Hypovolemia-induced Orthostatic Hypotension Relates To Hypo-sympathetic Responsiveness

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• All astronauts experience a reduction in plasma volume during flight.
  – This is an underlying cause of orthostatic hypotension.

• Those who can mount a supra-sympathetic response can maintain blood pressures during tilt tests on landing day.
  – those who cannot, experience orthostatic hypotension and presyncope.

• Preflight identification of susceptible crew members is difficult
  – prior to flight, large sympathetic responses are not needed
  – incidents of presyncope are rare.

• We tested the hypotheses that experimentally-induced hypovolemia:
  – would reproduce the incidence of presyncope during upright tilt on landing day.
  – the underlying cause would be inadequate compensatory sympathetic responses.

• If true, we would be able to:
  – predict before flight individual susceptibility
  – prospectively prescribe countermeasures for them.
Plasma volume losses are similar after short and long-duration spaceflight

Pre-flight to Post-flight
ΔPlasma Volume (ml)

Short Duration  n=29
Long Duration  n=5

Reduced Plasma Volume affects:
- Orthostatic Tolerance
- Cardiac Function
- Renal Function (i.e. kidney stones)
- Aerobic Capacity
- Vascular Function
Effects of plasma volume losses on left ventricular mass
After Short-Duration Flight, LVM is Recovered at R+3 as Measured by Ultrasound (loss of approximately 8%; n= 13)
LVM vs. Plasma Volume

![Graph showing the relationship between LV Mass (g) and Plasma Volume.](image_url)
Computer model showing that changes in left ventricular mass during spaceflight are due to loss of water rather than solids. These data reproduce our published R+0 findings.
After Long-Duration Flight LVM is NOT Recovered by R+3

(Long Duration LVM: Pre-, Post-, and Recovery
( n = 6))

(Decrease of 15%)
Effects of plasma volume losses on orthostatic tolerance
Loss of plasma volume is not different between astronauts who DO and astronauts who DO NOT suffer from postflight orthostatic hypotension.

<table>
<thead>
<tr>
<th></th>
<th>Preflight Plasma Vol, l/m²</th>
<th>Landing day Plasma Vol, l/m²</th>
<th>% Spaceflight-Induced Loss</th>
</tr>
</thead>
<tbody>
<tr>
<td>Presyncopal Men (n=6)</td>
<td>1.67 ± 0.1</td>
<td>1.55 ± 0.12*</td>
<td>7.1 ± 0.03</td>
</tr>
<tr>
<td>Non-Presyncopal (n=24)</td>
<td>1.73 ± 0.0</td>
<td>1.60 ± 0.05 **</td>
<td>7.1 ± 0.03</td>
</tr>
<tr>
<td>Men</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Values are means ± SE; *p ≤ 0.05, **p ≤ 0.01, vs. preflight
Cardiovascular responses to upright posture in a patient and an astronaut

Adrenergic Failure

Astronaut, Pre-Flight

Astronaut, Landing Day

BP, mmHg

HR, bpm

SBP

DBP

Time, Minutes

0 1 2 3 4

0 100 200

0 100 200

0 100 200
Norepinephrine Response to Tilt before and after Spaceflight

![Graph showing the change in norepinephrine levels before and after spaceflight for presyncopal and non-presyncopal conditions.](image)

**Y-axis:** Tilt-Induced Norepinephrine Change (pg/mL ± SEM)

**X-axis:** Pre-Spaceflight vs. Post-Spaceflight

- **Presyncopal**
- **Non-Presyncopal**
Responses to standing after a short (top) and a long (bottom) flight in the same astronaut.
Shuttle vs. Long Duration R+0 = p<0.02
Long Duration R+0 vs. Long Duration R+1 = p<0.03
Plasma volume losses are similar after short and long-duration spaceflight.

ΔPlasma Volume, ml

<table>
<thead>
<tr>
<th></th>
<th>Short Duration n=29</th>
<th>Long Duration n=5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preflight to Postflight ΔPlasma Volume (ml)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-500</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-250</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-500</td>
<td></td>
<td></td>
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</tbody>
</table>

Effects of plasma volume losses on aerobic capacity
Maximum Oxygen Uptake Preflight, In-flight and Postflight (all max tests)

ISS Relative Oxygen Consumption
Pre- vs. Post-flight (max pre, sub-max post)

Relative VO2peak Pre- vs. Post-flight

-15.6%

-0.97%

VO2 (ml/Kg/min)

Pre-flight  R + 7  R + 30
Hypovolemia Model
12 Men (40.1 ± 1.4 yrs; 182.5 ± 1.3 cm; 86.2 ± 2.4 kg)
5 Women (39.0 ± 3.6 yrs; 161.8 ± 2.7 cm; 56.6 ± 3.9 kg)

17 Total Subjects – 11 normal, 6 astronauts (5 male, 1 female)
Plasma Volume Change During Hypovolemia

Plasma Volume Index (L/m²)

NORMOVOLEMIA

HYPOTOXEMIA
Plasma Volume Changes During Hypovolemia and After Spaceflight

Diagram showing changes in plasma volume during preflight versus postflight and normovolemia versus hypovolemia stages. The y-axis represents Δ Plasma Volume (L) with values ranging from -1.5 to 0.0. The x-axis categorizes groups as Non-Presyncopal and Presyncopal, with subcategories for each group: Non-Presyncopal (n=9) and Presyncopal (n=8) for preflight vs. postflight, and Non-Presyncopal (n=8) and Presyncopal (n=7) for normovolemia vs. hypovolemia. The NS indicates no significant difference.
<table>
<thead>
<tr>
<th>Presyncopal?</th>
<th>Hypovolemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Astronaut 1</td>
<td>YES</td>
</tr>
<tr>
<td>Astronaut 2</td>
<td>YES</td>
</tr>
<tr>
<td>Astronaut 3</td>
<td>YES</td>
</tr>
<tr>
<td>Astronaut 4</td>
<td>YES</td>
</tr>
<tr>
<td>Astronaut 5</td>
<td>NO</td>
</tr>
<tr>
<td>Astronaut 6</td>
<td>NO</td>
</tr>
<tr>
<td>R+0 (Landing Day)</td>
<td>YES</td>
</tr>
</tbody>
</table>
Figure 2

Non-presyncopal subject

Control BP, mmHg

BP, mmHg

HR, bpm

Hypovolemia

Control BP, mmHg

BP, mmHg

HR, bpm

Presyncopal subject

0 60 120 180 240 300

Time, sec.

0 60 120 180 240 300

Time, sec.
Norepinephrine Response to Tilt during Normovolemia and Hypovolemia

Plasma Norepinephrine (pg/ml)

Normovolemia
Hypovolemia

0 200 400 600 800 1000

Supine
Upright

Presyncopal Subject

Non-presyncopal Subject

1000 800 600 400 200

Supine
Upright

Norepinephrine Response to Tilt during Normovolemia and Hypovolemia
Norepinephrine Response to Tilt before and after Spaceflight

![Graph showing the change in norepinephrine levels during tilt before and after spaceflight. The graph compares presyncopal and non-presyncopal groups. The y-axis represents the tilt-induced norepinephrine change (pg/mL ± SEM) with bars indicating the difference between pre-spaceflight and post-spaceflight conditions.]
0.2 L/m² PVI Loss (13% Plasma Volume Loss)

Tilt Time (minutes)

Survival

ΔNE = 750
ΔNE = 500
ΔNE = 250
ΔNE = 0

0 5 10 15
0.4 L/m² PVI Loss (22% Plasma Volume Loss)
0.6 L/m² PVI Loss (30% Plasma Volume Loss)

- ΔNE = 750
- ΔNE = 500
- ΔNE = 250
- ΔNE = 0

Survival vs. Tilt Time (minutes)
Summary

• We report a new model which uses hypovolemia to force humans into a hemodynamic state that is similar to that after spaceflight.

• This model can be used to test candidate countermeasures for postflight orthostatic hypotension and to identify crewmembers who will be most susceptible to that symptom on landing day.