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ORIGINAL ARTICLE

Modelling of cardiovascular response to graded orthostatic stress: role of capillary filtration

Karen E. Etter*, Nandu Goswami† and M. Keith Sharp*

*Department of Mechanical Engineering, University of Louisville, Louisville, KY, USA, †Institute of Physiology, Medical University of Graz, Graz, Austria

ABSTRACT

Background Of the many possible factors that may contribute to orthostatic intolerance, the loss of circulating blood because of capillary filtration is one of the few that can explain the gradual decline of arterial pressure during stand tests. This study used a computer model to investigate the relative importance of haemodynamic parameters, including capillary filtration, as potential contributors to orthostatic intolerance. Simulated orthostatic tolerance times were compared to previous experiments combining head-up tilt and lower body negative pressure graded orthostatic stress, which provided haemodynamic data, in particular haematocrit measurements that allowed subject-specific modelling of capillary transport.

Materials and methods The cardiovascular system was simulated using a seven-compartment model with measured heart rate, stroke volume, total peripheral resistance, mean arterial pressure and haematocrit data for 12 subjects. Simulations were controlled by decreasing the total blood volume at the measured rates of capillary filtration until cerebral pressure dropped below a threshold for consciousness. Predicted times to syncope were compared to actual times to presyncope, and sensitivity of arterial pressure and cardiac output to independent system parameters were determined.

Results There was no statistical difference in modelled times to syncope and actual times to presyncope. Both arterial pressure and cardiac output were most sensitive to total blood volume and least sensitive to caudal compliance parameters.

Conclusions The feasibility of subject-specific simulations of cardiovascular response to orthostatic stress was demonstrated, providing stronger evidence that capillary filtration is a prominent mechanism in causing orthostatic intolerance. These results may have clinical and spaceflight applications.

Keywords Capillary filtration, cardiovascular modelling, lower body negative pressure, orthostatic intolerance, stand test.

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Introduction

Orthostatic intolerance remains a problem upon return to Earth from the microgravity environment of spaceflight. A large fraction of astronauts demonstrate postflight orthostatic intolerance when tested between 3–4 h after space flight [1,2], with the fraction increasing with flight duration [3]. Because the data available from preflight and postflight tests of astronauts are predominantly for relatively short spaceflights and small sample sizes, meaningful statistical comparisons are generally not possible [4]. Equally important for the purposes of this study is that data essential for estimating circulating fluid volume are often missing.

Of the many possible factors advanced as potential contributors to postspaceflight orthostatic intolerance (POI), the loss of circulating blood volume because of capillary filtration, investigated by Broskey and Sharp [5] and Coats and Sharp [6], is one of the few that can explain the gradual decline of arterial pressure often observed during stand tests. During capillary filtration, fluid is transferred from the blood to the tissues, with the rate generally driven by capillary transmural pressure (CTP). Because CTP may be chronically decreased in microgravity, capillary hydraulic conductivity may increase to maintain normal transcapillary flow during spaceflight, which then results in temporarily increased capillary filtration when CTP returns to normal postflight. Broskey and Sharp [5] and then Coats and Sharp [6] adapted a simple cardiovascular model developed by White and Blomqvist [7] to investigate cardiovascular

responses to orthostatic stress, finding in both studies that capillary filtration plays an important role in the onset of orthostatic intolerance. The Broskey and Sharp model increased the number of compartments in the model from three to five and incorporated nonlinear compliance for the venous compartments. The model also included hydrostatic pressure based on posture-dependent compartment elevations and a modified solution technique that worked better for nonlinear compliance to simulate an average astronaut returning to Earth. The number of compartments was then increased to seven in the Coats and Sharp model to match the regions for which experimental plethysmography data were available and differences between male finishers and nonfinishers of stand tests and females (all nonfinishers) were incorporated, along with a continuous nonlinear compliance function. In addition to simulating stand tests on Earth, Mars and the Moon, the Coats and Sharp model simulated responses of individuals on a centrifuge. Using a constant 40-mL min^{-1} decrease in circulating volume for nonfinishers to represent capillary filtration, the model predicted syncope when cerebral pressure dropped below the 25–30 mmHg threshold for consciousness [8,9]. For the average astronaut in the Broskey and Sharp [5] study, the resulting simulated time to syncope in postflight stand tests on Earth was 7 min, which agreed well with average time to presyncope for returning astronauts [1]. Similar simulations performed by Coats and Sharp [6] produced 4 and 7 min times to syncope in females and male nonfinishers, respectively, which corresponds well with available data on returning astronauts [1,10].

This study undertakes the task of subject-specific simulations of cardiovascular response during orthostatic stress. Because of the limitations of astronaut experiments, validation data were provided by tests of nonastronauts at the Medical University of Graz, which combined head-up tilt (HUT) and graded lower body negative pressure (LBNP) until presyncope [11]. LBNP is known to reliably cause orthostatic intolerance and increases in lower body transmural pressures similar to the increases caused by returning to Earth [12]. The aim of this study was to determine the relative importance of cardiovascular and haemodynamic parameters in producing orthostatic intolerance in individual subjects, which may allow the identification of characteristics predictive of orthostatic intolerance.

Methodology

Model development

The cardiovascular model consists of seven compartments that represent the heart/lung and systemic arteries as well as the cephalic, chest, abdomen, thigh and calf venous segments. The independent and dependent model parameters included are listed in Table 1.

Independent parameters included factors characterizing cardiac performance, vascular and arterial resistance, extracardiac pressure, nonlinear, continuous venous compliance and circulating blood volume, which is decreased by the capillary filtration rate. Dependent parameters included cardiac output and compartmental pressures and volumes.

While many of the parameters and constants developed for the Coats and Sharp model [6] stand tests were retained, the current model incorporated a few differences. First, because the Medical University of Graz study [11] involved nonastronauts unadapted to spaceflight, the current model only utilized constants developed for preflight stand tests. Second, compartmental heights and extracardiac pressure were modified to simulate 70° tilt. Third, unstressed compartmental blood volumes, compliance steepness factors and the maximum heart rate pumping constant were updated to match data from the Medical University of Graz study.

The current model retains the Starling-like function originally devised by White and Blomqvist [7] to prescribe the cardiac flow rate

$$Q = \frac{S \cdot K}{1 + \alpha \cdot \exp[-\beta \cdot (P_1 - P_e)]} \quad (1)$$

where S is the effectiveness of the heart pumping, P_1 is the pressure of the heart/lung compartment, P_e is the extracardiac pressure, α and β are cardiac output coefficients, and K is the maximum achievable flow rate of the heart for a given operating condition

$$K = \mathrm{HR} \cdot \mathrm{SV} \cdot C_K \quad (2)$$

where HR is heart rate, SV is stroke volume, and C_K is a constant that was iteratively calculated to ensure predicted cardiac output (HR·SV) and the initial cardiac flow rate in Eqn 1 are within ± 0·2 L min^{-1} at the beginning of each simulation.

Linear relationships for heart rate and stroke volume during LBNP were used because only initial and final values were known for each subject, and because responses for these variables for Person I in a study with the same HUT + LBNP: graded orthostatic stress, (GOS) protocol by Goswami *et al.* [13] were nearly linear during the period of increasing LBNP. Heart rate was modelled using

$$\mathrm{HR} = \mathrm{HR}_0,\ t \le t_{\mathrm{LBNP}} \quad (3)$$

$$\mathrm{HR} = \mathrm{HR}_i + C_{\mathrm{HR}} \cdot (\Delta t_{\mathrm{stand}} - t_{\mathrm{LBNP}}),\ t > t_{\mathrm{LBNP}} \quad (4)$$

where t is the time into the simulation, HR_0 is the initial heart rate (t = 0 min), $\Delta t_{\mathrm{stand}}$ is total stand time, t_{LBNP} is the time at which LBNP is applied, and C_{HR} is a linear slope factor

$$C_{\mathrm{HR}} = \frac{\mathrm{HR}_f - HR_0}{\Delta t_{\mathrm{stand}} - t_{\mathrm{LBNP}}} \quad (5)$$

where HR_f is the heart rate at presyncope.

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Table 1 Independent and dependent parameters

Model parameters		
Parameter	**Reference values**	**Definition**
Independent parameters		
t (min)		Time into simulation
θ_{HUT} (deg)	70	Head-up tilt angle
t_{LBNP} (min)	5	Time at which initial LBNP first applied
P_{LBNP} (mmHg)		LBNP applied
Δt_{stand} (min)		Time between start of testing and subject presyncope
HCT_0 (%)		Subject haematocrit at 1 min before HUT
HCT_{LBNP} (%)		Haematocrit approximated at start of LBNP
HCT_f (%)		Subject haematocrit at 1 min after presyncope
$V_{blood,0}$ (L)		Initial blood volume at start of HUT
$V_{blood,0,exp}$ (L)	5·230	Expected average initial blood volume from Nadler and Allen's formula
$V_{blood,LBNP}$ (L)		Blood volume at start of LBNP
CF_f (L min^{-1})		Constant for assumed capillary filtration rate at subject presycope
CF (L min^{-1})		Capillary filtration rate
H (cm or m)	182	Subject height
W (kg)	75	Subject weight
SA_{body} (m^2)	1·958	Bodily surface area, calculated from height and weight using Dubois and Dubois formula
H_1 (cm)	–3·289	Height of heart/lung region above right atrium (RA)
H_2 (cm)	0	Height of arterial region above RA
H_{ceph} (cm)	27·981	Height of cephalic region above RA
H_{chest} (cm)	0	Height of thoracic region above RA
H_{abs} (cm)	–25·372	Height of abdominal region above RA
H_{thigh} (cm)	–56·570	Height of thigh region above RA
H_{calf} (cm)	–102·802	Height of calf region above RA
α	7·809	Cardiac output coefficient
β (mmHg^{-1})	0·381	Cardiac output coefficient
S	1	Effectiveness of heart pumping
C_K	1·35	Maximum heart pumping rate constant
K (L min^{-1})		Maximum heart pumping rate
Q_{pred} (L min^{-1})		Predicted cardiac output = HR(SV)
HR_0 (beats min^{-1})		Subject heart rate at start of HUT
HR_f (beats min^{-1})		Subject heart rate at presyncope
$C_{HR,LBNP}$ (beats min^{-2})		Constant for heart rate linear slope approximation during LBNP
HR (beats min^{-1})		Heart rate

Table 1 *Continued*

Model parameters		
Parameter	**Reference values**	**Definition**
SI_0 (mL m^{-2})		Subject stroke volume index at start of HUT = SV_0/SA_{body}
SI_f (mL m^{-2})		Subject stroke volume index at presyncope = SV_f/SA_{body}
$C_{SV,LBNP}$ (beats min^{-2})		Constant for stroke volume linear slope approximation during LBNP
SV (mL $beat^{-1}$)		Cardiac stroke volume
P_e (mmHg)	−5·000	Extracardiac (intrapleural) pressure
P_c (mmHg)	−3·000	Pressure of venous collapse in heart/lung compartment = P_e + 2 mmHg
$TPRI_0$ (dyne-s-m^2 cm^{-5})		Subject total peripheral resistance index at start of HUT = TPR_0/SA_{body}
$TPRI_f$ (dyne-s-m^2 cm^{-5})		Subject total peripheral resistance index at start of HUT = TPR_f/SA_{body}
C_{TPR} (mmHg L^{-1} min^{-2})		Constant for total peripheral resistance linear slope approximation during LBNP
TPR (mmHg L^{-1} min^{-1})		Total peripheral resistance
R_v (mmHg L^{-1} min^{-1})	0·8	Venous resistance
R_a (mmHg L^{-1} min^{-1})		Arterial resistance = TPR-R_v
V^*_{10} (L)	0·8912	Component of V_{10} independent of P_e
V_{10} (L)	0·9512	Unstressed volume of blood in heart/lung compartment = V^*_{10}–C_1P_e
V_{20} (L)	0·4446	Unstressed volume in arterial compartment
V_{ceph0} (L)	0·4707	Unstressed volume in cephalic veins
V_{chest0} (L)	0·7322	Unstressed volume in chest (thoracic) veins
V_{abs0} (L)	0·8891	Unstressed volume in abdominal veins
V_{thigh0} (L)	0·3347	Unstressed volume in veins of the thighs
V_{calf0} (L)	0·3138	Unstressed volume in veins of the calves
V_{30} (L)	2·7406	Total unstressed volume of blood in venous compartments = V_{ceph0} + V_{chest0} + V_{abs0} + V_{thigh0} + V_{calf0}
$V_{blood,0}$ (L)	0·4184	Unstressed blood volume in noncapacitive regions
V_{T0} (L)	4·5549	Total unstressed blood volume = $V_{blood,0}$ + V_{30} + V_{20} + V_{10}
V_{blood} (L)		Total blood volume = $V_{blood,0}$ + V_1 + V_2 + V_3
C_1 (L $mmHg^{-1}$)	0·01200	Compliance of heart/lung compartment
C_2 (L $mmHg^{-1}$)	0·00355	Compliance of arterial compartment
C_{ceph0} (L $mmHg^{-1}$)	0·0629	Maximum compliance of cephalic venous compartment
C_{chest0} (L $mmHg^{-1}$)	0·1715	Maximum compliance of chest venous compartment
C_{abs0} (L $mmHg^{-1}$)	0·0912	Maximum compliance of abdominal venous compartment
C_{thigh0} (L $mmHg^{-1}$)	0·0133	Maximum compliance of thigh venous compartment
C_{calf0} (L $mmHg^{-1}$)	0·0106	Maximum compliance of calf venous compartment
N	0·01	Ratio of asymptotic to peak compliance
$a_{ceph,high}$	0·28	Compliance steepness factor for cephalic veins for high pressure
$a_{ceph,low}$	3·36	Compliance steepness factor for cephalic veins for low pressure

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Table 1 *Continued*

Model parameters		
Parameter	**Reference values**	**Definition**
$a_{cent,high}$	0·264	Compliance steepness factor for central veins for high pressure
$a_{cent,low}$	2·464	Compliance steepness factor for central veins for low pressure
$a_{abs,high}$	0·264	Compliance steepness factor for caudal veins for high pressure
$a_{abs,low}$	2·464	Compliance steepness factor for caudal veins for low pressure
Dependent parameters		
Q (L min^{-1})		Cardiac flow rate
P_1 (mmHg)		Pressure within heart/lung compartment, found by iteration
P_2 (mmHg)		Pressure within arterial compartment = $P_1 + Q(R_a+R_v)$
P_{2g} (mmHg)		Arterial pressure with gravity
$P_{2gcereb}$ (mmHg)		Cerebral arterial pressure with gravity
P_3 (mmHg)		Combined venous pressure
P_{cephg} (mmHg)		Cephalic venous pressure with gravity
P_{chestg} (mmHg)		Thoracic venous pressure with gravity
P_{absg} (mmHg)		Abdominal venous pressure with gravity
P_{thighg} (mmHg)		Venous pressure of thigh with gravity
P_{calfg} (mmHg)		Venous pressure of calf with gravity
V_1 (L)		Volume of blood in heart/lung compartment
V_2 (L)		Volume of blood in arterial compartment
V_{ceph} (L)		Volume of blood in cephalic venous compartment
V_{chest} (L)		Volume of blood in chest (thoracic) venous compartment
V_{abs} (L)		Volume of blood in abdominal venous compartment
V_{thigh} (L)		Volume of blood in thigh venous compartment
V_{calf} (L)		Volume of blood in calf venous compartment
V_3 (L)		Total volume of blood in venous compartments = $V_{ceph} + V_{chest} + V_{abs} + V_{thigh} + V_{calf}$
C_{ceph} (L mmHg^{-1})		Compliance of cephalic venous compartment
C_{chest} (L mmHg^{-1})		Compliance of chest venous compartment
C_{abs} (L mmHg^{-1})		Compliance of abdominal venous compartment
C_{thigh} (L mmHg^{-1})		Compliance of thigh venous compartment
C_{calf} (L mmHg^{-1})		Compliance of calf venous compartment
C_3 (L mmHg^{-1})		Total compliance of venous compartments = $C_{ceph} + C_{chest} + C_{abs} + C_{thigh} + C_{calf}$

HUT, head-up tilt; LBNP, lower body negative pressure; TPR, total peripheral resistance.

Similarly, stroke volume was modelled using the initial and presyncopal stroke volumes,

$$SV = SV_0, t \leq t_{LBNP} \quad (6)$$

$$SV = SV_0 + C_{SV} \cdot (\Delta t_{stand} - t_{LBNP}),\ t > t_{LBNP} \quad (7)$$

where SV_0 is the initial stroke volume (t = 0 min) and C_{SV} is a linear slope factor

$$C_{SV} = \frac{SV_f - SV_0}{\Delta t_{stand} - t_{LBNP}} \quad (8)$$

where SV_f is the stroke volume at presyncope.

Initial and presyncopal stroke volumes were calculated from available stroke volume indexes, SI,

$$SV = SI \cdot SA_{body} \quad (9)$$

where body surface area, SA_{body}, was calculated using the Dubois and Dubois [14] formula

$$SA_{body} = 0{\cdot}007184 W^{0{\cdot}425} \cdot H^{0{\cdot}725} \quad (10)$$

where W is the average weight in kg, and H is the average height in cm of the subjects.

While total peripheral resistance data were not available from the Goswami study, one by Levenhagen [15] involving oscillatory LBNP showed that heart rate, stroke volume and total peripheral resistance were all proportional to LBNP. Therefore, for simplicity, a linear model for total peripheral resistance was also used,

$$TPR = TPR_0, t \leq t_{LBNP} \quad (11)$$

$$TPR = TPR_0 + C_{TPR} \cdot (\Delta t_{TPR} - t_{LBNP}), t > t_{LBNP} \quad (12)$$

where TPR_0 is the initial total peripheral resistance (t = 0 min), and C_{TPR} is a linear slope factor

$$C_{TPR} = \frac{TPR_f - TPR_0}{\Delta t_{stand} - t_{LBNP}} \quad (13)$$

where TPR_f is the total peripheral resistance at presyncope.

Initial and presyncopal total peripheral resistances were calculated from measured total peripheral resistance indexes, TPRI,

$$TPR = \frac{TPRI}{SA_{body}} \quad (14)$$

Pressures at heart level within the arterial and venous compartments, P_2 and P_3, respectively, were related to flow

$$Q = \frac{P_2 - P_3}{R_a} \quad (15)$$

where R_a is the arterial resistance.

Flow through the veins was also modelled as viscous, with the potential for collapse,

$$Q = \frac{P_3 - P_1}{R_v}, P_1 > P_c \quad (16)$$

$$Q = \frac{P_3 - P_c}{R_v}, P_1 < P_c \quad (17)$$

where P_1 is the pressure within the heart/lung compartment, P_c is the pressure of partial collapse, and R_v is the venous resistance. As in the Coats and Sharp study [6], a venous resistance of 0·8 mmHg L^{-1} min^{-1} was used for all subjects.

The compliance of each venous compartment was given by

$$C_i = C_{i,0} \cdot [N + (1 - N)\mathrm{sech}(a_i(P_{ig} - 4))] \quad (18)$$

where $C_{i,0}$ is the peak compliance of compartment i, a_i is a parameter controlling the steepness of the compliance curve, N is the ratio of asymptotic to peak compliance, and P_{ig} is the transmural pressure of the compartment with gravity

$$P_{ig} = P_i - \gamma G(H_i - H_1) \quad (19)$$

where P_i is the transmural pressure of the compartment, γ is the specific weight of blood, G is the nondimensional gravity level, H_i and H_1 are the compartmental height and the height of the heart/lung region, respectively. To simulate the application of LBNP, negative extramural pressure equal to the LBNP level was applied to P_{ig} for the thigh and calf venous compartments.

Because detailed subject-specific data were not available, the $C_{i,0}$ and N values developed for the Coats and Sharp model [6] were used. The iterative process used to find a_i values for each compartment is described later.

The compliance curve was used to find the volume shift by integration with respect to pressure

$$V_i - V_{i,0} = \int_{P_0}^{P_{ig}} C_i dP_{ig} \quad (20)$$

where V_i is the volume of each compartment at the current pressure, and $V_{i,0}$ and P_0 are the initial volume and pressure, respectively. Total volume was conserved

$$V_{blood} = \sum V_i \quad (21)$$

where V_{blood} is the total blood volume.

As in the Coats and Sharp [6] model for male stand test finishers, a capillary filtration rate CF_0 = 0·01 L min^{-1} was used during the HUT only portion of the simulation. Additional capillary filtration proportional to LBNP pressure was included during the LBNP period. The only haematocrit data available were for 1 min before the HUT (t = −1 min) began and 1 min after presyncope; therefore, these values were assumed to hold at the beginning of HUT (t = 0) and the exact time of presyncope, respectively. As in Broskey and Sharp [5] and Coats and Sharp [6], it was assumed that fluid lost through capillary filtration was red blood cell free because red blood cells are too large to pass through the capillaries. The linear capillary filtration rate was modelled as

$$CF = CF_0, t \leq t_{LBNP} \quad (22)$$

$$CF = CF_0 + \left(\frac{CF_f - CF_0}{\Delta t_{stand} - t_{LBNP}}\right) \cdot (t - t_{LBNP}), t > t_{LBNP} \quad (23)$$

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where CF_f is the capillary filtration rate at subject presyncope and was estimated as

$$CF_f = 2 \cdot \left(\frac{V_{blood,LBNP} \cdot (HCT_f - HCT_{LBNP})}{HCT_f \cdot (\Delta t_{stand} - t_{LBNP})} - 0{\cdot}005 \right) \quad (24)$$

where HCT_f is the measured haematocrit at presyncope, HCT_{LBNP} is the estimated haematocrit at the beginning of LBNP, and $V_{blood,LBNP}$ is the blood volume at the beginning of LBNP

$$V_{blood,LBNP} = V_{blood,0} - CF_0 t_{LBNP} \quad (25)$$

where $V_{blood,0}$ is the initial volume of blood at t = 0 min. The haematocrit at the beginning of LBNP was calculated as

$$HCT_{LBNP} = HCT_0 \left(\frac{V_{blood,0}}{V_{blood,LBNP}} \right) \quad (26)$$

where HCT_0 is the initial haematocrit.

To estimate initial blood volume and to set up the initial cardiovascular state for each subject simulation, subject initial mean arterial pressure (P_2 at t = 0 min) was used to calculate the initial pressure in the heart/lung compartment and other dependent parameters so that total blood volume at t = 0 min could be found from Eqn 21. Because compliance steepness a_i values from the Coats and Sharp study [6] gave overestimated total blood volumes for this study, they were iteratively changed so the average of the simulated initial blood volumes matched the average, expected initial blood volume from Nadler and Allen's [16,17] formula for males

$$V_{blood,0,exp} = 0{\cdot}3669H^3 + 0{\cdot}03219W + 0{\cdot}6041 \quad (27)$$

where H is height in m, and W is weight in kg. The average blood volume in Eqn 27 was also used to scale unstressed blood volumes from the Coats and Sharp study [6] to match the subjects for this study.

Based on the capillary filtration rates (Eqns 22 and 23), subject blood volume was

$$V_{blood} = V_{blood,0} - CF_0 t, t \le t_{LBNP} \quad (28)$$

$$V_{blood} = V_{blood,0} - CF_0 t - \left(\frac{CF_f - CF_0}{\Delta t_{stand} - t_{LBNP}} \right) \cdot \left(\frac{1}{2}(t^2 + t_{LBNP}^2) - t_{LBNP} \cdot t \right), t > t_{LBNP} \quad (29)$$

Finally, for a particular simulation time, the subject's cardiovascular state and the dependent parameters were determined by iterating until the total blood volume in Eqn 21 was equal to the blood volume controlled by capillary filtration in Eqns 28 and 29.

Simulated GOS test

Subject-specific simulations that mimicked the cardiovascular response to progressive loss of circulating volume during a GOS test were run for each of the twelve Medical University of Graz study [11] subjects (all male) for which both cardiovascular and haemodynamic data were available. As described in the methodology earlier, subject data were used to estimate unstressed blood volumes and initial total blood volume. Subject-specific data were also used to control heart rate, stroke volume, total peripheral resistance and the capillary filtration rate. Simulations were iteratively run for progressing time until cerebral arterial pressure dropped below 30 mmHg, which is the minimum pressure for adequate brain perfusion. Below this level, unconsciousness (syncope) quickly follows. Cerebral arterial pressure was approximated by subtracting 28 mmHg (the estimated hydrostatic pressure because of the difference in height between the heart and the brain for a 70° tilt) from the arterial pressure with gravity.

Sensitivity analysis

The sensitivity of arterial pressure and cardiac output was defined as [7]

$$Sen(f, z) = \left(\frac{\partial \log f}{\partial \log z} \right)_0 \quad (30)$$

where f and z represent any combination of independent and dependent parameters, respectively, and the subscript zero represents that the calculation is made at a baseline condition. The derivatives were approximated by the change to the dependent parameter caused by a finite change in the independent variable. Absolute pressures were used in these calculations rather than gage pressures. Sensitivity for a 5% change in the independent variable is reported for simulated tests involving subjects with the longest, shortest and average stand times at simulation start (t = 0 min), right before LBNP was applied (t = 5 min) and at presyncope.

Experimental methodology

For the Medical University of Graz study [11], subjects were selected to avoid effects of confounding variables such as height, gender or athletic training on orthostatic tolerance [12]. Fifteen healthy males (31 ± 2 years, 75 ± 3 kg, 182 ± 2 cm, BMI 23 ± 1 kg m^{-2}) were enrolled who had no history of syncope, pathological conditions (neurological, cardiovascular, or endocrine) and were on no medications. Test subjects abstained from alcohol, smoking and caffeine as well as from vigorous exercise for 48 h prior to examination and were advised not to change their fluid and salt intake as governed by their usual dietary habits. A light breakfast with sufficient fluid intake was allowed pretest. All studies occurred between 09·00 and 12·00 h

in an air-conditioned, semi-dark room (Temp: 22 ± 1 °C and humidity: 55%). The Graz Medical University's Ethics Committee approved the study, and written informed consent was obtained from each subject.

Experimental protocol

Subjects were tested on an electronically driven tilt table (with LBNP box incorporated) that allowed for < 10 s postural changes and LBNP build-up. The sealing was maintained at the iliac crest, because sealing position has been shown to affect haemodynamic responses [18]. Test subjects were secured on the table and had access to an emergency shutdown (automatic return to supine and pressure neutralization) at all times. The experiment commenced with 5 min of 70° passive head-up tilt, which was followed by graded LBNP, starting with 20 mmHg suction, and increasing by 10 mmHg each in 3-min intervals, until presyncope occurred. Total time in the upright position was recorded as standing time (or orthostatic tolerance time).

The criteria of presyncope were the development of any of the following: (i) systolic blood pressure less than 80 mmHg or

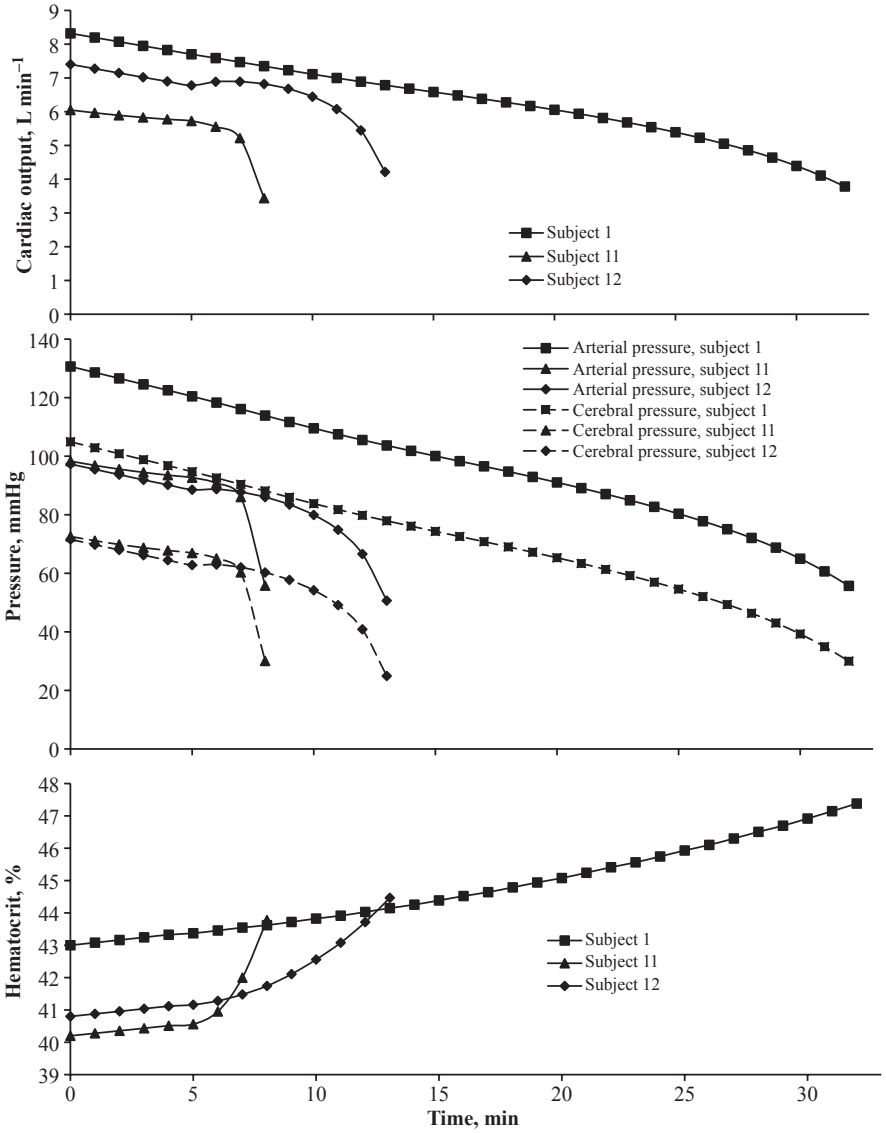

Figure 1 Arterial and cerebral pressure, cardiac output and haematocrit during simulated graded orthostatic stress tests. Subjects 1, 11 and 12 had longest, shortest and average simulated stand times.

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rate of decrease ≥ 25 mmHg min^{-1}, diastolic rate of decrease ≥ 15 mmHg min^{-1}, or heart rate decrease by ≥ 15 bpm (ii) lightheadedness, dizziness, visual disturbances, nausea, stomach awareness, clammy skin, excessive sweating, or skin pallor.

Haemodynamics

Cardiovascular data such as heart rate, stroke index, blood pressure, total peripheral resistance and haematocrit taken 1 min before HUT and at the time of presyncope were used to calibrate the model for each subject. A Task Force Monitor® (CNSystems, Graz, Austria) was used for blood pressure, ECG and thoracic impedance $Z_0(t)$ monitoring. Impedance variation $dZ(t)/dt$ was used to calculate beat-to-beat stroke volume, cardiac output and total peripheral resistance [19]). Arterial pressure was monitored using a finger cuff (Penaz principle) and regular calibration to standard arm cuff measurements. Mean arterial pressure was computed as MAP = DBP + 1/3 (SBP−DBP), where DBP and SBP are diastolic and systolic blood pressures, respectively.

Task force monitor® ECG/impedance (CNSystems, Graz, Austria) electrodes were positioned together with upper arm and finger blood pressure cuffs [19]. Electrode strips were placed at the neck and thoracic regions, the latter specifically at the midclavicular line at the xiphoid process level. Recorded and calculated data were stored real-time beat-to-beat throughout the entire experiment.

Blood sampling

Blood was sampled from an uncongested vein maintained at the heart level during supine and upright positions. Haematocrit was measured 1 min before HUT and 1 min after presyncope, immediately after reaching the supine position.

Subject-specific modelling focused on the 12 subjects for which full haemodynamic data sets were available. Detailed data of all the measured values (mean and standard deviation) during the GOS experiments are presented in [11].

Results

Simulated GOS test

Cardiac output, aortic and cerebral arterial pressure, and haematocrit for three simulated GOS tests are shown in Fig. 1. Subjects 1, 11 and 12 are shown because they had the longest, shortest and average simulated GOS times at 32·00, 8·00 and 12·70 min, respectively. While the cardiac output and pressure drop occur smoothly for Subject 1, there is an abrupt drop in output and pressure for Subject 11 shortly after LBNP is first applied (t = 5 min). The cardiovascular response of Subject 12 was between these extremes, with a small increase in output and pressure when LBNP was applied before a slower decrease. As blood volume was progressively decreased to simulate capillary filtration losses, haematocrit increased. While the haematocrit increase for Subject 1 with LBNP was similar to that during only HUT, Subject 11 shows a large and sudden increase in haematocrit and Subject 12 shows an intermediate increase after LBNP application.

A comparison of simulated times to syncope and actual times to presyncope for each subject is shown in Fig. 2. A Wilcoxon signed-rank test found no statistical difference between these two groups, at an alpha level of 0·05.

With a cerebral arterial pressure threshold of 30 mmHg for adequate brain perfusion, the simulated mean arterial pressure at syncope of approximately 58 mmHg was the same for every subject. Actual mean arterial pressures during the last 3 min of orthostatic stress are shown in Fig. 3. As examples of the range of responses, included on the graph are curves for the subjects with the highest and lowest pressures at the beginning of this period and for the subjects with the highest and lowest pressures at the end of this period. The bold curve represents means (with standard deviations) for all 25 subjects over 20-s intervals, except for the last 20 s, which was averaged over ten-second intervals. Using the slope of pressure between the last two 10-s intervals, the mean arterial pressure at the termination of orthostatic stress was extrapolated to be 68 mmHg.

Sensitivity analysis

The sensitivity of cardiac output, Q, and arterial pressure, P_{2g}, to changes in the independent parameters is given in Table 2 for subjects with the longest, shortest and average stand times at simulation start (t = 0 min), right before LBNP was applied (t = 5 min) and at the predicted time of syncope. As cerebral arterial pressure $P_{2gcereb}$ is determined directly from P_{2g}, sensitivity values for P_{2g} provide indication of the influence of independent parameters on syncope.

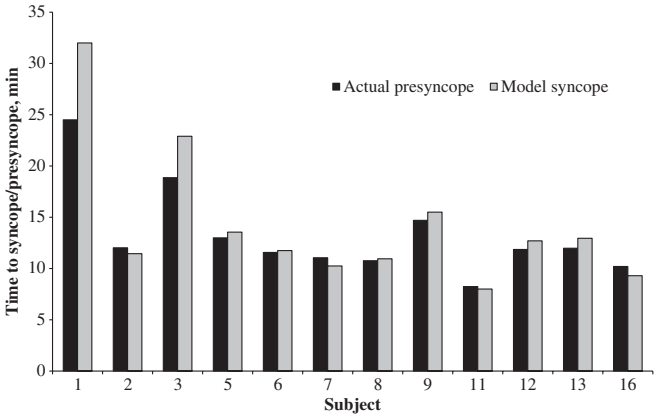

Figure 2 Simulated and actual stand times for each subject.

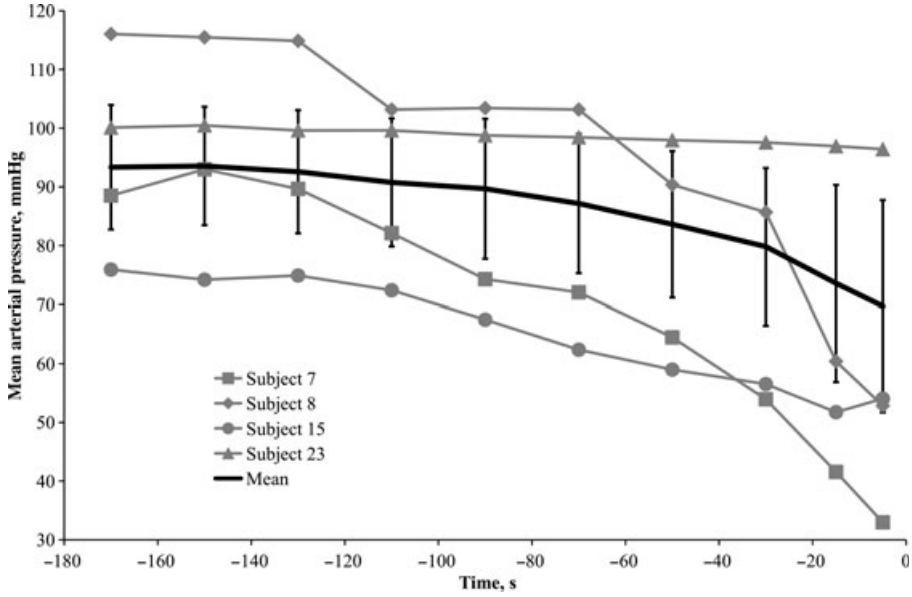

Figure 3 Measured mean arterial pressure at presyncope.

Total blood volume, V_{blood}, had by far the greatest affect on cardiac flow rate and arterial pressure for each subject. Unstressed blood volumes V_{10}*, V_{abs0}, V_{chest0} and V_{ceph0} were the next most sensitive parameters for each subject at the start, for Subjects 1 and 12 at the application of LBNP, and at syncope. For Subject 11, V_{10}* remained the second most sensitive parameter for cardiac output while R_a became the second most sensitive for arterial pressure at the application of LBNP. At the application of LBNP and onset of syncope, cardiac output also became more sensitive to cardiac performance parameters such as β, S and K for Subject 11.

Discussion

The experiments provide valuable data, unavailable from other studies, on blood volume changes during orthostatic stress. These data facilitated subject-specific modelling that provided the most convincing evidence yet that capillary filtration is a prominent mechanism in causing orthostatic intolerance. These results may have applications in understanding the pathogenesis of postflight orthostatic intolerance, which has multiple potential aetiologies.

Capillary filtration rate

The results of these simulations show a good correlation between capillary filtration rate and stand time. Total blood volume was the most important dependent parameter, and the decrease in total blood volume was controlled by the capillary filtration rate of the individual. The resulting, statistically significant simulation stand times can, therefore, be directly related to capillary filtration rate. The obvious similarities among haematocrit, cardiac output and arterial pressure trends also support the theory that total blood volume losses are closely related to the cardiovascular state. The high degree of sensitivity of cardiac output and arterial pressure to total blood volume also supports this hypothesis. Figure 4 compares simulation stand time and the slope of the capillary filtration rate during LBNP. It clearly shows that individuals with lower capillary filtration rate slopes were more likely to have longer stand times.

Total peripheral resistance

During the Medical University of Graz study [11], subjects with similar stand times had very different total peripheral resistance responses to the orthostatic stress, such as the four subjects with stand time differences of < 1·5 min shown in Table 3. The similarity of their stand times, despite the difference in peripheral resistance response, supports Broskey and Sharp's findings [5] that arterial resistance is a minor POI mechanism compared to blood volume loss. Astronauts experiencing postflight intolerance during postflight stand tests commonly display lower increases in peripheral resistance during preflight stand test levels [1,4,10].

Sensitivity results also support this hypothesis. While the arterial pressure of Subject 11, who had the lowest stand time, became more sensitive to arterial resistance, R_a, as syncope

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Table 2 Sensitivity values for cardiac output Q (upper half of tables) and arterial pressure P_{2g} (lower half of tables) for the independent parameters in the model. Subjects 1, 11 and 12 had longest, shortest and average simulated stand times

	α	β	S	K	R_a	R_v	C_1	C_2	C_{ceph}	C_{chest}	C_{abs}	C_{thigh}	C_{calf}	A_{ceph}	A_{cent}	A_{caud}	V_{10star}	V_{20}	V_{ceph0}	V_{chest0}	V_{abs0}	V_{thigh0}	V_{calf0}	V_{blood}	$V_{blood,0}$	P_e
Start of HUT (t = 0 min)																										
Subject 1	−0·077	0·232	0·279	0·279	−0·641	−0·044	−0·145	−0·691	0·219	−0·349	−0·212	−0·035	−0·034	−0·393	0·468	0·043	−1·399	−0·686	−0·727	−1·144	−1·396	−0·514	−0·481	5·411	−0·645	0·060
Subject 12	−0·091	0·286	0·366	0·366	−0·548	−0·047	−0·178	−0·603	0·257	−0·408	−0·248	−0·042	−0·040	−0·464	0·546	0·051	−1·609	−0·805	−0·853	−1·329	−1·605	−0·603	−0·565	5·189	−0·757	0·072
Subject 11	−0·109	0·339	0·419	0·419	−0·432	−0·085	−0·141	−0·466	0·226	−0·309	−0·198	−0·034	−0·033	−0·365	0·480	0·043	−1·034	−0·590	−0·620	−0·892	−1·032	−0·458	−0·432	5·627	−0·560	0·132
Subject 1	−0·009	0·027	0·033	0·033	0·038	−0·007	−0·022	−0·105	0·034	−0·054	−0·033	−0·005	−0·005	−0·060	0·073	0·007	−0·210	−0·105	−0·111	−0·172	−0·209	−0·079	−0·074	0·990	−0·098	0·004
Subject 12	−0·008	0·026	0·033	0·033	0·037	−0·006	−0·022	−0·073	0·032	−0·049	−0·030	−0·005	−0·005	−0·056	0·068	0·006	−0·189	−0·097	−0·102	−0·157	−0·189	−0·073	−0·068	0·800	−0·091	0·003
Subject 11	−0·010	0·033	0·040	0·040	0·053	−0·010	−0·017	−0·057	0·028	−0·038	−0·024	−0·004	−0·004	−0·044	0·060	0·005	−0·124	−0·072	−0·075	−0·107	−0·124	−0·056	−0·053	0·863	−0·068	0·010
Start of LBNP (t = 5 min)																										
Subject 1	−0·091	0·251	0·276	0·276	−0·609	−0·060	−0·141	−0·652	0·237	−0·360	−0·223	−0·038	−0·038	−0·414	0·502	0·045	−1·318	−0·700	−0·738	−1·113	−1·318	−0·532	−0·498	6·381	−0·660	0·082
Subject 12	−0·120	0·348	0·393	0·393	−0·431	−0·103	−0·146	−0·469	0·253	−0·342	−0·219	−0·038	−0·036	−0·404	0·537	0·047	−1·128	−0·650	−0·684	−0·974	−1·125	−0·506	−0·479	6·589	−0·617	0·144
Subject 11	−0·158	0·459	0·529	0·529	−0·216	−0·220	−0·068	−0·232	0·123	−0·144	−0·104	−0·016	−0·016	−0·189	0·231	0·023	−0·550	−0·307	−0·322	−0·469	−0·550	−0·237	−0·223	6·249	−0·290	0·267
Subject 1	−0·010	0·028	0·031	0·031	0·041	−0·009	−0·020	−0·092	0·034	−0·051	−0·032	−0·005	−0·005	−0·059	0·073	0·006	−0·184	−0·099	−0·104	−0·156	−0·184	−0·076	−0·071	1·088	−0·093	0·006
Subject 12	−0·010	0·030	0·034	0·034	0·048	−0·011	−0·016	−0·052	0·029	−0·038	−0·024	−0·004	−0·004	−0·045	0·061	0·005	−0·123	−0·072	−0·075	−0·106	−0·122	−0·056	−0·053	0·917	−0·068	0·010
Subject 11	−0·015	0·045	0·052	0·052	0·077	−0·025	−0·008	−0·027	0·014	−0·017	−0·012	−0·002	−0·002	−0·022	0·027	0·003	−0·063	−0·035	−0·037	−0·054	−0·063	−0·027	−0·026	0·887	−0·034	0·025
Syncope																										
Subject 1	−0·166	0·407	0·420	0·420	−0·497	−0·071	−0·219	−0·543	0·387	−0·015	−0·376	−0·062	−0·059	−0·763	0·313	0·076	−2·829	−1·319	−1·400	−2·272	−2·819	−0·973	−0·907	3·803	−1·235	0·149
Subject 12	−0·170	0·350	0·342	0·342	−0·563	−0·070	−0·211	−0·609	0·450	−0·015	−0·420	−0·070	−0·070	−0·850	0·342	0·084	−3·046	−1·446	−1·537	−2·463	−3·037	−1·074	−1·004	4·636	−1·359	0·132
Subject 11	−0·302	0·536	0·532	0·532	−0·182	−0·280	−0·053	−0·186	0·150	0·009	−0·124	−0·018	−0·018	−0·257	0·106	0·031	−0·889	−0·432	−0·459	−0·725	−0·889	−0·324	−0·302	8·579	−0·410	0·529
Subject 1	−0·009	0·023	0·023	0·023	0·026	−0·005	−0·016	−0·040	0·029	−0·001	−0·028	−0·005	−0·004	−0·056	0·024	0·006	−0·198	−0·096	−0·101	−0·161	−0·198	−0·071	−0·066	0·315	−0·090	0·005
Subject 12	−0·009	0·020	0·019	0·019	0·022	−0·005	−0·016	−0·045	0·034	−0·001	−0·031	−0·005	−0·005	−0·063	0·026	0·006	−0·213	−0·105	−0·111	−0·175	−0·213	−0·079	−0·074	0·388	−0·099	0·004
Subject 11	−0·019	0·035	0·035	0·035	0·053	−0·021	−0·004	−0·014	0·011	0·001	−0·009	−0·001	−0·001	−0·019	0·008	0·002	−0·065	−0·032	−0·034	−0·053	−0·065	−0·024	−0·022	0·781	−0·030	0·034

HUT, head-up tilt; LBNP, lower body negative pressure.

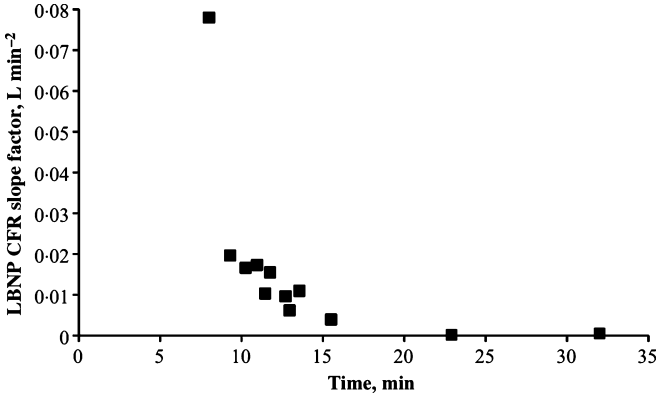

Figure 4 Capillary filtration rate slopes during lower body negative pressure vs. simulation stand times for each subject.

Table 3 Variations in total peripheral resistance (TPR) responses of four subjects with similar simulation stand times

Parameter	Units	Subject 2	Subject 6	Subject 12	Subject 13
Initial TPR	mmHg L^{-1} min^{-1}	15·35	18·99	12·68	8·31
Final TPR	mmHg L^{-1} min^{-1}	10·65	12·21	12·03	9·89
Actual stand time	min	12·02	11·57	11·86	11·98

approached, in general, both cardiac output and arterial pressure showed only an average sensitivity to arterial resistance, with sensitivity to total blood volume always an order of magnitude higher.

Mean arterial pressure

Mean arterial pressure for subject 23 dropped only 4 mmHg during the last three minutes of orthostatic stress and remained above 95 mmHg at the end of the test (Fig. 3). For several other subjects, however, pressure drops over this time exceeded 50 mmHg, with final pressures below 50 mmHg. This range of responses shows that low/decreasing mean arterial pressure is important, but is not the key parameter for all manifestations of presyncope. The average for all 25 subjects of mean arterial pressure at test termination was 10 mmHg higher than the simulated mean arterial pressures at syncope (Fig. 3), perhaps indicating that the many varied symptoms of presyncope arise from haemodynamic responses that are preliminary to the loss of adequate brain perfusion. Only one of the 25 subjects progressed fully to syncope at test termination. Figure 2 further reinforces the difference between the syncope threshold used in the model and the presyncope criteria used in the experiments, in that simulated times to syncope were generally greater than measured times to presyncope, by up to 7·5 min for subject 1. Yet the times to presyncope are statistically similar to the times to syncope, suggesting a common mechanism, and that syncope may be eminent soon after presyncope. Capillary filtration may be the common mechanism underlying both test termination conditions. Dizziness and loss of vision are classic symptoms of reduced brain perfusion, while the causes of sweating, nausea and stomach awareness are less certain. Investigation of the mechanisms of these other symptoms of presyncope may lead to improvements in the model, particularly in matching terminal mean arterial pressure.

Other observations

While caudal compliances are often thought to have a strong role in producing postflight orthostatic intolerance [1,4], lower body venous compliance factors C_{calf}, C_{thigh} and a_{caud} were consistently among the five least sensitive parameters for each subject at each condition, indicating that their roles may be minor.

Finally, during all simulations, there was a fairly consistent decrease in the blood volumes of all compartments except the calf and thigh. The venous blood volumes of those compartments remained relatively constant over time, or showed modest increases each time a higher level of LBNP was applied, confirming that blood does pool in the veins of the legs, at least on the basis of their fraction of total circulating volume. This response exacerbates blood volume decreases in other regions of the body and represents a mechanism by which LBNP increases orthostatic stress and decreases stand times.

Limitations

Because only initial and final values for cardiovascular and haematocrit data were known, a number of modelling assumptions had to be made to estimate how those parameters changed with time. While linear increases in heart rate and stroke volume were valid based on time course data for Person I in the study by Goswami *et al.* [13], Person J in the same study had a large drop in stroke volume before a linear decrease took place, showing that a strictly linear model may not be accurate for every individual. The linear change in total peripheral resistance for individuals may also be over simplified. For instance, during the same GOS routine in the Goswami *et al.* study [13], the drop in total peripheral resistance occurred fairly quickly when syncope was imminent. The instantaneous capillary filtration rate for an individual may also differ from the linearly increasing function as modelled. Improved modelling of all of these parameters could be incorporated if more continuously monitored cardiovascular and haematocrit data were available. The use of only cerebral arterial pressure to determine the occurrence of syncope is also a limitation of this model, as individuals suffering from orthostatic intolerance often present presyncopal symptoms in a number of other ways. This model

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does not account for any of the complex chemical and hormonal changes that occur during orthostatic stress, which is an area of current research [20].

To the extent that differences have long been recognized between biomechanical forces and adaptations in spaceflight vs. ground-based HUT/LBNP tests, these results may not be representative of the physiological state of astronauts returning from space. Further, the model may not be appropriate for other subject populations, such as the elderly or for disease states, for which a number of other potential aetiologies have been identified for orthostatic intolerance.

Conclusions

The results demonstrate the feasibility of simulating subject-specific cardiovascular responses to orthostatic stress. This capability may be useful in identifying parameters that cause susceptibility to orthostatic intolerance, so that such individuals can be targeted for treatment. This modelling may also provide insights into the mechanisms of orthostatic intolerance, which may also be subject-specific, and for which countermeasures may be most effective if applied on an individual basis.

The results of this study of nonastronauts subjected to combined HUT and LBNP support the same hypothesis as previous modelling of astronauts in stand tests on Earth [5] and on a centrifuge [6] that capillary filtration is an important mechanism in the onset of orthostatic intolerance. To validate this mechanism, further experimental studies are needed to quantify total blood volumes throughout the course of testing, and especially to provide measurements of capillary filtration rates in astronauts. Additional studies should focus on determining whether finishers of postflight stand tests, and individuals with above average tolerance times during other forms of orthostatic stress, have special adaptations or mechanisms that limit capillary filtration rates.

Conflicts of interest

None.

Address

Department of Mechanical Engineering, University of Louisville, 200 Sackett Hall, Louisville, KY 20299, USA (K.E. Etter, M. K. Sharp); Institute of Physiology, Harrachgasse 21/5, Medical University of Graz, 8010 Graz, Austria (N. Goswami).
Correspondence to: Nandu Goswami, Institute of Physiology, Harrachgasse 21/5, Medical University of Graz, 8010 Graz, Austria. Tel.: +43 316 3804278; fax: +43 316 380-96 30; e-mail: Nandu.goswami@medunigraz.at

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