Role for lower extremity interstitial fluid volume changes in the
development of orthostasis after simulated microgravity.

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Abstract

Introduction: Reentry orthostasis after exposure to the conditions of spaceflight is a persistent problem among astronauts. In a previous study, a computer model systems analysis was used to examine the physiologic mechanisms involved in this phenomenon. In this analysis, it was determined that an augmented capacitance of lower extremity veins due to a fluid volume contracture of the surrounding interstitial spaces during spaceflight results in an increase in sequestered blood volume upon standing and appears to be the initiating mechanism responsible for reentry orthostasis. In this study, we attempt to validate the central premise of this hypothesis using a ground-based spaceflight analog.

Methods: 10 healthy subjects were placed at bed rest in a 6° head down tilt position for 60 days of bed rest. The impact of adaptations in interstitial fluid volume and venous capacitance in the lower extremities were then observed during a standard tilt test protocol performed before and after the confinement period. The interstitial thickness superficial to the calcaneous immediately below the lateral malleolus was measured using ultrasound with a 17-5 MHz linear array transducer. Measurements of the changes in anterior tibial vein diameter during tilt were obtained by similar methods. The measurements were taken while the subjects were supine and then during upright tilt (80°) for thirty minutes, or until the subject had signs of presyncope. Additional measurements of the superficial left tibia interstitial thickness and stroke volume by standard echocardiographic methods were also recorded. In addition, calf compliance was measured over a pressure range of 10-60 mmHg, using plethysmography, in a subset of these subjects (n = 5).

Results: There was a average of 6 % diminution in the size of the lower extremity interstitial space as compared to measurements acquired prior to bed rest. This contracture of the interstitial space coincided with a subsequent relative increase in the percentage change in tibial vein diameter and stroke volume upon tilting in contrast to the observations made before bed rest (54 vs 23% respectively). Compliance in the calf increased by an average of 36% by day 27 of bedrest.

Conclusions: A systems analysis using a computer model of cardiovascular physiology suggests that microgravity induced interstitial volume depletion results in an accentuation of venous blood volume sequestration and is the initiating event in reentry orthostasis. This hypothesis was tested in volunteer subjects using a ground-based spaceflight analog model that simulated the body fluid redistribution induced by microgravity exposure. Measurements of changes in the interstitial spaces and observed responses of the anterior tibial vein with tilt, together with the increase in calf compliance, were consistent with our proposed mechanism for the initiation of postflight orthostasis often seen in astronauts.
Role for lower extremity interstitial fluid volume changes in the development of orthostasis after simulated microgravity.

Steven H. Platts, Richard L. Summers, David S. Martin, Janice V. Meck, Thomas G. Coleman
Orthostatic intolerance after exposure to the conditions of spaceflight continues to be a problem among astronauts. 20-30% of returning short-duration crew members experience hypotension that progresses to presyncope during a 10 minute tilt test, while 83% of long-duration crew experience presyncope. Several mechanisms have been proposed to account for this phenomenon including altered cardiac function, vascular function and adrenergic control.

In a previous study, a computer model systems analysis was used to examine the physiologic mechanisms involved in orthostatic intolerance. In this analysis, it was determined that an augmented capacitance of lower extremity veins due to a fluid volume contracture of the surrounding interstitial spaces during spaceflight results in an increase in sequestered blood volume upon standing and appears to be an initiating mechanism responsible for reentry orthostasis.

In this study, we attempt to validate the central premise of this hypothesis using 60 days of head down tilt bed rest as a ground-based spaceflight analog.
Orthostatic Tolerance in Context

Hydration status
  → Plasma Volume

Cardiac Function
  → Stroke Volume
  → Contractility
  → Heart Rate

Vascular function
  → Venous Return
  → Total Peripheral Resistance

Orthostatic Tolerance

Central Nervous System
  → Sympathetic Nerve Activity

Fitness for Duty
  → Ability to sustain the upright posture and work in a gravitational field
Spaceflight-induced plasma volume changes

<table>
<thead>
<tr>
<th>Day of Testing</th>
<th>Presyncopal on Landing Day</th>
<th>Nonpresyncopal on Landing Day</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Supine</td>
<td>Upright</td>
</tr>
<tr>
<td>Hematocrit, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preflight</td>
<td>39±1 (8)</td>
<td>42±2* (8)</td>
</tr>
<tr>
<td>Landing day</td>
<td>39±1 (8)</td>
<td>42±1 (8)</td>
</tr>
<tr>
<td>3 Days after landing</td>
<td>38±1 (8)</td>
<td>40±1(8)</td>
</tr>
<tr>
<td>Plasma volume, l/m²</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preflight</td>
<td>1.83±0.11 (8)</td>
<td></td>
</tr>
<tr>
<td>Landing day</td>
<td>1.70±0.09 (8)</td>
<td></td>
</tr>
<tr>
<td>3 Days after landing</td>
<td>1.91±0.12* (8)</td>
<td></td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th></th>
<th>Presflight</th>
<th>Landing day</th>
<th>Three Days Postflight</th>
<th>% Spaceflight-Induced Loss</th>
</tr>
</thead>
<tbody>
<tr>
<td>Presyncopal Women (n=5)</td>
<td>1.81 ± 0.17</td>
<td>1.44 ± 0.08*$</td>
<td>2.02 ± 0.11 (n=4)</td>
<td>19.5 ± 0.04$</td>
</tr>
<tr>
<td>Presyncopal Men (n=6)</td>
<td>1.67 ± 0.12</td>
<td>1.55 ± 0.12*</td>
<td>1.66 ± 0.12</td>
<td>7.1 ± 0.03</td>
</tr>
<tr>
<td>Non-Presyncopal Men (n=24)</td>
<td>1.73 ± 0.04</td>
<td>1.60 ± 0.05 **$</td>
<td>1.81 ± 0.05</td>
<td>7.1 ± 0.03</td>
</tr>
</tbody>
</table>

Values are means ± SE; n, No. of subjects. *p ≤ 0.05, **p ≤ 0.01, vs. preflight $p ≤ 0.01, vs. three days postflight. $p < 0.05 vs. presyncopal men and non-presyncopal men.

Waters et al, 2002
Where does the plasma volume go?

Fig. 3. Mean fluid compartment volumes before and during space flight. Data from Leach and colleagues (Leach et al., 1996) (N=6). TBW, total body water; ECF, extracellular fluid; PV, plasma volume; ISF, interstitial fluid; ICF, intracellular fluid; FD7–8, flight days 7–8.

Fig. 4. Mean percentage change in fluid compartment volumes from pre-flight to flight days 7–8. Data from Leach and colleagues (Leach et al., 1996) (N=6). ICF, intracellular fluid; ISF, interstitial fluid; ECF, extracellular fluid; PV, plasma volume.

# Plasma Volume Loss in Bed Rest

Table 4. *Effects of strict −6° head-down bed rest variables collected at rest and in response to orthostatic stress*

<table>
<thead>
<tr>
<th>Study</th>
<th>Days of Strict −6° HDBR</th>
<th>n</th>
<th>Rate of Presyncope After Bed Rest</th>
<th>Volume Loss, %</th>
<th>HR</th>
<th>Stroke Volume</th>
<th>Peripheral Vascular Resistance</th>
<th>Venous Pressure</th>
<th>Muscle SNA</th>
<th>Plasma Norepinephrine</th>
<th>PRA or Active Renin</th>
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</thead>
<tbody>
<tr>
<td>Beck et al. (2)</td>
<td>10</td>
<td>6</td>
<td>6/0</td>
<td>33%</td>
<td>16</td>
<td>⇄</td>
<td>⇄</td>
<td>⇄</td>
<td>⇄</td>
<td>⇄</td>
<td>⇄</td>
</tr>
<tr>
<td>Convertino et al. (9)</td>
<td>30</td>
<td>11</td>
<td>11/0</td>
<td>40%</td>
<td>15</td>
<td>↑</td>
<td>⇄</td>
<td>⇄</td>
<td>⇄</td>
<td>⇄</td>
<td>⇄</td>
</tr>
<tr>
<td>Convertino et al. (10)</td>
<td>7</td>
<td>11</td>
<td>11/0</td>
<td></td>
<td>13</td>
<td>↑</td>
<td>⇄</td>
<td>⇄</td>
<td>⇄</td>
<td>⇄</td>
<td>⇄</td>
</tr>
<tr>
<td>Convertino et al. (12)</td>
<td>14</td>
<td>8</td>
<td>8/0</td>
<td></td>
<td>16</td>
<td>↑</td>
<td>⇄</td>
<td>⇄</td>
<td>⇄</td>
<td>⇄</td>
<td>⇄</td>
</tr>
<tr>
<td>Convertino et al. (11)</td>
<td>30</td>
<td>8</td>
<td>8/0</td>
<td></td>
<td>16</td>
<td>↑</td>
<td>⇄</td>
<td>⇄</td>
<td>⇄</td>
<td>⇄</td>
<td>⇄</td>
</tr>
<tr>
<td>Crandall et al. (13)</td>
<td>15</td>
<td>7</td>
<td>7/0</td>
<td></td>
<td>16</td>
<td>↑</td>
<td>⇄</td>
<td>⇄</td>
<td>⇄</td>
<td>⇄</td>
<td>⇄</td>
</tr>
<tr>
<td>Goldstein et al. (18)</td>
<td>14</td>
<td>8</td>
<td>Not reported</td>
<td></td>
<td>16</td>
<td></td>
<td>⇄</td>
<td>⇄</td>
<td>⇄</td>
<td>⇄</td>
<td>⇄</td>
</tr>
<tr>
<td>Kamiya et al. (22)</td>
<td>14</td>
<td>20</td>
<td>20/0</td>
<td></td>
<td>12</td>
<td>↑</td>
<td>⇄</td>
<td>⇄</td>
<td>⇄</td>
<td>⇄</td>
<td>⇄</td>
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<tr>
<td>Kamiya et al. (23)</td>
<td>14</td>
<td>22</td>
<td>22/0</td>
<td></td>
<td>13, 12</td>
<td>⇄</td>
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<td>⇄</td>
<td>⇄</td>
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<tr>
<td>Levine et al. (28)</td>
<td>14</td>
<td>12</td>
<td>11/1</td>
<td></td>
<td>17</td>
<td>⇄</td>
<td>⇄</td>
<td>⇄</td>
<td>⇄</td>
<td>⇄</td>
<td>⇄</td>
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<tr>
<td>Millet et al. (34)</td>
<td>7</td>
<td>8</td>
<td>0/8</td>
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<td>9</td>
<td>⇄</td>
<td>⇄</td>
<td>⇄</td>
<td>⇄</td>
<td>⇄</td>
<td>⇄</td>
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<tr>
<td>Millet et al. (34)</td>
<td>7</td>
<td>8</td>
<td>8/0</td>
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<td>9</td>
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<td>⇄</td>
<td>⇄</td>
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<td>⇄</td>
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<tr>
<td>Shoemaker et al. (48)</td>
<td>14</td>
<td>15</td>
<td>15/0</td>
<td></td>
<td>40%</td>
<td>↑</td>
<td>⇄</td>
<td>⇄</td>
<td>⇄</td>
<td>⇄</td>
<td>⇄</td>
</tr>
<tr>
<td>Siguado et al. (49)</td>
<td>42</td>
<td>8</td>
<td>8/0</td>
<td></td>
<td>57%</td>
<td>↑</td>
<td>⇄</td>
<td>⇄</td>
<td>⇄</td>
<td>⇄</td>
<td>⇄</td>
</tr>
<tr>
<td>Vernikos et al. (54)</td>
<td>7</td>
<td>8</td>
<td>0/8</td>
<td></td>
<td>8</td>
<td>↑</td>
<td>⇄</td>
<td>⇄</td>
<td>⇄</td>
<td>⇄</td>
<td>⇄</td>
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<tr>
<td>Vernikos et al. (54)</td>
<td>7</td>
<td>8</td>
<td>8/0</td>
<td></td>
<td>4</td>
<td>↑</td>
<td>⇄</td>
<td>⇄</td>
<td>⇄</td>
<td>⇄</td>
<td>⇄</td>
</tr>
</tbody>
</table>

Waters, *et al*, 2005
Fluid Intake Minus Urine Output in Bed Rest

![Graph showing fluid intake minus urine output during bed rest.](image-url)
Current computerized model contains over 4,000 equations relating to human physiological responses
Interstitial Thickness in Space

From: Kirsch, KA. et al, 1993
Methods

17 healthy subjects (9 men, 8 women) were placed at strict bed rest in a 6° head down tilt position for 60 days (one subject for 54 days).

The interstitial thickness superficial to the calcaneous, immediately below the lateral malleolus, was measured using ultrasound with a 17-5 MHz linear array transducer before bedrest and following 60 days of bedrest. Forehead interstitial thickness was measured one inch cephalad from the eyebrows with the transducer perpendicular to the bone and centered on the forehead.

Measurements of the changes in anterior tibial vein area and anterior tibial artery diameter during tilt were obtained by similar methods.

The measurements were taken while the subjects were supine and then for the first six minutes of upright tilt (80°).

Additional measurements included stroke volume (pulsed wave doppler), blood pressure (dynamap and finapres) and heart rate (ECG).
Pre-Tibial Supine Interstitial Thickness

Pre-Bed Rest

Bed Rest Day 60

5.28 mm

3.46 mm
Anterior Tibial Vein Area

ATV Pre Bedrest Supine

4.5 mm²

ATV Pre Bedrest Tilt

5.9 mm²
# Results

<p>| | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td>32.76 ± 1.82 years</td>
<td></td>
</tr>
<tr>
<td><strong>Height</strong></td>
<td>169 ± 2.25 cm</td>
<td></td>
</tr>
<tr>
<td><strong>Weight</strong></td>
<td>pre</td>
<td>71.93 ± 3.57</td>
</tr>
<tr>
<td></td>
<td>Day 60</td>
<td>70.76 ± 3.50</td>
</tr>
<tr>
<td><strong>BMI</strong></td>
<td>pre</td>
<td>25.0 ± 0.91</td>
</tr>
<tr>
<td></td>
<td>Day 60</td>
<td>24.6 ± 0.88</td>
</tr>
</tbody>
</table>
Effects of 60 Days Bed Rest on Plasma Volume

PV
\( p = 0.008 \)

<table>
<thead>
<tr>
<th>Days of Bed Rest</th>
<th>Pre</th>
<th>60</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma Volume (Liters)</td>
<td>2.6</td>
<td>2.2</td>
</tr>
</tbody>
</table>

PVI
\( p = 0.001 \)

<table>
<thead>
<tr>
<th>Days of Bed Rest</th>
<th>Pre</th>
<th>60</th>
</tr>
</thead>
<tbody>
<tr>
<td>PVI (l/m²)</td>
<td>1.4</td>
<td>1.3</td>
</tr>
</tbody>
</table>
Effects of 60 Days Bed Rest Leg Interstitial Thickness

![Graph showing interstitial thickness over standing time](image)
Effect of bed rest on supine forehead interstitial thickness

The graph shows the thickness (in mm) of the forehead interstitial tissue before and after 60 days of bed rest. The thickness decreases from the pre-bed rest period to the 60-day period, but the difference is not statistically significant (p = NS).
Effects of 60 Days Bed Rest on Stroke Volume

- Prebedrest
- Day 60
Effects of 60 Days Bed Rest on Anterior Tibial Artery Diameter

![Graph showing the effects of bed rest on anterior tibial artery diameter. The graph displays the diameter measurements at different standing times, with significant differences indicated by asterisks. The P-value for the comparison is 0.06.]
Effects of 60 Days Bed Rest on Anterior Tibial Vein Area: percent change from supine
Capacitance

Preliminary Data

Model Prediction

Cuff pressure (mmHg)

change in volume (ml/dl of tissue)

n = 5

- Pre bed rest
- Bed rest
day 27

Sequestered Blood - Vein

Pressure - Volume

Blood Volume = 119

Transmural Pressure = 0.5

Basic Capacity = 1.
Conclusions

A systems analysis using a computer model of cardiovascular physiology suggests that microgravity induced interstitial volume depletion results in an accentuation of venous blood volume sequestration.

We hypothesized that long term bed rest would replicate this pattern.

Measurements, before and after 60 days of bed rest, of changes in the interstitial spaces and observed responses of the anterior tibial vein with tilt were consistent with our hypothesis.
Back-up Slides
Interstitial Thickness

% change (day 60 to prebedrest)

-10 -8 -6 -4 -2 0

interstitial thickness

supine min 3 min 6

% change (day 60 to prebedrest)

-10 -8 -6 -4 -2 0

interstitial thickness

supine min 3 min 6
Stroke Volume

% change (day 60 to prebedrest)

-40
-30
-20
-10
0

supine min 3 min 6

-40
Anterior Tibial Artery

% change (day 60 to prebedrest)

-16 -14 -12 -10 -8 -6 -4 -2 0

supine min 3 min 6

Anterior Tibial Artery

% change (day 60 to prebedrest)
Anterior Tibial Vein

% change (day 60 to prebedrest)

-60  -40  -20  0  20  40

supine  min 3  min 6
Effects of 60 Days Bed Rest on Anterior Tibial Vein Area

![Graph showing the changes in Anterior Tibial Vein Area with Standing Time over 60 days of bed rest.](image-url)
Tilt Test Survival Analysis Before and After 60 days of Bed Rest

Tilt Survival

Tilt Time (min)

Pre Bedrest

Day 60

P = 0.01