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.
Fluid Intake Minus Urine Output

PRE
HEAD DOWN TILT
RECOVERY

In - Out (mls)
Plasma volume losses are similar after short and long-duration spaceflight

<table>
<thead>
<tr>
<th></th>
<th>Pre-flight to Post-flight</th>
<th>ΔPlasma Volume (ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Short Duration</strong></td>
<td>n=29</td>
<td>-250</td>
</tr>
<tr>
<td><strong>Long Duration</strong></td>
<td>n=5</td>
<td>-500</td>
</tr>
</tbody>
</table>

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)
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

(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 PlasmaVol, 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

![Graphs showing cardiovascular responses during Adrenergic Failure, Astronaut, Pre-Flight, and Astronaut, Landing Day.]
Norepinephrine Response to Tilt before and after Spaceflight

Tilt-Induced Norepinephrine Change (pg/mL ± SEM)

- **Presyncopetal**
- **Non-Presyncopetal**

**Pre-Spaceflight**
- Presyncopetal: ~200 pg/mL
- Non-Presyncopetal: ~200 pg/mL

**Post-Spaceflight**
- Presyncopetal: ~700 pg/mL
- Non-Presyncopetal: ~700 pg/mL

NASA
Responses to standing after a short (top) and a long (bottom) flight in the same astronaut
Survival Analysis

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

-500 -250 0

Preflight to Postflight

A Short Duration n=29

A Long Duration n=5

Pre-flight to Post-flight

ΔPlasma Volume (ml)

-250 -500

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%

Pre-flight
R + 7
R + 30
Hypovolemia Model
METHODS

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  Hypovolemia

1.0  1.2  1.4  1.6  1.8  2.0  2.2  2.4
Plasma Volume Changes During Hypovolemia and After Spaceflight
<table>
<thead>
<tr>
<th>Astronaut</th>
<th>R+0 (Landing Day)</th>
<th>Hypovolemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Astronaut 1</td>
<td>YES</td>
<td>YES</td>
</tr>
<tr>
<td>Astronaut 2</td>
<td>YES</td>
<td>YES</td>
</tr>
<tr>
<td>Astronaut 3</td>
<td>YES</td>
<td>YES</td>
</tr>
<tr>
<td>Astronaut 4</td>
<td>YES</td>
<td>YES</td>
</tr>
<tr>
<td>Astronaut 5</td>
<td>NO</td>
<td>NO</td>
</tr>
<tr>
<td>Astronaut 6</td>
<td>NO</td>
<td>NO</td>
</tr>
</tbody>
</table>
Figure 2

Non-presyncopal subject

Control
BP, mmHg

HR, bpm

Hypovolemia
BP, mmHg

HR, bpm

Time, sec.

Presyncopal subject

Control
BP, mmHg

HR, bpm

Hypovolemia
BP, mmHg

HR, bpm

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

![Graph showing plasma norepinephrine levels in non-presyncopal and presyncopal subjects during normovolemia and hypovolemia in supine and upright positions.](image-url)
Norepinephrine Response to Tilt during Normovolemia and Hypovolemia

Tilt-Induced Norepinephrine Change (pg/mL ± SEM)

- **Presyncopal**
- **Nonpresyncopal**

**Normovolemia**
- Presyncopal: 150 ± 20
- Nonpresyncopal: 100 ± 15

**Hypovolemia**
- Presyncopal: 600 ± 50
- Nonpresyncopal: 800 ± 30
Norepinephrine Response to Tilt before and after Spaceflight

Tilt-Induced Norepinephrine Change (pg/mL ± SEM)

- **Presyncopal**
- **Non-Presyncopal**

Pre-Spaceflight Post-Spaceflight

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0.2 L/m² PVI Loss (13% Plasma Volume Loss)
0.4 L/m² PVI Loss (22% Plasma Volume Loss)
0.6 L/m² PVI Loss (30% Plasma Volume Loss)
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.