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

Steven H. Platts[3], Richard L. Summers[1], David S. Martin[2], Janice V. Meck[4],Thomas G. Coleman[1]

[1]Department of Emergency Medicine, University of Mississippi Medical Center, Jackson, Mississippi 39216; [2]Wyle Laboratories, National Aeronautics and Space Administration Johnson Space Center, Houston, Texas 77058; [3]Universities Space Research Association, Houston, TX, 77058; [4]Human Adaptation and Countermeasures Office, Space and Life Sciences Directorate, National Aeronautics and Space Administration Johnson Space Center, Houston, Texas 77058

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 6º 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

Introduction

Orthostatic intolerance after exposure to the conditions of spaceflight continues to be a problem among astronauts

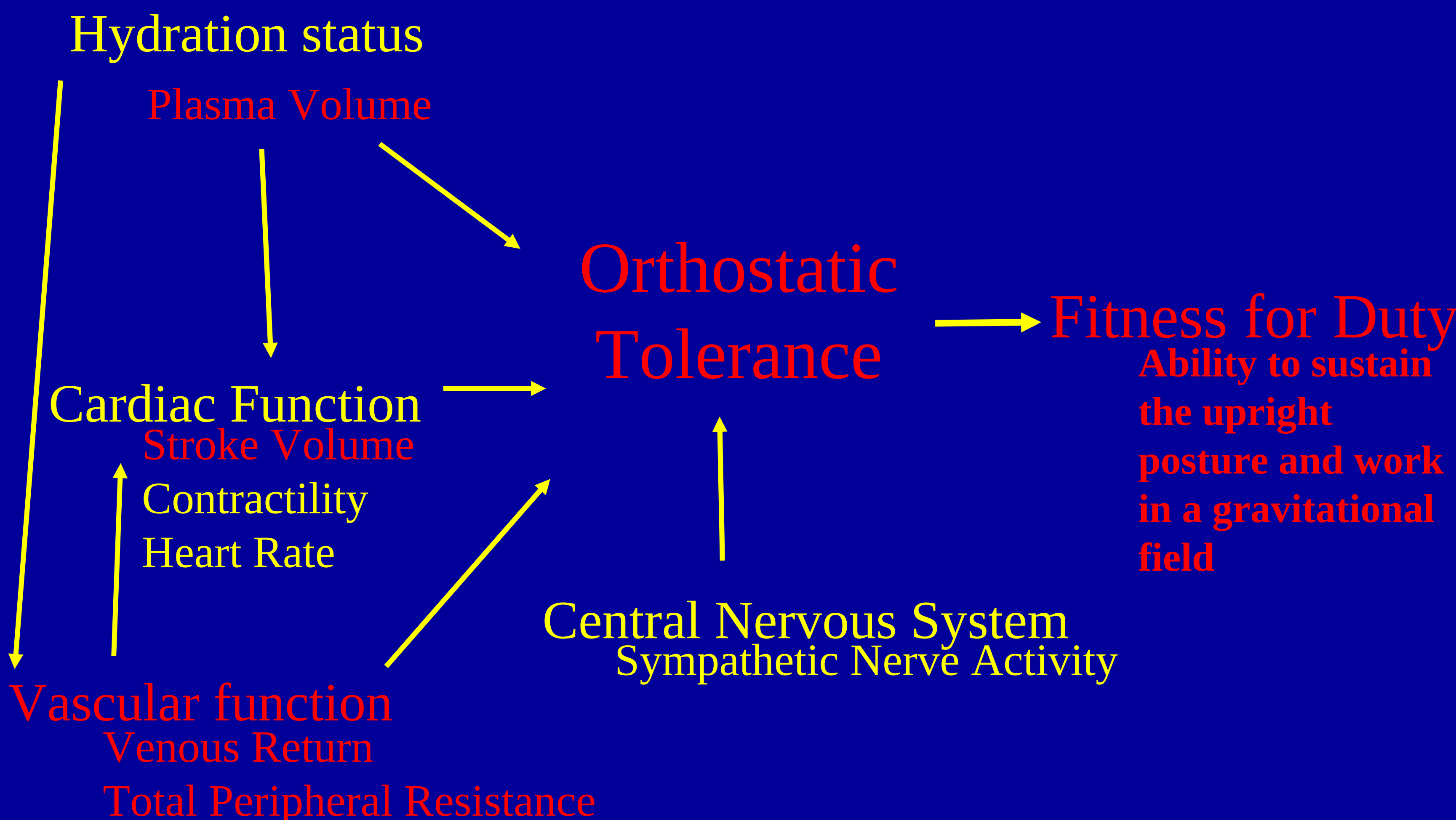
20-30% of returning short-duration crew members experience hypotension that progresses to presyncope during a 10 minute tilt test, while 83% of long-duration crew experience presyncope

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



Spaceflight-induced plasma volume changes

	Day of Testing	Presyncopal on Landing Day: Supine	Presyncopal on Landing Day: Upright	Presyncopal on Landing Day: Upright-supine	Nonpresyncopal on Landing Day: Supine	Nonpresyncopal on Landing Day: Upright	Nonpresyncopal on Landing Day: Upright-supine
Hematocrit, %	Preflight	39±1 (8)	42±2[a] (8)	2.8±0.6 (8)	40±1 (13)	44±1[a] (13)	3.3±0.4 (13)
	Landing day	39±1[b] (8)	42±1[a] (8)	3.1±0.7 (8)	42±1 (13)	44±1[a] (12)	2.8±0.9 (12)
	3 Days after landing	38±1 (8)	40±1[a,d] (8)	2.2±0.6 (8)	38±1[c,d] (13)	41±1[a,c,d] (13)	2.6±0.4 (13)
Plasma volume, l/m²	Preflight	1.83±0.11 (8)			1.84±0.07 (9)		
	Landing day	1.70±0.09[e] (8)			1.65±0.08[e] (9)		
	3 Days after landing	1.91±0.12[d] (8)			1.92±0.12[d] (9)		

Meck et al, 2004

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

	Preflight	Landing day	Three Days Postflight	% Spaceflight-Induced Loss
Presyncopal Women (n=5)	1.81 ± 0.17	1.44 ± 0.08*‡	2.02 ± 0.11 (n=4)	19.5 ± 0.04§
Presyncopal Men (n=6)	1.67 ± 0.12	1.55 ± 0.12*	1.66 ± 0.12	7.1 ± 0.03
Non-Presyncopal Men (n=24)	1.73 ± 0.04	1.60 ± 0.05 **‡	1.81 ± 0.05	7.1 ± 0.03

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

Waters et al, 2002

Where does the plasma volume go?

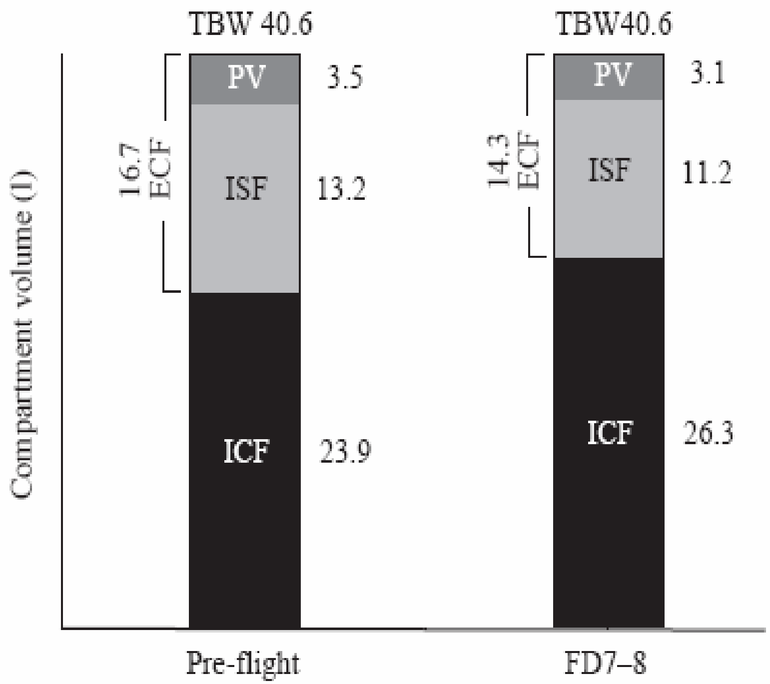


Fig. 3. Mean fluid compartment volumes before and during space flight. Data from Leach and colleagues (Leach et al., 1996) (*N*=6). TBW, total body water; ECF, extracellular fluid; PV, plasma volume; ISF, interstitial fluid; ICF, intracellular fluid; FD7–8, flight days 7–8.

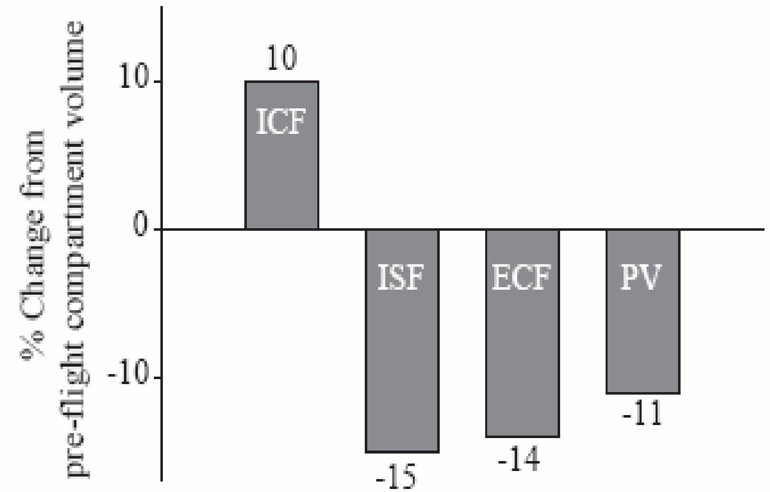


Fig. 4. Mean percentage change in fluid compartment volumes from pre-flight to flight days 7–8. Data from Leach and colleagues (Leach et al., 1996) (*N*=6). ICF, intracellular fluid; ISF, interstitial fluid; ECF, extracellular fluid; PV, plasma volume.

Figures from Leach et al. 1996 in Watenpaugh DE. Fluid volume control during short-term space flight and implications for human performance. J Exp Biology 204 (18):3209-3215, 2001.

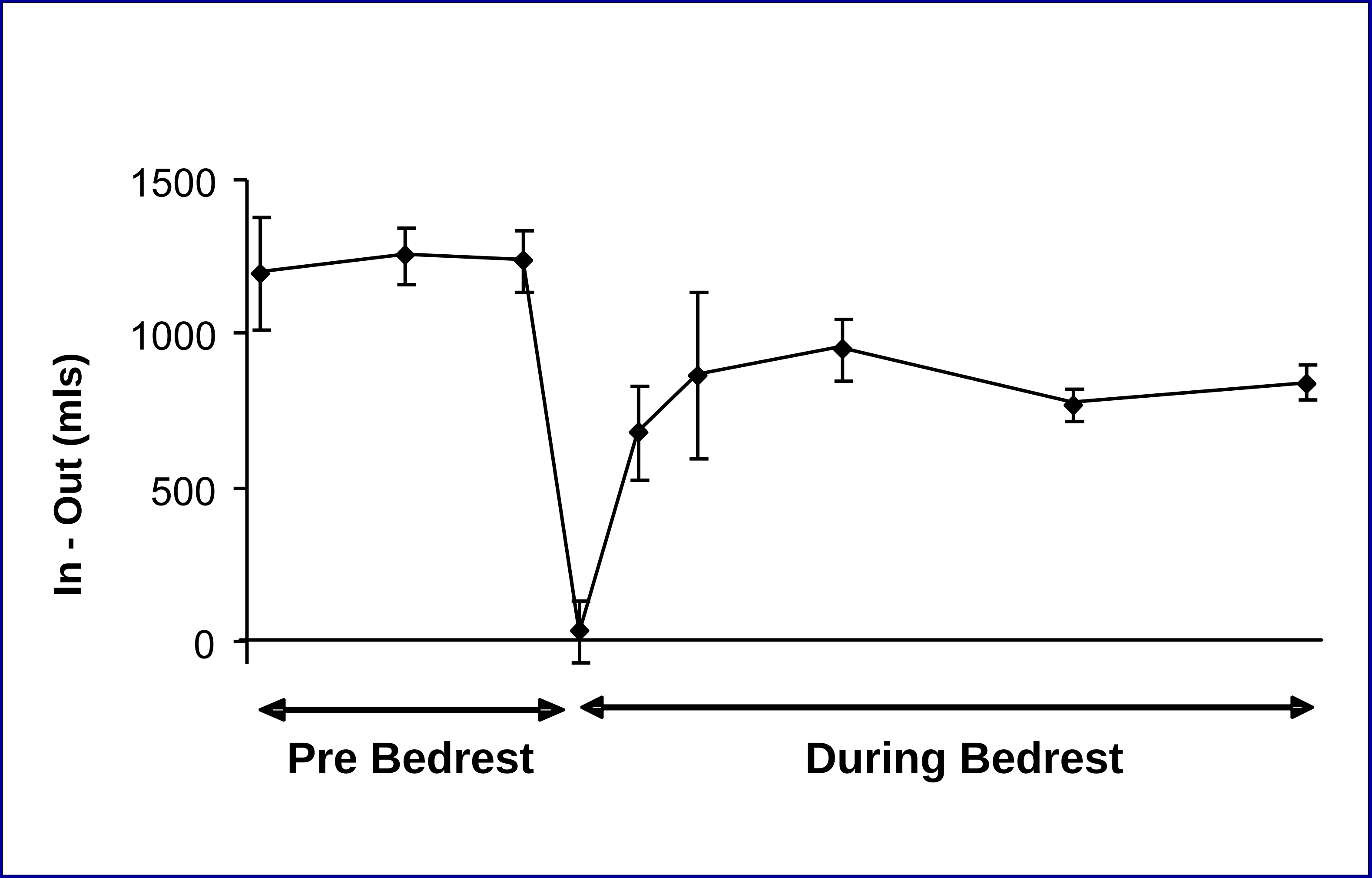
Plasma Volume Loss in Bed Rest

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

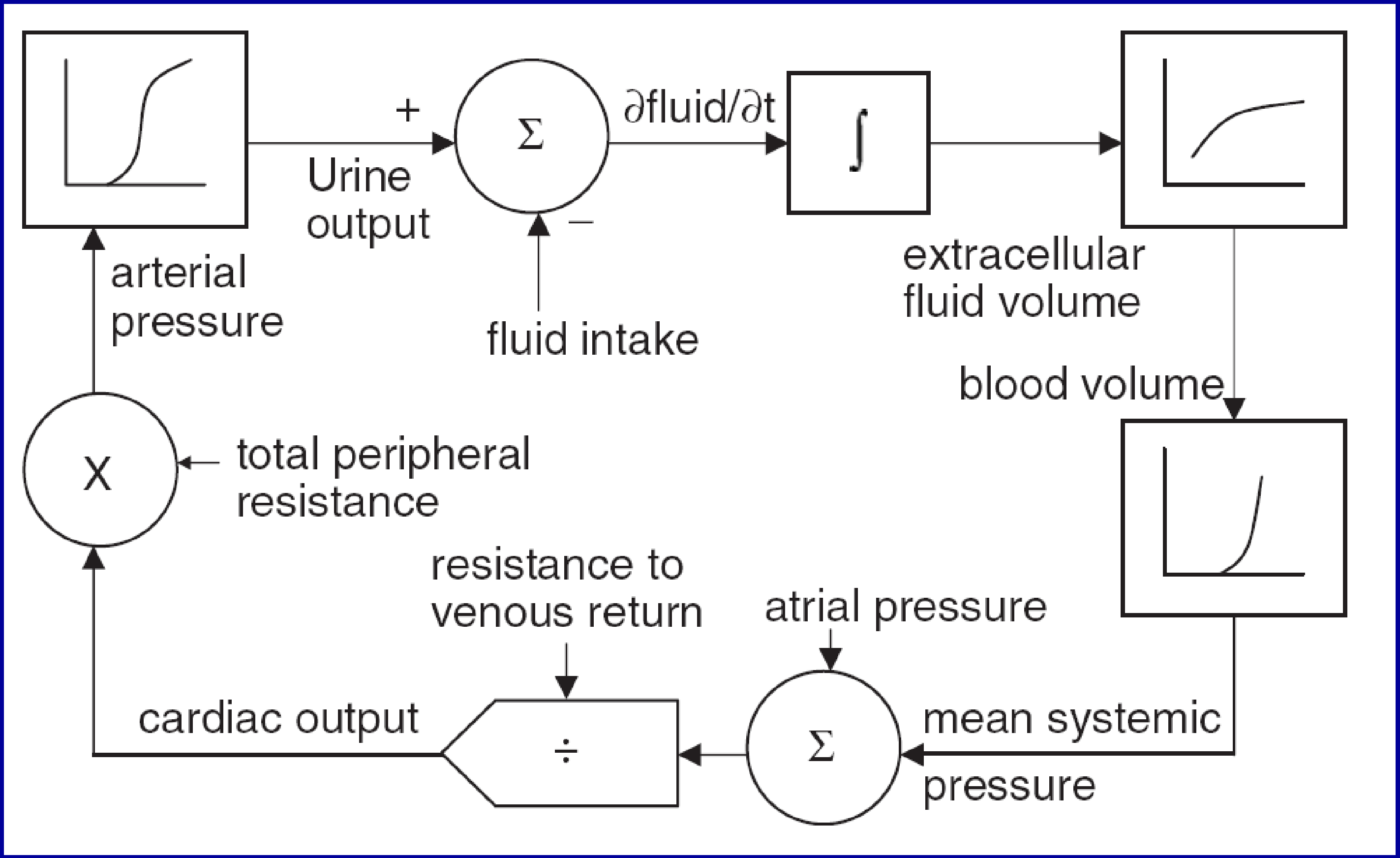
Study	Days of Strict −6° HDBR	*n* Total	*n* Men/women	Rate of Presyncope After Bed Rest	Volume Loss, %	HR	Stroke Volume	Peripheral Vascular Resistance	Venous Pressure	Muscle SNA	Plasma Norepinephrine	PRA or Active Renin
Beck et al. (2)	10	6	6/0	33%	16	↔⇧	↓⇩	↑⇧				
Convertino et al. (9)	30	11	11/0	40%[a]	15	↑⇧[d]					↔⇔	
Convertino et al. (10)	7	11	11/0		13	↑⇧	↓⇩	⇧	↓⇩		↓	
Convertino et al. (12)	14	8	8/0		16	↑		↑			↓	
Convertino et al. (11)	30	8	8/0		16	↑					↓	↑
Crandall et al. (13)	15	7	7/0		16	↑	↓	↑	↓			
Goldstein et al. (18)	14	8	Not reported		16				↓		↔	
Kamiya et al. (22)	14	20	20/0		12	↑		↑		↑		
Kamiya et al. (23)	14	22	22/0	45%	13, 12[c]	↔⇧			↓	↔⇔⇩[f]		
Levine et al. (28)	14	12	11/1	↑[b]	17	↔	↓⇩	↑	↔			
Millet et al. (34)	7	8	0/8	71%[a]	9	↔⇔					↔⇔	↑⇧
Millet et al. (34)	7	8	8/0	75%	9	↔⇔					↔⇔	↑⇧
Shoemaker et al. (48)	14	15	15/0	40%		↑↔[e]⇧	↔⇔	↔⇔		↔↑[g] ⇔⇩[f]		
Siguado et al. (49)	42	8	8/0	57%[a]	12	↑					↔↑[g]	↑
Vernikos et al. (54)	7	8	0/8		8	⇧						↑⇧
Vernikos et al. (54)	7	8	8/0		4	⇧						↔⇧

Waters, *et al*, 2005

Fluid Intake Minus Urine Output in Bed Rest

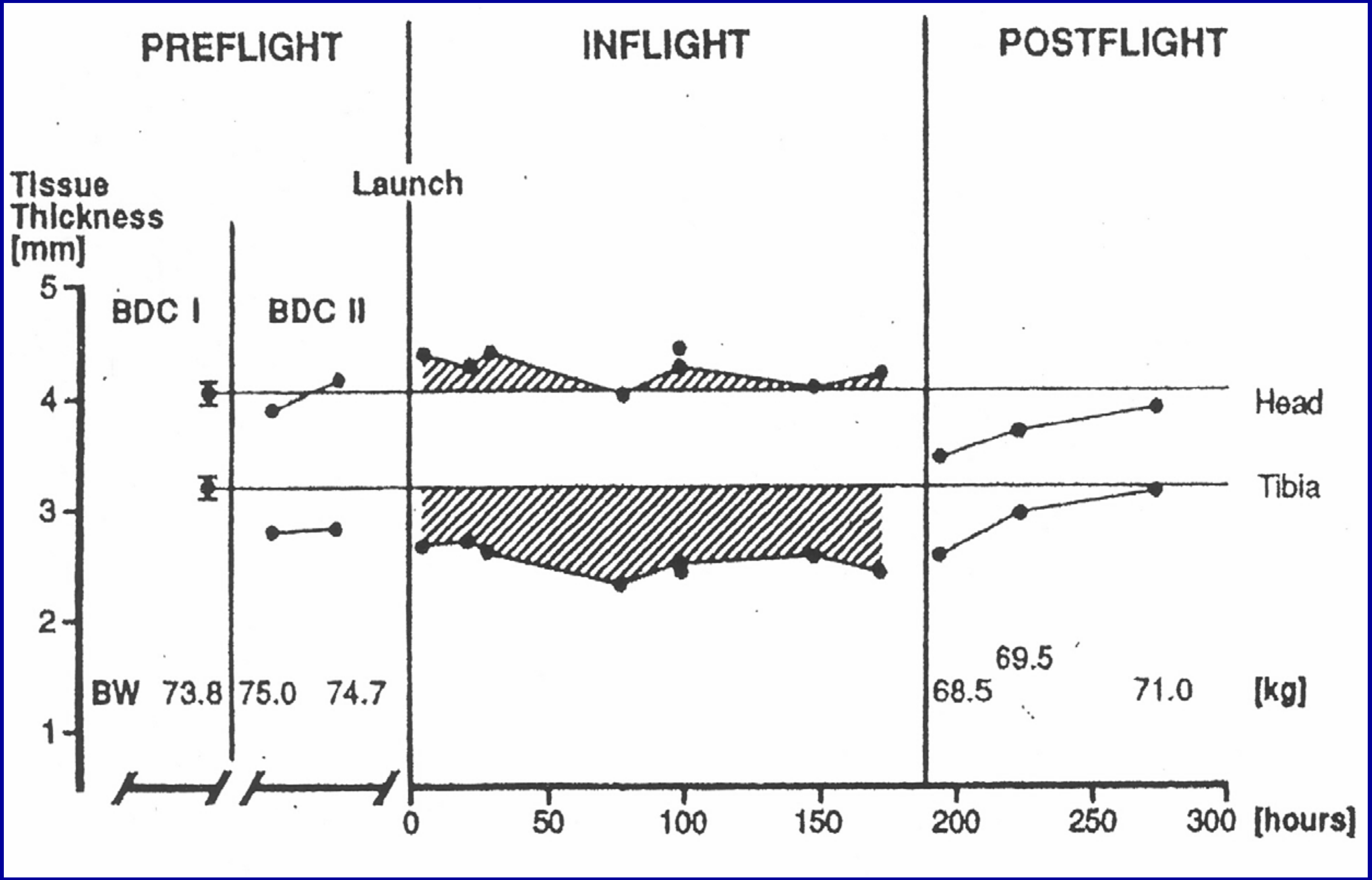


Body fluid feedback loop



Current computerized model contains over 4,000 equations relating to human physiological responses

Interstitial Thickness in Space



From: Kirsch, KA. et al, 1993

Methods

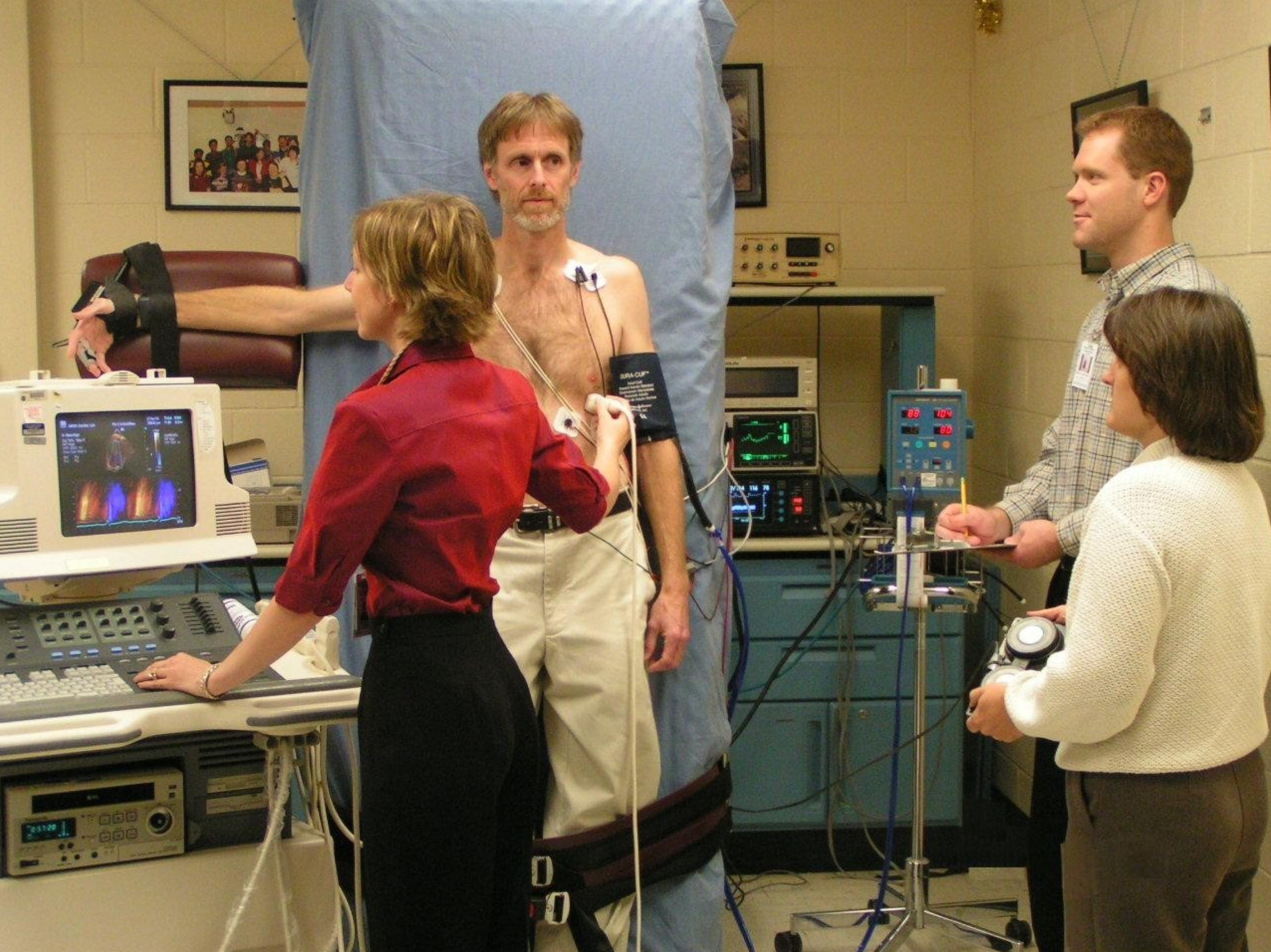
17 healthy subjects (9 men, 8 women) were placed at strict bed rest in a 6º head down tilt position for 60 days (one subject for 54 days).

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 cepahlad 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.

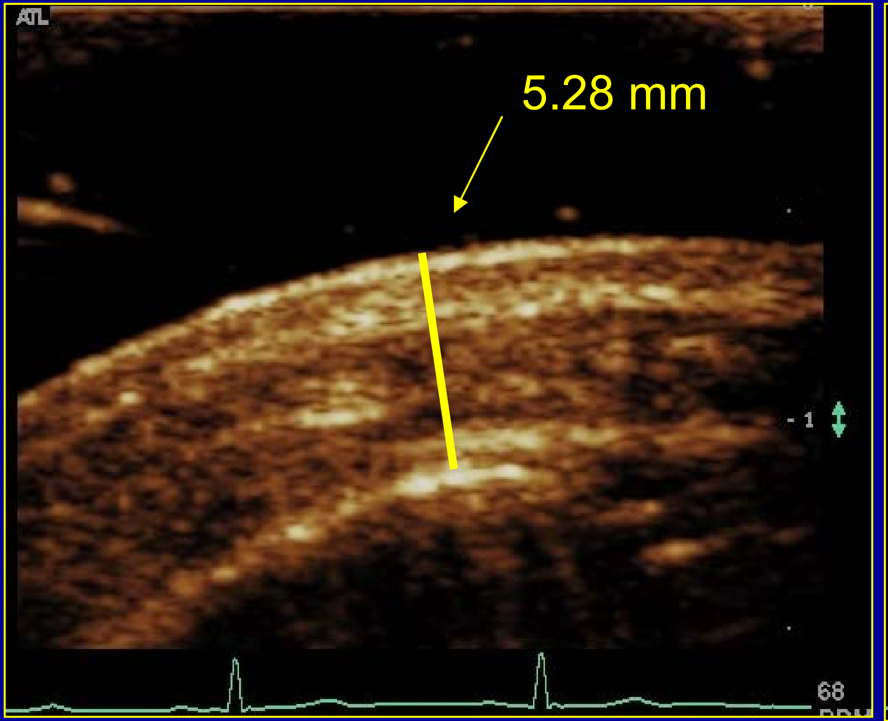
The measurements were taken while the subjects were supine and then for the first six minutes of upright tilt (80°).

Additional measurements included stroke volume (pulsed wave doppler), blood pressure (dynamap and finapres) and heart rate (ECG).

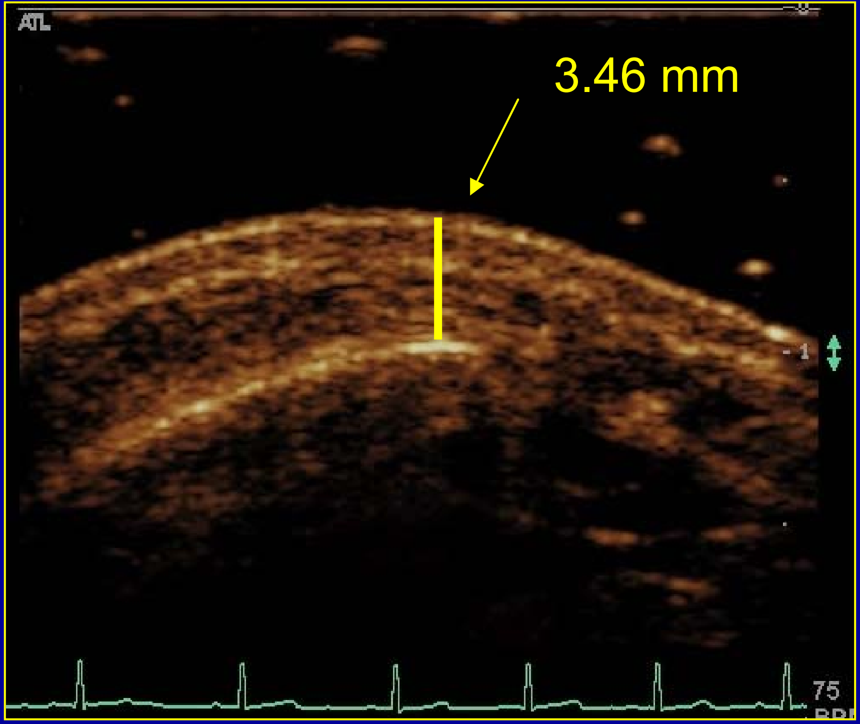

DURA-CUF

Pre-Tibial Supine Interstitial Thickness

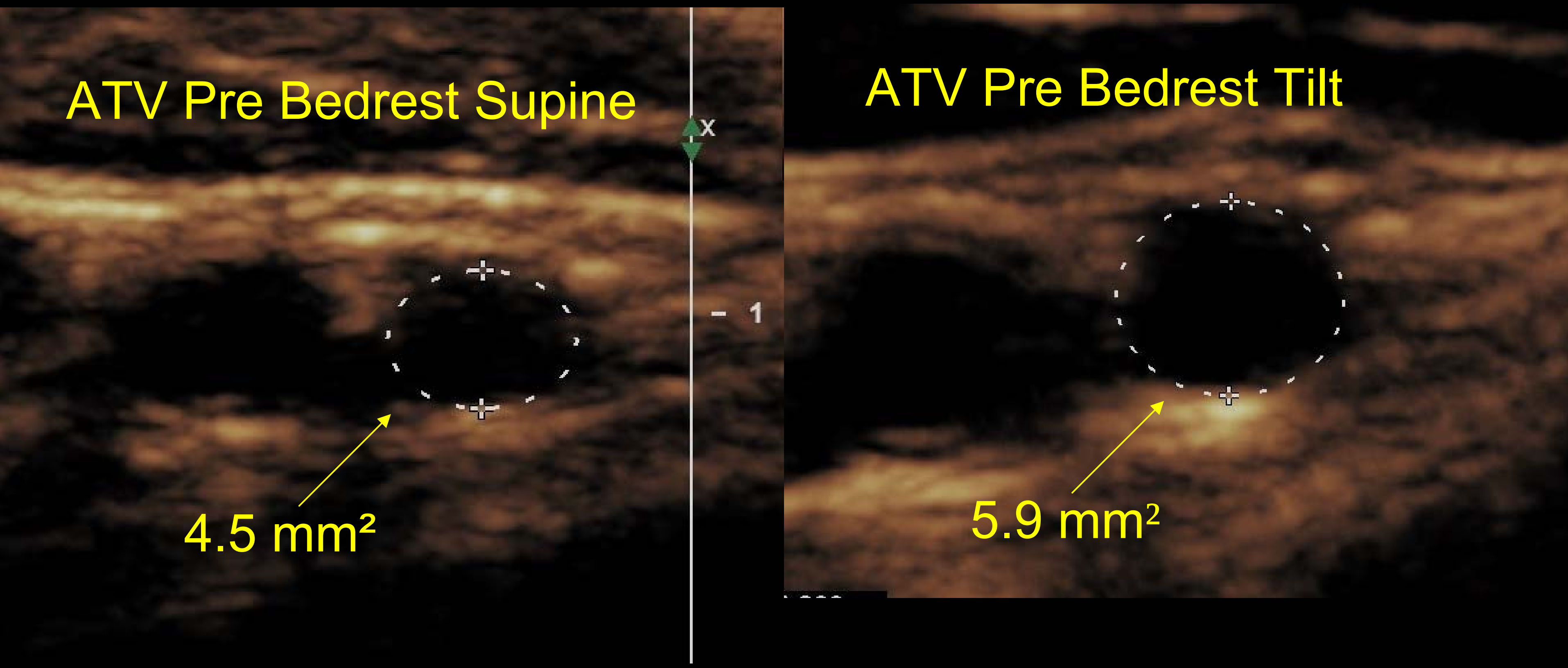
Pre-Bed Rest



Bed Rest Day 60



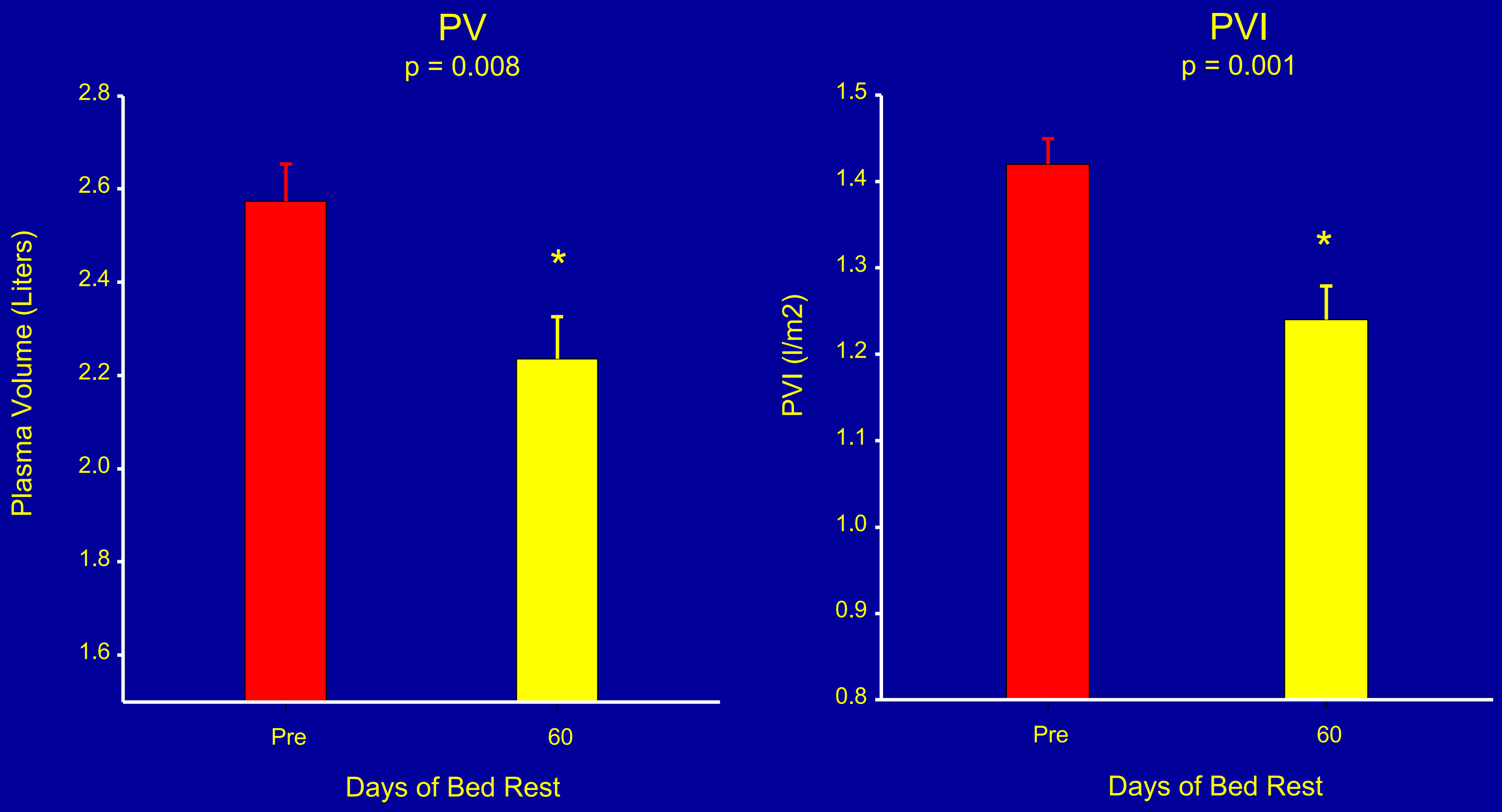
Anterior Tibial Vein Area



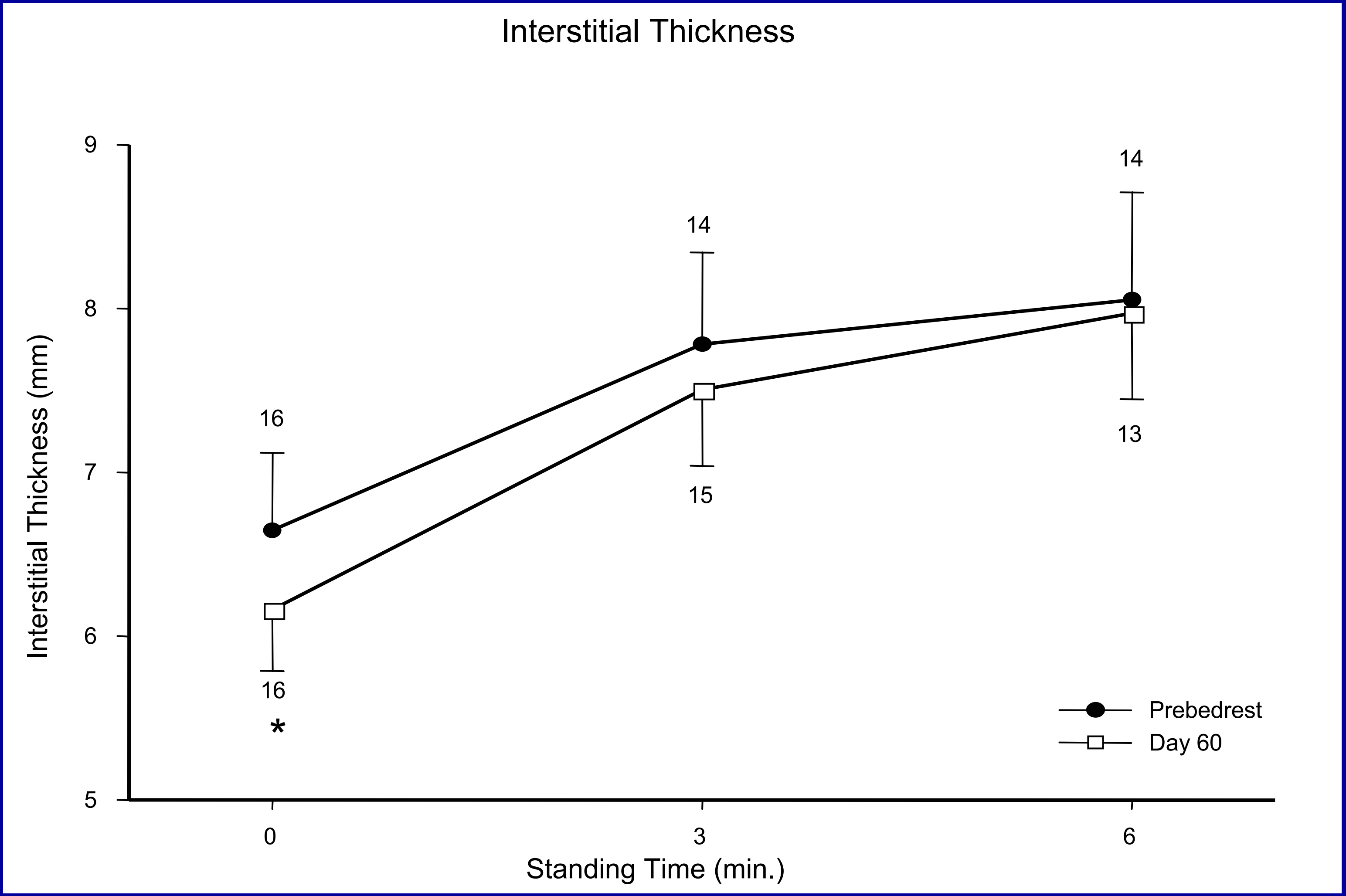
Results

Age	32.76 ± 1.82 years	
Height	169 ± 2.25 cm	
Weight	pre	71.93 ± 3.57
	Day 60	70.76 ± 3.50
BMI	pre	25.0 ± 0.91
	Day 60	24.6 ± 0.88

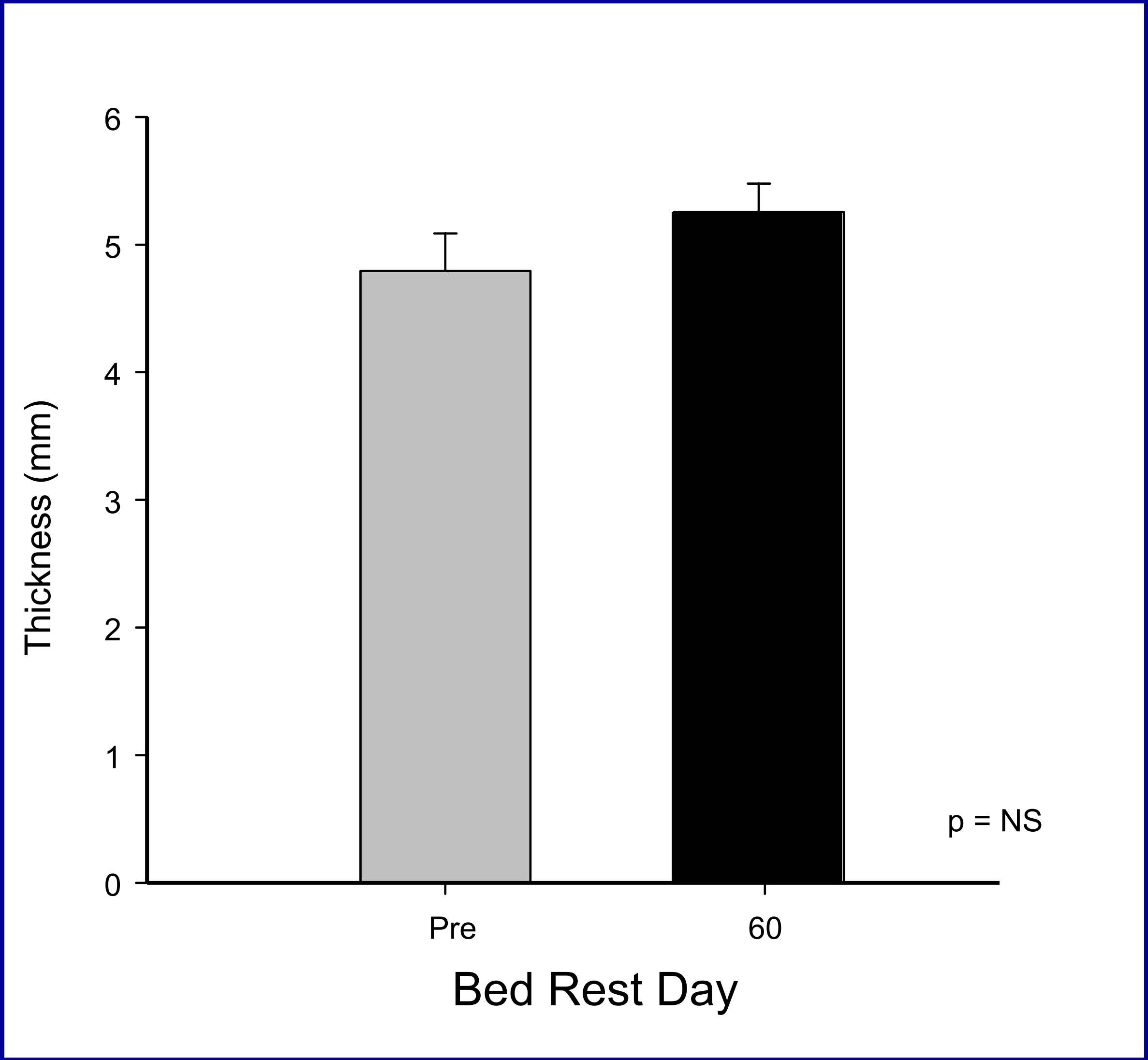
Effects of 60 Days Bed Rest on Plasma Volume



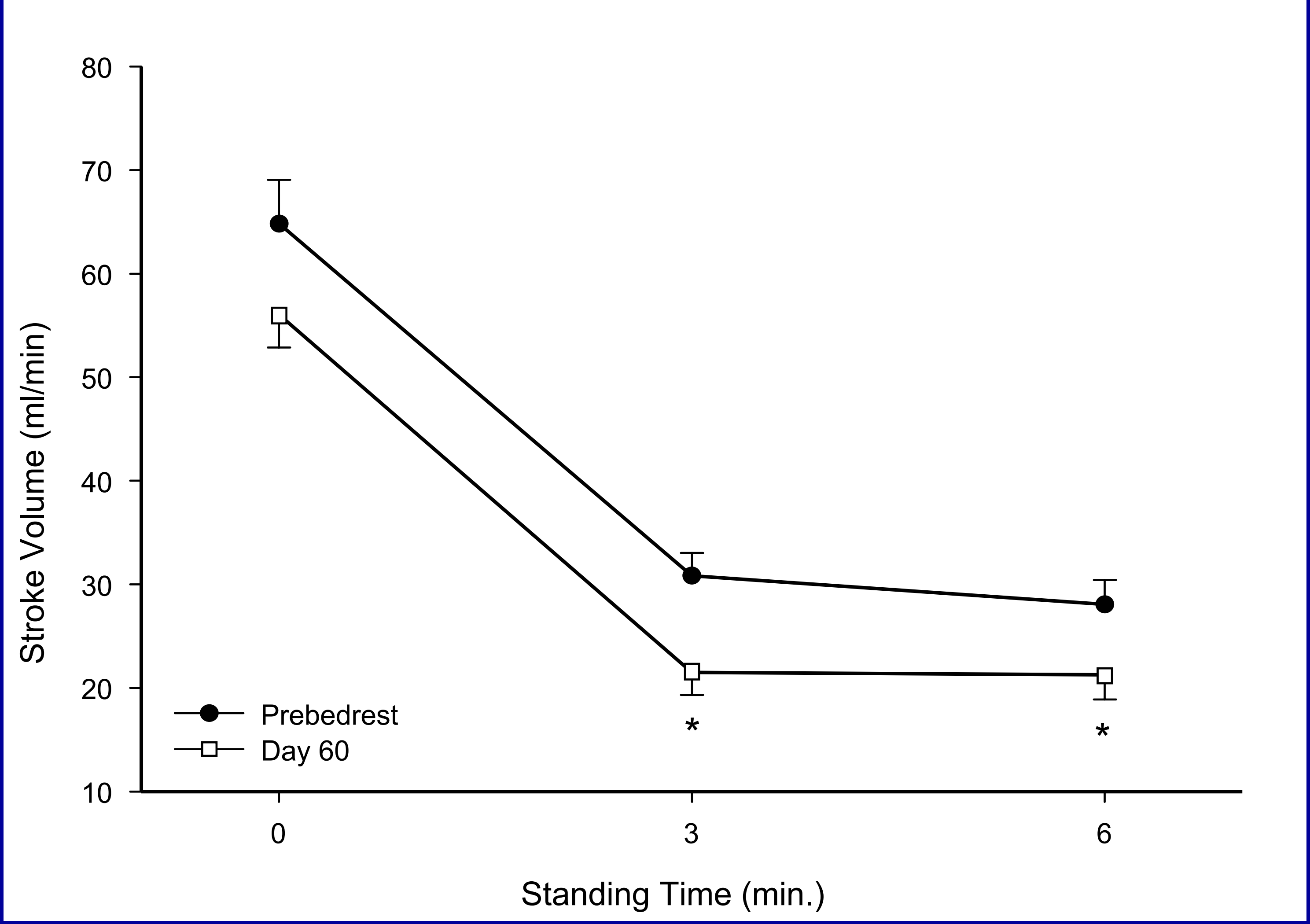
Effects of 60 Days Bed Rest Leg Interstitial Thickness



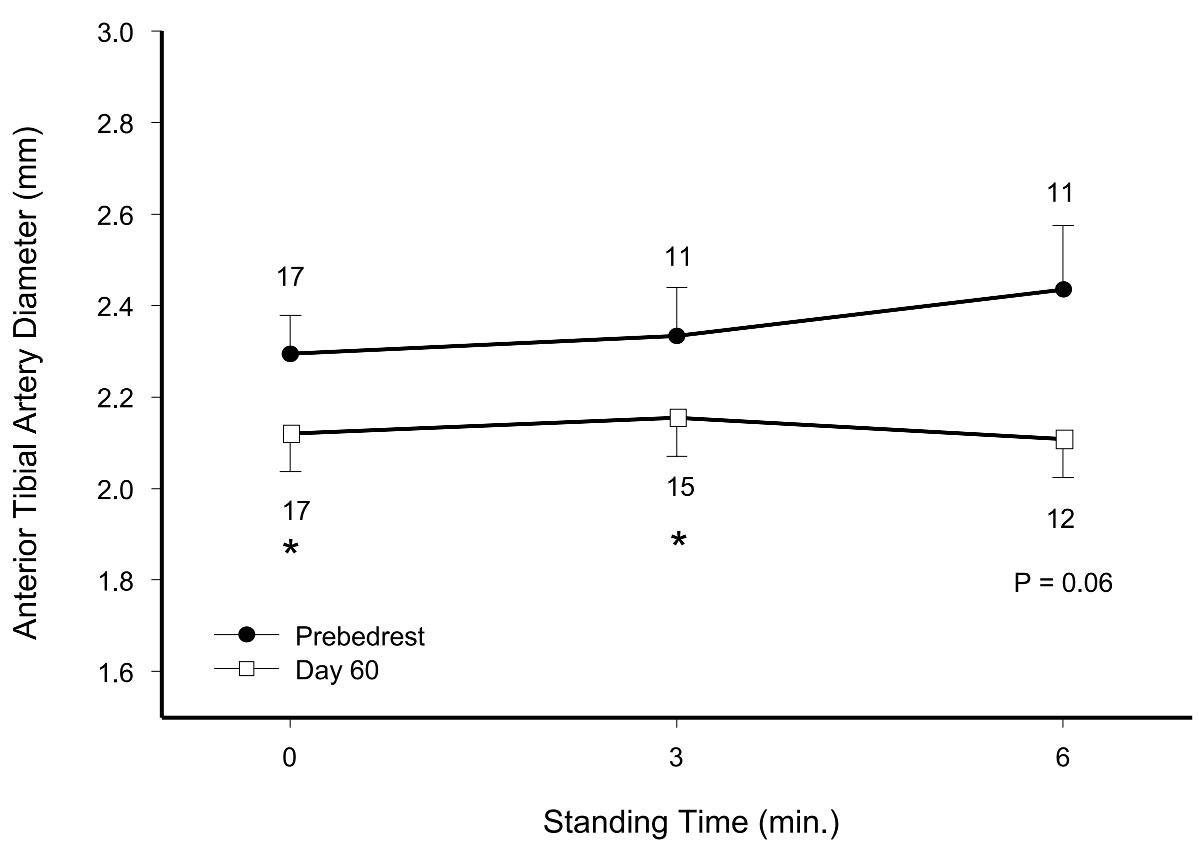
Effect of bed rest on supine forehead interstitial thickness



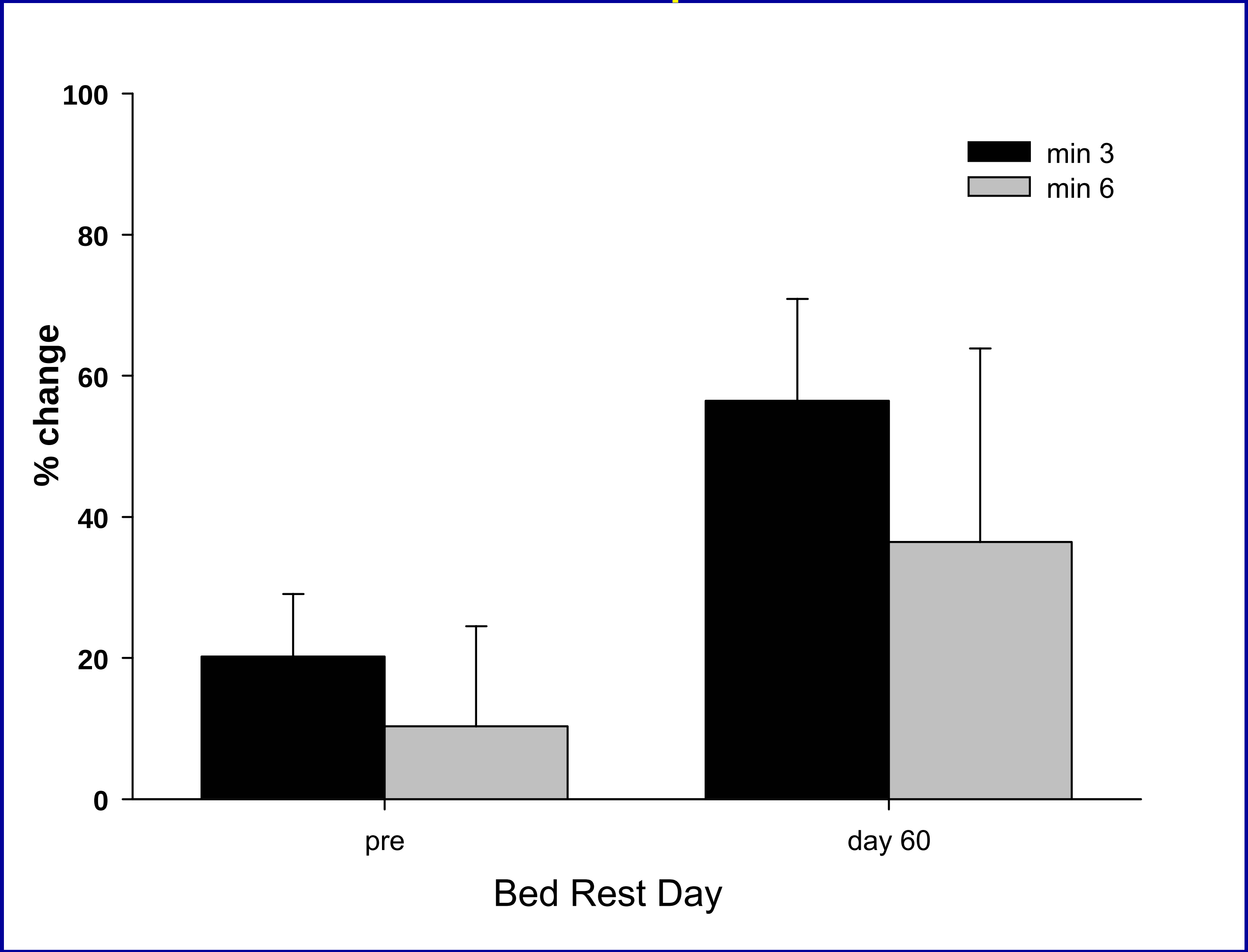
Effects of 60 Days Bed Rest on Stroke Volume



Effects of 60 Days Bed Rest on Anterior Tibial Artery Diameter

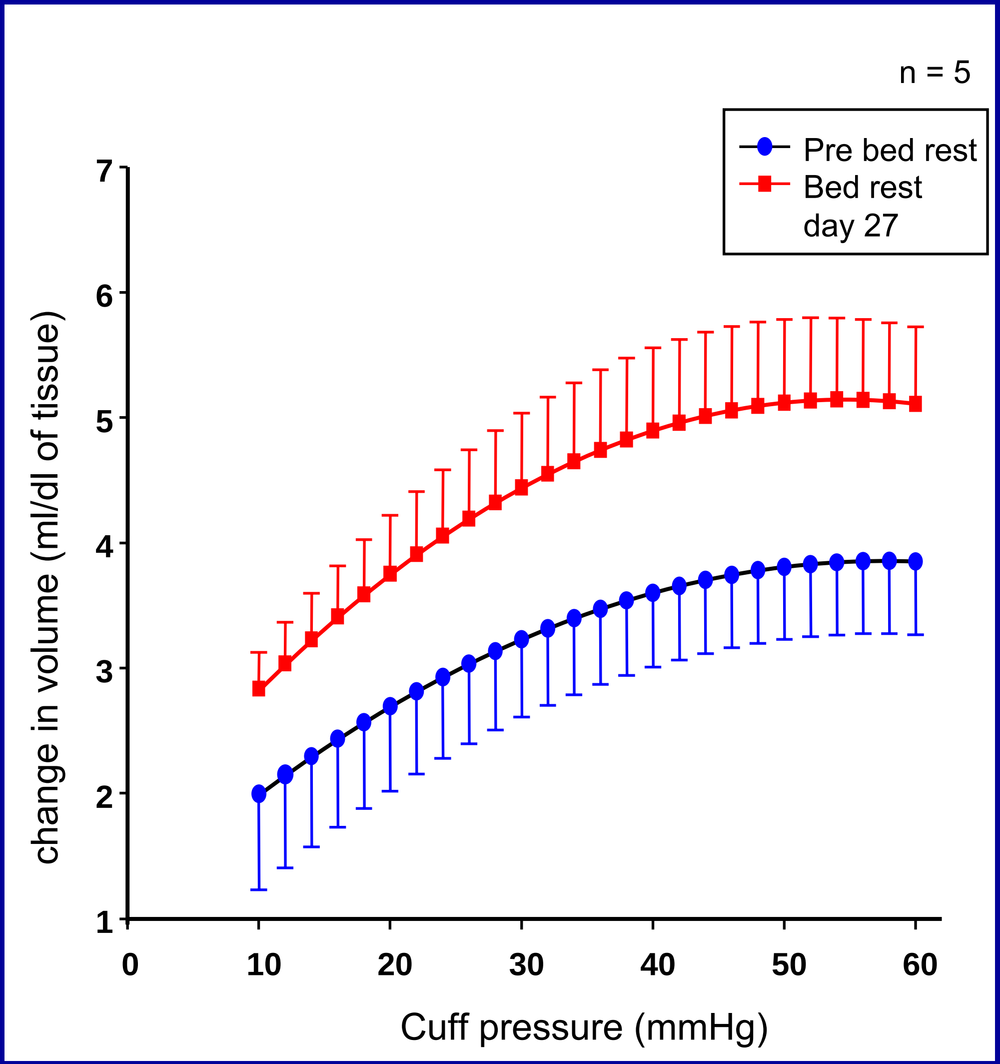


Effects of 60 Days Bed Rest on Anterior Tibial Vein Area: percent change from supine

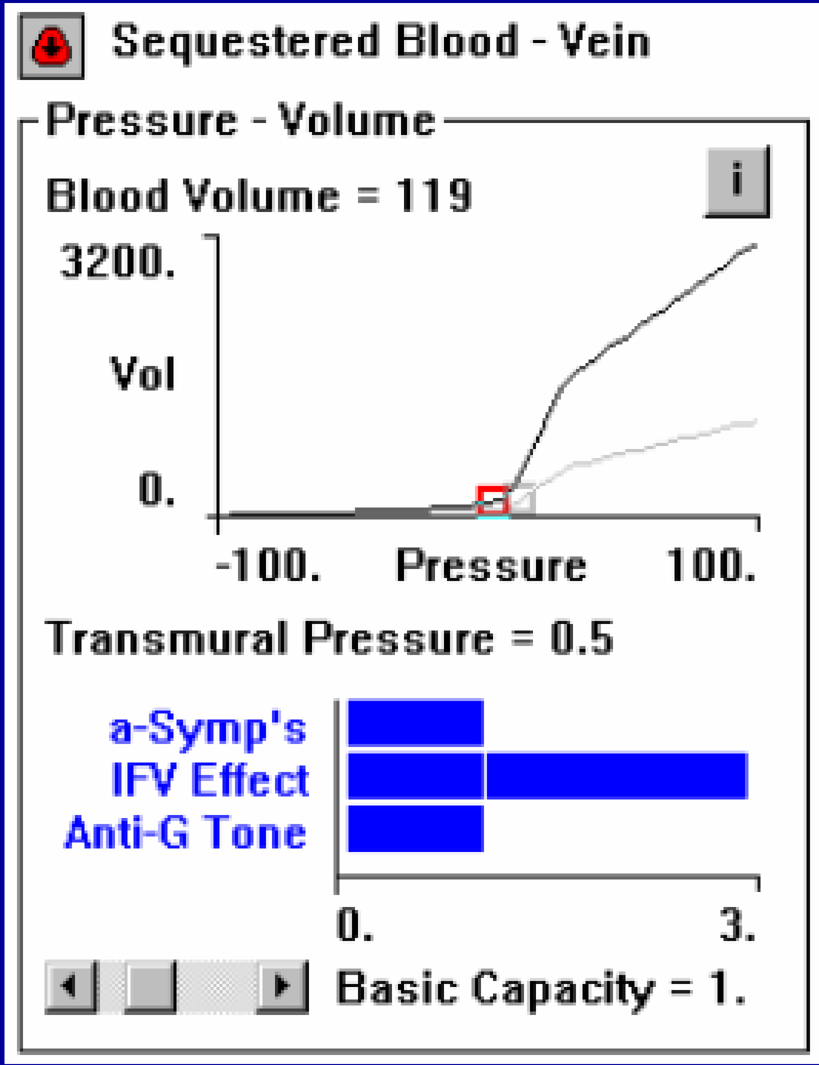


Capacitance

Preliminary Data



Model Prediction



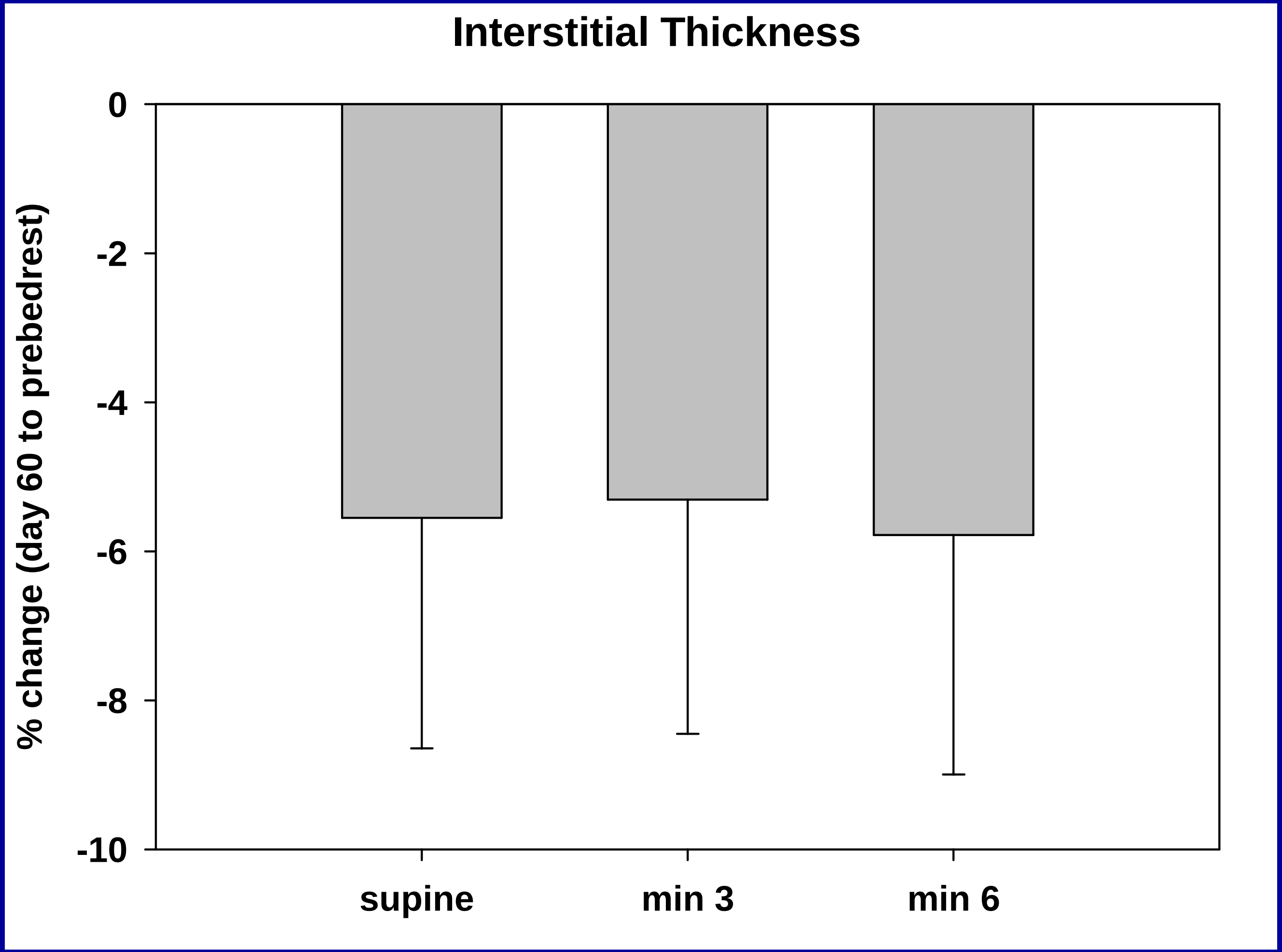
Conclusions

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

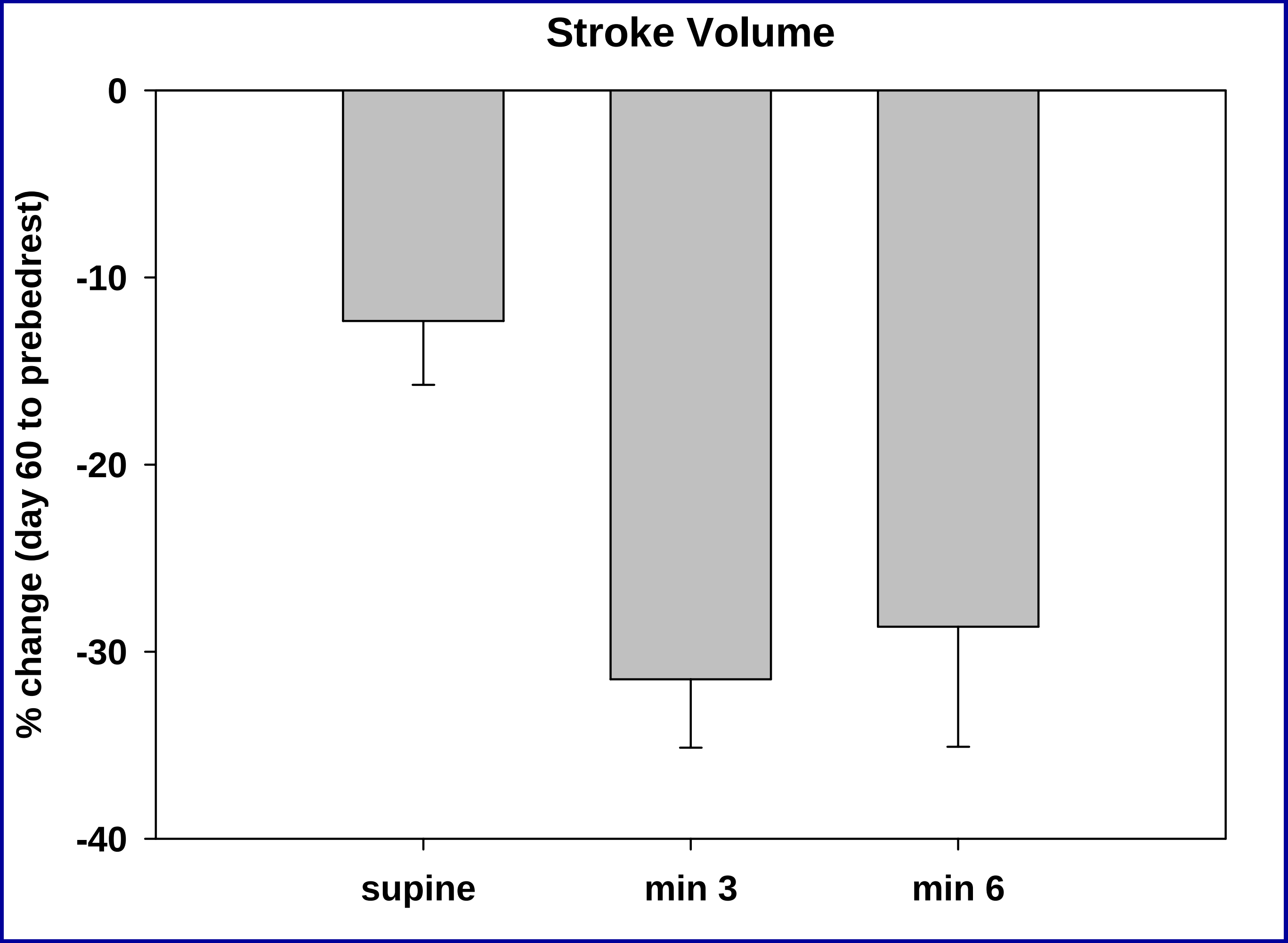
We hypothesized that long term bed rest would replicate this pattern

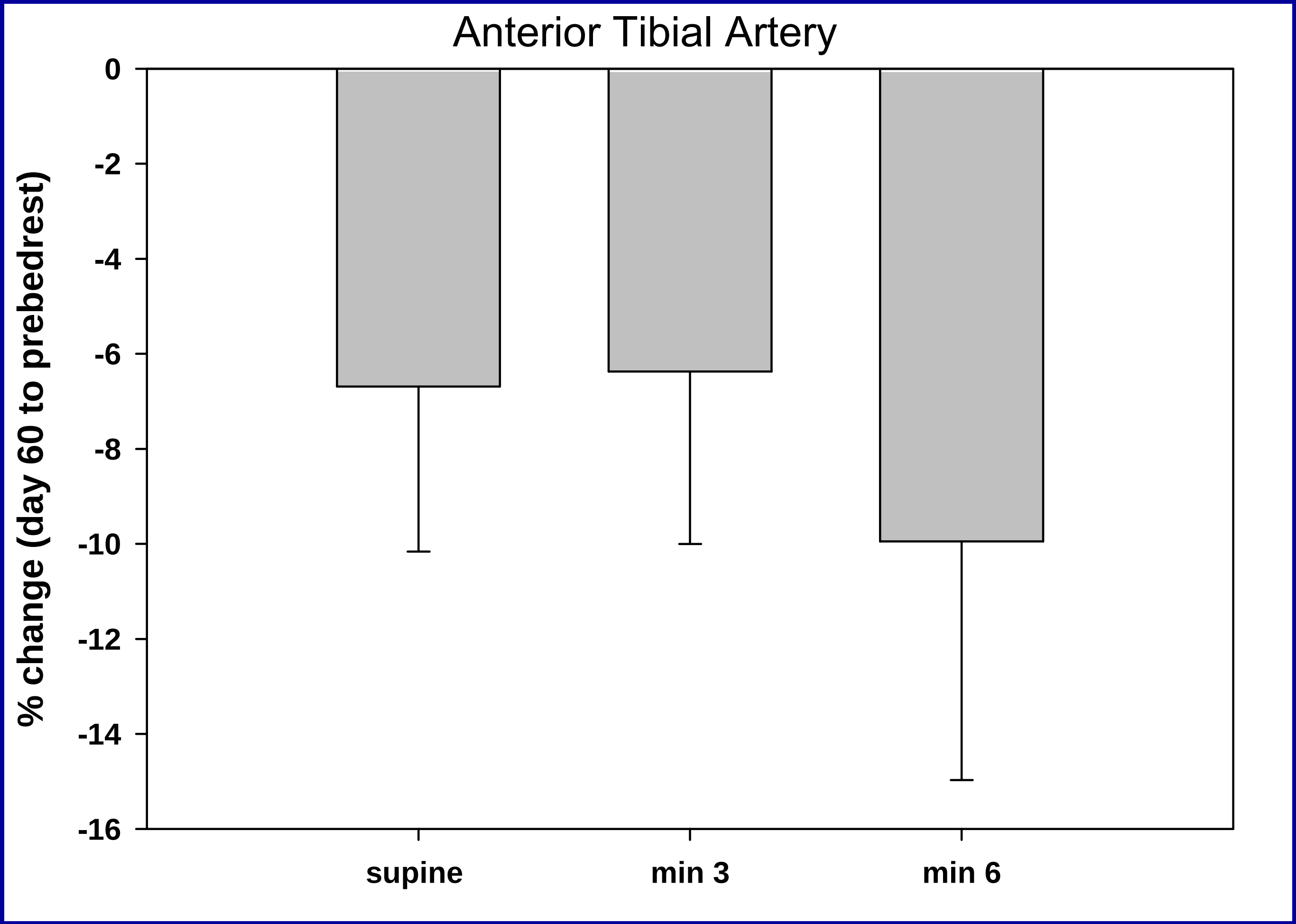
Measurements, before and after 60 days of bed rest, of changes in the interstitial spaces and observed responses of the anterior tibial vein with tilt were consistent with our hypothesis.

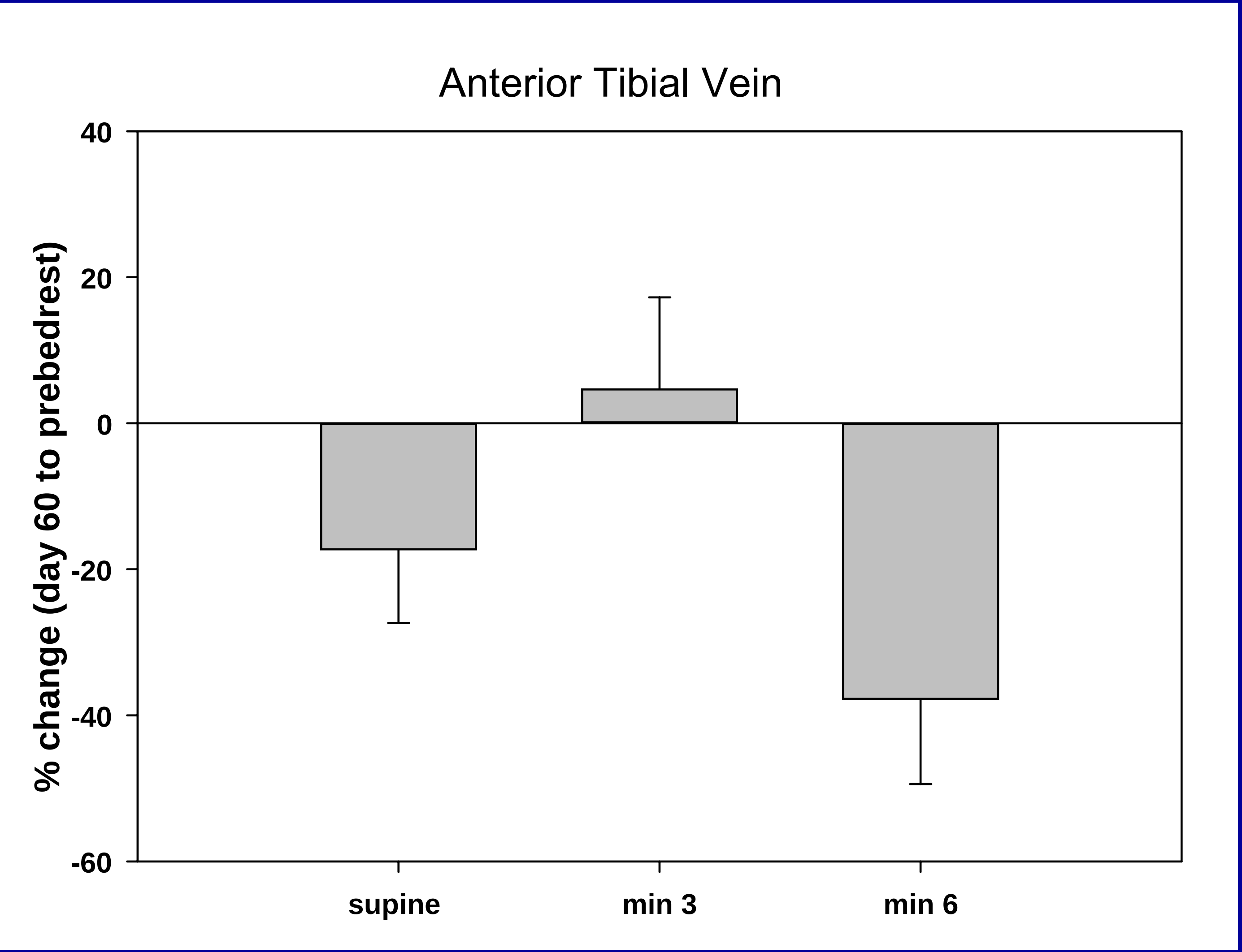
Back-up Slides



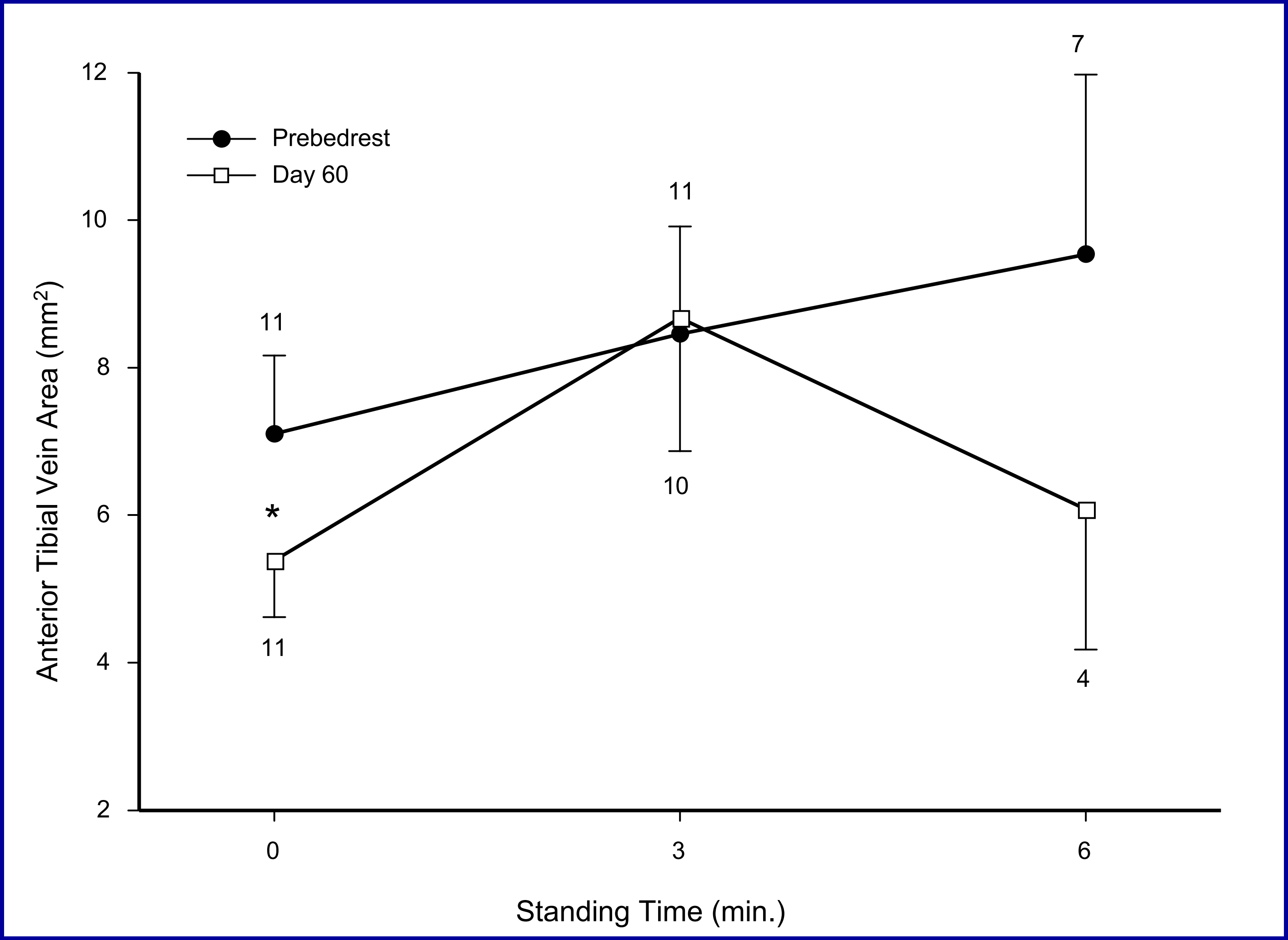
Interstitial Thickness
% change (day 60 to prebedrest)
0
-2
-4
-6
-8
-10
supine
min 3
min 6


Stroke Volume
0
-10
-20
-30
-40
% change (day 60 to prebedrest)
supine
min 3
min 6


Anterior Tibial Artery
0
-2
-4
-6
-8
-10
-12
-14
-16
% change (day 60 to prebedrest)
supine
min 3
min 6


Anterior Tibial Vein
40
20
0
-20
-40
-60
% change (day 60 to prebedrest)
supine
min 3
min 6

Effects of 60 Days Bed Rest on Anterior Tibial Vein Area



Tilt Test Survival Analysis Before and After 60 days of Bed Rest