would be inadequate compensatory sympathetic responses. If true, we would have a model that could provide a means by which individuals that would become presyncopal after spaceflight could be identified before launch, so that countermeasures could be prescribed prospectively for them.

METHODS

This study was approved by the Johnson Space Center Committee for the Protection of Human Subjects. All subjects signed informed consent documents. Subjects were 13 men and 7 women, aged 40.9 ± 2 years. Nine of these were astronauts (six men and three women), for whom we were able to compare their previous preflight and postflight tilt test outcomes with their current normovolemia and hypovolemia tilt test outcomes. Subjects came to the laboratory on three occasions. On day 1 (normovolemia day), subjects had consumed a minimum of 2 grams of NaCl every day for a week. On day 2, subjects had voluntarily reduced their salt intake for the prior three days. Initial hypovolemia was achieved by the slow infusion of 0.5 mg/kg of furosemide at a rate of 4 mg/min. This was followed by 36 hours of a very low sodium diet (10mEq/day). Day 3 (hypovolemia day) began 40 hours after the furosemide infusion. Days 2 and 3 were separated by at least two weeks. For all female subjects, Days 1 and 3 were always performed during menses, and in random order. Tilt tests were performed on days 1 and 3. On each study day, subjects had abstained from taking any medications for the previous 24 hours, had not eaten a heavy meal within 4 hours, had consumed a

light snack within 2 hours, and had not exercised maximally within 24 hours. Subjects were placed supine on a tilt table and instrumented for ECG, brachial artery pressure and beat-to-beat finger arterial pressure. An intravenous catheter was placed in an antecubital vein for blood draws. The subject then rested supine on the table for 20 minutes, at which time plasma volume was measured using the carbon monoxide rebreathing technique (1, 6). A blood sample was drawn for plasma norepinephrine and epinephrine levels. Measurements of heart rate and arterial pressure were obtained for 5 minutes, after which the tilt table was inclined to 80° upright. Measurements continued for 15 minutes and a final blood sample was drawn. If presyncopal symptoms caused early termination of the tilt test, the table was returned to the supine position and blood was drawn immediately. Catecholamines were later measured by radioenzymatic assay (4).

Statistics

Statistical comparisons were made only for the normovolemia and hypovolemia data collected in the current study. All results are presented as means \pm SE. All data from the current study were tested for normalcy and equal variance using the Kolmogorov-Smirnov test and the Levene Median test. Subjects were grouped into presyncopal or non-presyncopal, based on their ability to complete the tilt test on the hypovolemia test day (Day 3). Differences were analyzed by using a two-way repeated measures analysis of variance. The effects of interest were group (presyncopal or non-presyncopal) and day (normovolemia or hypovolemia). The Tukey test for multiple comparisons was performed to document differences when there were significant main effects. For all tests, significance was set at $P \leq 0.05$.

Statistical comparisons were not made between prior flight data and current hypovolemia data. Of the nine astronauts who participated in this ground-based study, preflight/postflight catecholamine and plasma volume data were available for only six. Of those six, four were presyncopal on landing day and two were not. These numbers were not large enough to allow statistical comparisons between their flight and their hypovolemia data. However, flight data from previous publications have been re-plotted and are presented in figures 1, 4 and 5 for comparison with the current data.

RESULTS

Plasma Volumes

Figure 1 presents plasma volume losses in the non-presyncopal and presyncopal subjects in the current study (right). Previously published spaceflight-induced plasma volume loss data have been re-plotted and are presented for comparison on the left. There were no differences between presyncopal and non-presyncopal subjects in either situation.

Supine Arterial Pressure and Heart Rate

There were no differences in baseline arterial pressure between normovolemia and hypovolemia or between presyncopal and non-presyncopal groups, but heart rates were higher with hypovolemia in both groups. In the non-presyncopal group baseline systolic and diastolic pressures were 118 ± 6 mmHg and 69 ± 4 mmHg during normovolemia and 120 ± 4 mmHg and 70 ± 3 mmHg during hypovolemia ($P = NS$). In the presyncopal group pressures were 113 ± 3 mmHg and 64 ± 3 mmHg during normovolemia and 111 ± 4 mmHg and 66 ± 2 mmHg during hypovolemia ($P = NS$). Heart rates were higher during hypovolemia than normovolemia in both groups; 63 ± 3 bpm vs. 70 ± 5 bpm ($P =$

0.003) in the non-presyncopal group and 52 ± 2 bpm vs. 59 ± 2 bpm ($P = 0.003$) in the presyncopal group. Resting heart rate was significantly lower in the presyncopal group than in the non-presyncopal group during both normovolemia ($P = 0.04$, between groups) and hypovolemia ($P = 0.03$, between groups).

Orthostatic Tolerance

Of the nine astronaut subjects who participated in this study, their landing day tilt test outcomes were reproduced by hypovolemia with 100% fidelity. Six of them became presyncopal during tilt tests both on landing day and during hypovolemia; three did not. Of all subjects in this study, 55% were presyncopal during hypovolemia. Figure 2 presents original tilt tests during normovolemia and hypovolemia for one non-presyncopal subject (top two panels) and one presyncopal subject (bottom two panels). The susceptible subject became presyncopal at five minutes of tilt on the hypovolemia day.

Norepinephrine Responses

Figure 3 presents supine and standing plasma norepinephrine levels for the same two subjects during normovolemia and hypovolemia. The two subjects had similar increases in norepinephrine levels during upright tilt when they were normovolemic. During hypovolemia, they had similar increases in supine plasma norepinephrine levels. However, when hypovolemic, the presyncopal subject had no additional increase in response to tilt, while the non-presyncopal subject had a greater than two-fold increase. Complete norepinephrine and epinephrine data were obtained in 17 of the 25 subjects in the current study. Figure 4 presents normovolemia vs. hypovolemia norepinephrine responses to upright tilt in non-presyncopal (top, right) and presyncopal (bottom, right)

subjects in the current study. Previously published preflight vs. postflight norepinephrine responses to tilt in non-presyncopal and presyncopal astronauts have been re-plotted and are presented for comparison on the left. It is significant that, both on landing day and during hypovolemia alone, presyncopal subjects do not increase their release of norepinephrine, while, non-presyncopal subjects have at least a two-fold increase.

Epinephrine Responses

Figure 5 presents norepinephrine responses to upright tilt during normovolemia and hypovolemia in non-presyncopal (top, right) and presyncopal (bottom, right) subjects in the current study. Previously published preflight vs. postflight epinephrine responses to upright tilt in non-presyncopal and presyncopal astronauts have been re-plotted and are presented for comparison on the left. Unlike the norepinephrine response, the epinephrine response to tilt is significantly greater during presyncopal episodes after spaceflight, but significantly smaller during presyncopal episodes during hypovolemia.

DISCUSSION

This study describes a very important finding; that if astronauts and normal subjects are subjected to a similar level of hypovolemia as that experienced after spaceflight, they will self-separate into those who do and those who do not become presyncopal during a simple upright tilt test. In the astronauts whom we tested in both conditions, the hypovolemia reproduced the occurrence of presyncope with 100% fidelity. Moreover, the mechanism of presyncope in both conditions is the same; the failure to mount the super-sympathetic response needed to overcome the hemodynamic compromise caused by the hypovolemia.

This model can provide new opportunities for the study of mechanisms of blood pressure control. By driving subjects into this compromised hemodynamic state, the limits of sympathetic responsiveness can be measured. Within the astronaut population, it offers the means by which astronauts who will be susceptible to postflight orthostatic hypotension can be identified prior to their first flight, so that countermeasure treatments can be individualized and prescribed prospectively. Within patient populations the model could be useful in the study of the interaction of volemic state and the sympathetic nervous system in both hypotension and hypertension

Spaceflight Relevance

Our group has several publications about post-spaceflight orthostatic hypotension that include data from over 100 astronaut subjects. In each study we found subtle differences, before flight, in the responses of presyncopal and non-presyncopal astronauts to upright tilt (2, 3, 10, 13). However, the differences were not great enough to allow us to predict which crew members would experience orthostatic hypotension and presyncope after landing. The current study is a breakthrough in this effort. We have shown that post-spaceflight orthostatic hypotension and presyncope can be reproduced with a hypovolemia regimen on the Earth. Furthermore, we have shown that the underlying cause of the orthostatic hypotension in both situations is hypo-adrenergic responsiveness. It will now be possible to test potential countermeasures on susceptible individuals with some confidence that, if the countermeasure is effective during hypovolemia, it will be effective on landing day. This model also offers the opportunity to perform preliminary screening of potential countermeasures before expensive head-down tilt bed rest studies (the human ground-based analog of spaceflight) are undertaken.

This model already has allowed us to compare the effects of hypovolemia alone with the effects of spaceflight on left ventricular mass, an area of some controversy. It had been suggested by some that decreases in left ventricular mass after spaceflight might indicate cardiac atrophy associated with cardiovascular deconditioning (5). However, this same hypovolemia regimen reproduces the postflight decrease in left ventricular mass (12). This suggests that the postflight reductions in mass may be secondary to simple physiologic fluid exchanges. Other cardiovascular changes after spaceflight, such as decreased aerobic capacity, also have a large hypovolemic component. The same hypovolemia regimen could be used for evaluation of that phenomenon.

Many attempts have been made to restore plasma volume losses in astronauts prior to their return to Earth. To date they have not been successful. All of the astronaut subjects who have been evaluated in our flight studies had consumed the required fluid load of salt tablets and water (or its equivalent) prior to landing. Still they average a 9% loss of plasma volume after both short (3, 13), and long-duration flights (8). However, the key to postflight orthostatic tolerance has been shown not to be the degree of plasma volume loss, but rather the degree that the sympathetic nervous system can compensate for that loss (3, 8, 13). Therefore, our more recent countermeasure development efforts have focused on α -adrenergic agonists to supplement sympathetic responses. The α -agonist midodrine has shown initial success in preventing postflight orthostatic hypotension (11), probably will not be appropriate for all crew members. The new hypovolemia model would be very effective in identification of target crew members. It may also be used to compare relative efficacy of other new countermeasures, as they

become available. It could eventually be used as a selection criterion for flight assignments.

It is important to note that this model may “under-predict” susceptibility after longer duration missions, which last months rather than days. We have shown that even crew members who were classified as non-presyncopal after short Shuttle flights become presyncopal after long flights (9). It is thought that a central remodeling occurs as flight progresses due to lack of afferent baroreceptor input, such that efferent sympathetic responses may be blunted (10). The usefulness of this hypovolemia model for longer flights will be mostly in preflight comparisons of the efficacy of various countermeasures or combinations of countermeasures.

Clinical Relevance

The implications of these findings extend beyond the arena of space medicine and physiology. They also have relevance for the study of clinical populations who have poor control of blood pressure. Our results show that within the normal population, there are at least two different patterns that reflect differences in sympathetic control of arterial pressure. It is possible that these patterns are exaggerated in pathological conditions. It is clear that one pattern of response results in hypotension. Many patients with autonomic neuropathies have symptoms similar to those of returning astronauts, and their volume status is critical to their overall status. Thus this model could be used to study those patients.

Could the other pattern of sympathetic response during hypovolemia relate to hypertension? Yun et al. have suggested that, in salt-resistant hypertension, fluid losses associated with prescribed diuretics may actually trigger a reflex-mediated increase in

sympathetic drive which acts to increase pressure. They suggest that these patients might be better treated with hydration, which has beneficial effects on many conditions that are associated with heightened sympathetic activity (such as acute coronary syndrome, asthma, cancer and stroke) (14). Our results directly relate to this possibility, which also warrants further study.

Summary

We report a new model with which sympathetic control of blood pressure can be studied. We identified two patterns of sympathetic responsiveness within the normal population. One group of subjects was unable to increase sympathetic responsiveness to upright tilt when hypovolemia. These subjects experienced orthostatic hypotension and presyncope. Subjects who were able to mount a larger sympathetic response when dehydrated did not experience such symptoms. This model can facilitate study of differences in autonomic control of blood pressure after spaceflight, between genders and in several disease states.

Limitations

This study suffered from the fact that not all of the plasma volumes and norepinephrine data were available for preflight and postflight studies. Consequently statistical analyses were appropriate only between the normovolemia and hypovolemia data. Statistical comparisons were not performed between flight and hypovolemia data. However, since astronauts are, in fact, normal healthy subjects, and the patterns of adrenergic insufficiency are so similar between landing day and hypovolemia alone, we do not believe this distorts the results.

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Figure Legends

Figure 1. Normovolemia to hypovolemia plasma volume losses in non-presyncopal and presyncopal subjects (right). Previously published preflight to postflight plasma volume losses in astronauts have been re-plotted and are presented for comparison on the left (10). There are no differences between presyncopal and non-presyncopal subjects in either group.

Figure 2. Original tracings of arterial pressure and heart rate from tilt tests during normovolemia and hypovolemia in one non-presyncopal subject (top) and one presyncopal subject (bottom). Note that the presyncopal subject remained upright for the entire test on the normovolemia day, but only withstood five minutes upright on the hypovolemia day. The heavy arrows begin at the time of tilt.

Figure 3. Supine and standing plasma norepinephrine levels from the two subjects shown in Figure 2, during normovolemia and hypovolemia. The presyncopal subject had the same change in norepinephrine on both days. The non-presyncopal subject had twice the response during hypovolemia compared to normovolemia.

Figure 4. Norepinephrine responses to tilt during normovolemia and hypovolemia in non-presyncopal and presyncopal subjects (right). Previously published preflight and postflight norepinephrine responses to tilt have been re-plotted and are presented for comparison on the left (11). Note the similarity between the change from preflight to postflight with that from normovolemia to hypovolemia.

Figure 5. Epinephrine responses to tilt during normovolemia and hypovolemia in non-presyncopal and presyncopal subjects (right). Previously published preflight and

postflight epinephrine responses to tilt have been re-plotted and are presented for comparison on the left (11).

References

1. **Dahms TE and Horvath SM.** Rapid, accurate technique for determination of carbon monoxide in blood. *Clin Chem* 20: 533-537, 1974.
2. **Fritsch-Yelle JM, Charles JB, Jones MM, Beightol LA and Eckberg DL.** Spaceflight alters autonomic regulation of arterial pressure in humans. *J Appl Physiol* 77: 1776-1783, 1994.
3. **Fritsch-Yelle JM, Whitson PA, Bondar RL and Brown TE.** Subnormal norepinephrine release relates to presyncope in astronauts after spaceflight. *J Appl Physiol* 81: 2134-2141, 1996.
4. **Kennedy B and Ziegler M.** A more sensitive and specific radioenzymatic assay for catecholamines. *Life Sci* 47: 2143-2153, 1990.
5. **Levine BD, Zuckerman JH and Pawelczyk JA.** Cardiac atrophy after bed-rest deconditioning: a non-neural mechanism for orthostatic intolerance. *Circulation* 96: 517-525, 1997.
6. **Maas AHJ, Hamelink ML and de Leeuw RJ.** An evaluation of the spectrophotometric determination of HbO₂, HbCO, and HB in blood with the co-oximeter IL 182. *Clin Chem Acta* 29: 303-309, 1970.

7. **Martin DS and Meck JV.** Presyncopal/non-presyncopal outcomes of post spaceflight stand tests are consistent from flight to flight. *Aviat Space Environ Med* 75: 65-67, 2004.
8. **Meck JV, Reyes CJ, Perez SA, Goldberger AL and Ziegler MG.** Marked exacerbation of orthostatic intolerance after long- vs. short-duration spaceflight in veteran astronauts. *Psychosomatic Medicine* 63: 865-873, 2001.
9. **Meck JV, Reyes CJ, Perez SA, Goldberger AL and Ziegler MG.** Marked exacerbation of orthostatic intolerance after long- vs. short-duration spaceflight in veteran astronauts. *Psychosom Med* 63: 865-873, 2001.
10. **Meck JV, Waters WW, Ziegler MG, deBlock HF, Mills PJ, Robertson D and Huang PL.** Mechanisms of postspaceflight orthostatic hypotension: low alpha1-adrenergic receptor responses before flight and central autonomic dysregulation postflight. *Am J Physiol Heart Circ Physiol* 286: H1486-H1495, 2004.
11. **Platts SH, Ziegler MG, Waters WW, Mitchell BM and Meck JV.** Midodrine prescribed to improve recurrent post-spaceflight orthostatic hypotension. *Aviat Space Environ Med* 75: 554-556, 2004.
12. **Summers RL, Martin DS, Meck JV and Coleman TG.** Mechanism of spaceflight-induced changes in left ventricular mass. *Am J Cardiol* 95: 1128-1130, 2005.

13. **Waters WW, Ziegler MG and Meck JV.** Post-spaceflight orthostatic hypotension occurs mostly in women and is predicted by low vascular resistance. *J Appl Physiol* 92: 586-594, 2002.

14. **Yun AJ, Lee PY and Bazar KA.** Clinical benefits of hydration and volume expansion in a wide range of illnesses may be attributable to reduction of sympatho-vagal ratio. *Med Hypotheses* 64: 646-650, 2005.

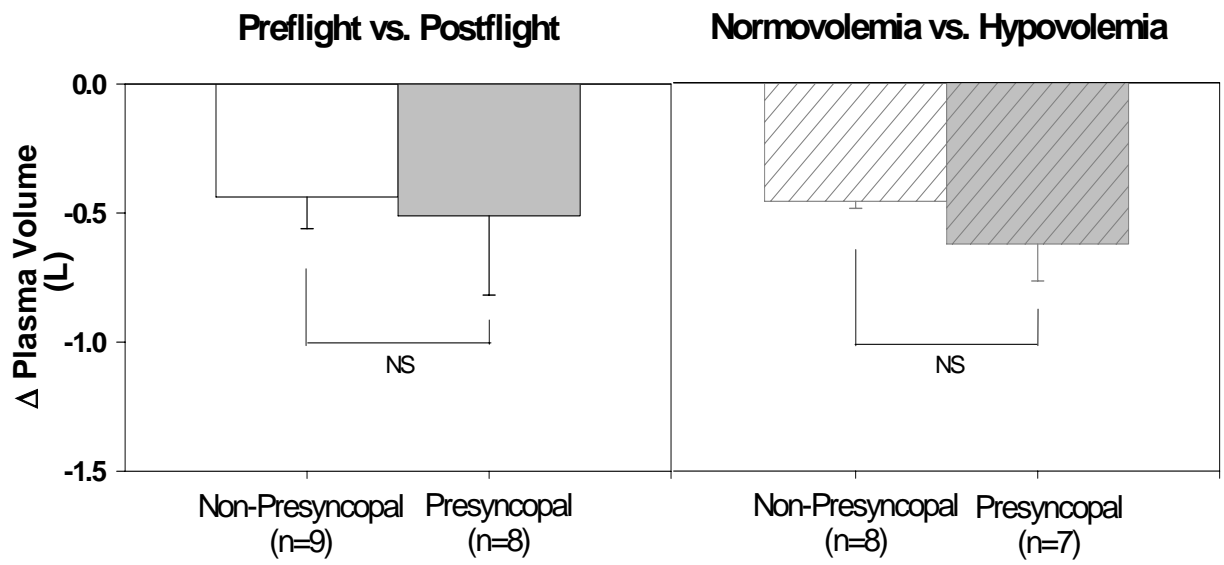


Figure 1

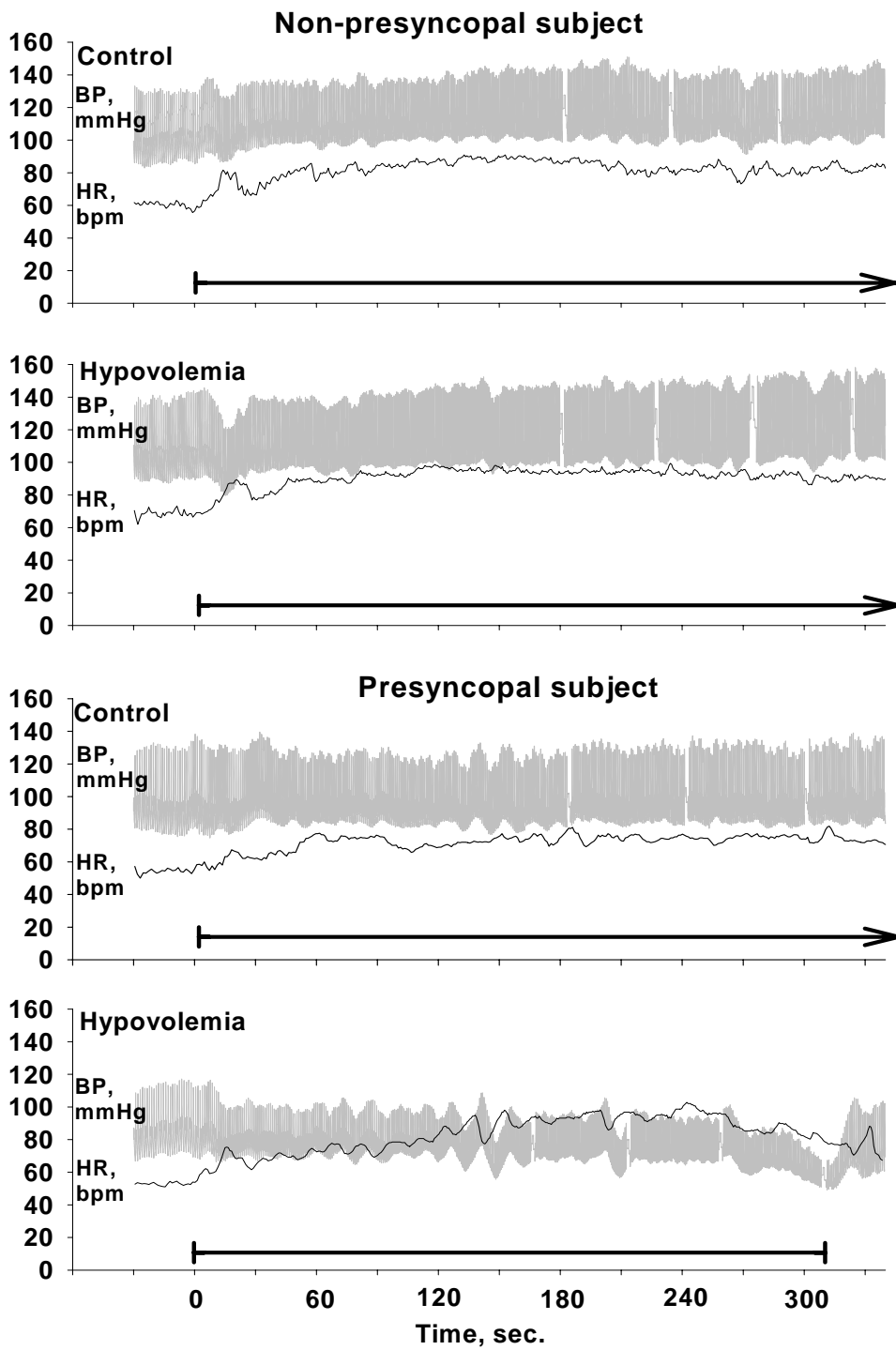


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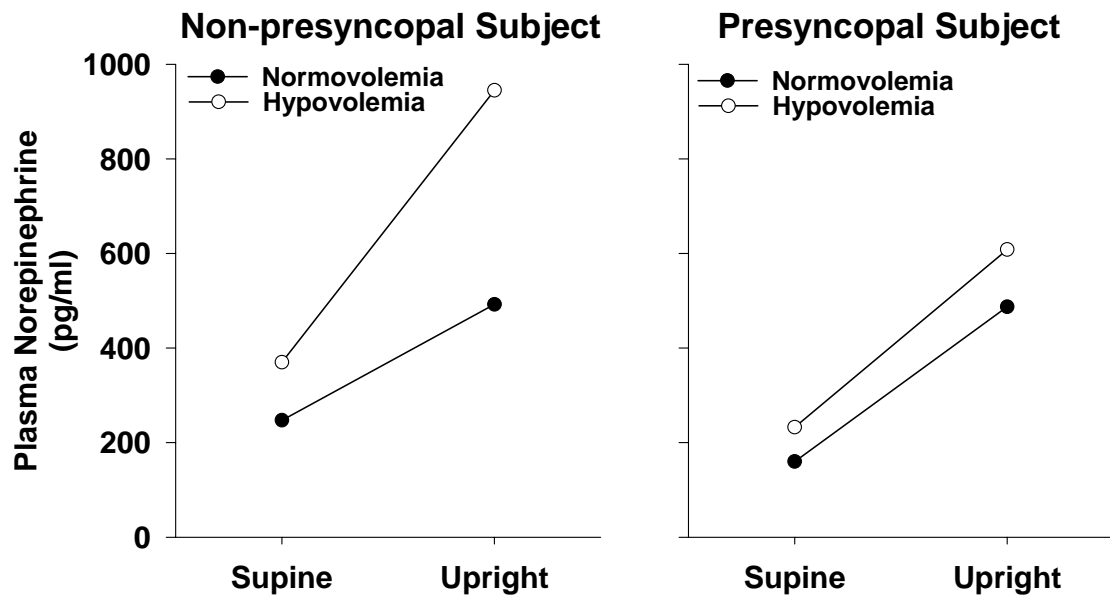


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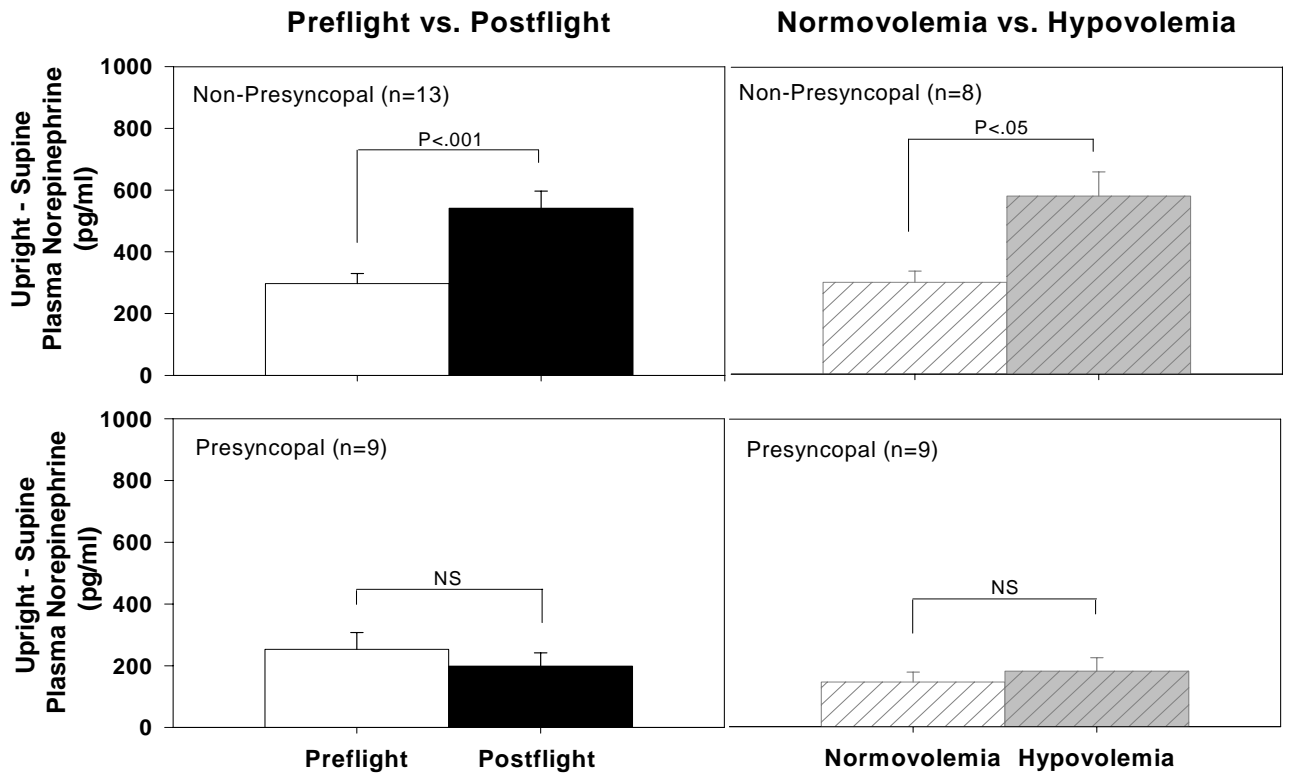


Figure 4

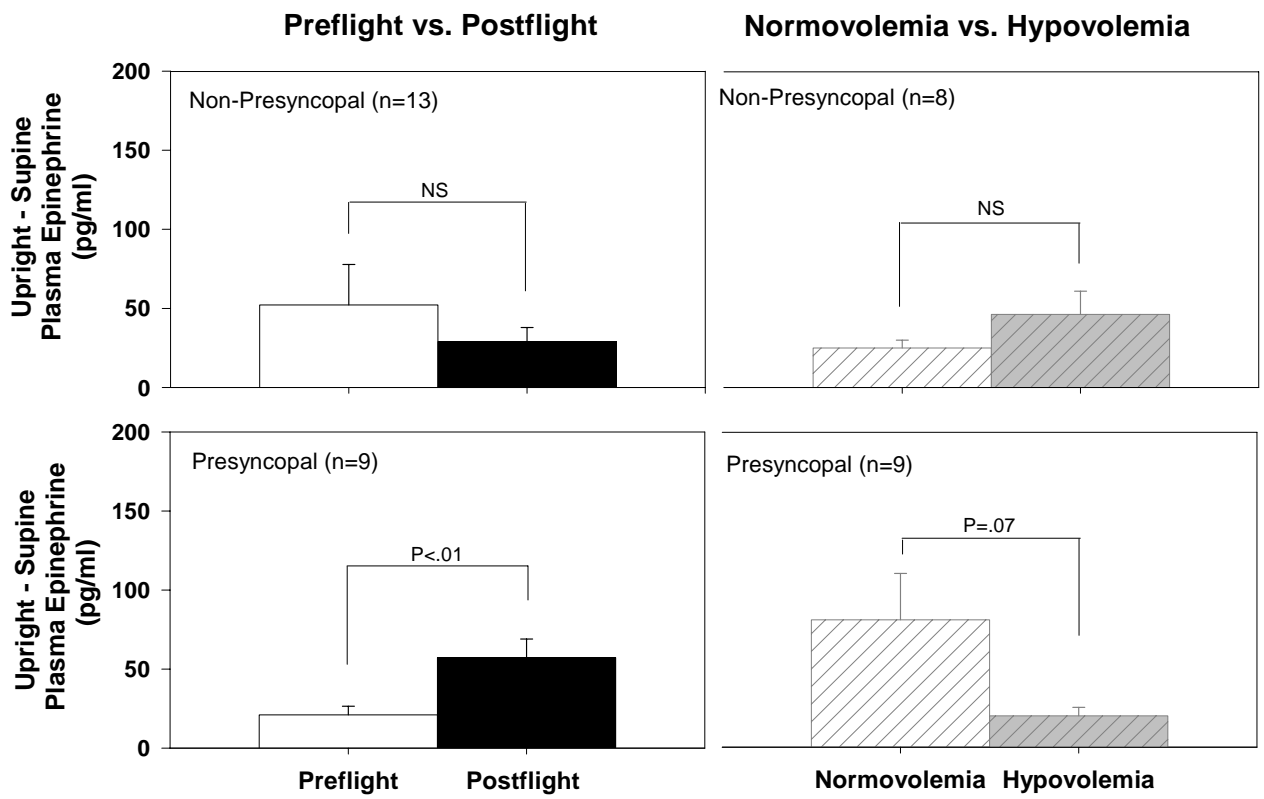


Figure 5