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Simulated Stand Tests and Centrifuge Training to Prevent Orthostatic Intolerance on Earth, Moon, and Mars

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Abstract—One proposed method to overcome postflight orthostatic intolerance is for astronauts to undergo inflight centrifugation. Cardiovascular responses were compared between centrifuge and gravitational conditions using a seven-compartment cardiovascular model. Vascular resistance, heart rate, and stroke volume values were adopted from literature, while compartmental volumes and compliances were derived from impedance plethysmography of subjects ($n = 8$) riding on a centrifuge. Three different models were developed to represent the typical male subject who completed a 10-min postflight stand test ("male finisher"), "non-finishing male" and "female" (all non-finishers). A sensitivity analysis found that both cardiac output and arterial pressure were most sensitive to total blood volume. Simulated stand tests showed that female astronauts were more susceptible to orthostatic intolerance due to lower initial blood pressure and higher pressure threshold for presyncope. Rates of blood volume loss by capillary filtration were found to be equivalent in female and male non-finishers, but four times smaller in male finishers. For equivalent times to presyncope during centrifugation as those during constant gravity, lower G forces at the level of the heart were required. Centrifuge G levels to match other cardiovascular parameters varied depending on the parameter, centrifuge arm length, and the gravity level being matched.

Keywords—Spaceflight, Syncope, Stand test, Centrifuge, Gender.

INTRODUCTION

Adaptations to spaceflight cause de-conditioning of the cardiovascular system, creating negative side effects upon return to a gravitational environment, including postflight orthostatic intolerance (POI).[1,2,5,9,15,16] POI limits an astronaut's ability to perform physical tasks during landing and the immediate postflight period.

In one study, 100% of women and 20% of men could not finish a 10 min postflight stand test, with an average time to presyncope of about 6 min.[18] It is reasonable to expect that if POI occurs in environments with lower gravitational acceleration, such as the moon or Mars, that the time to presyncope might be much longer. Such a long time delay is potentially problematic because the astronaut may be otherwise asymptomatic and performing a number of different tasks when presyncope ensues. To avoid potentially catastrophic accidents and injuries in these extreme environments, investigation of the underlying causes of POI is warranted.

In landing day stand tests of astronauts, non-finishing males were noted to have an inability to raise their total peripheral resistance (TPR) during standing.[8] On the other hand, women (all non-finishing) were shown to have the ability to increase their TPR from supine to standing by margins even larger than most male finishers, but had lower pretest TPR and blood pressure, as well as a higher arterial pressure threshold at which presyncope occurred.[18] This comparison suggests that while an increase in TPR may be necessary to maintain arterial pressure and prevent presyncope, it may be insufficient if pretest arterial pressure is too near to its presyncopal threshold.

Broskey and Sharp[2] used a computer model of the cardiovascular system to find that, while a number of factors may influence maintenance of arterial pressure high enough to preclude presyncope, the rate of loss of circulating blood volume by capillary filtration is one of the few factors that can explain the gradual decline in arterial pressure during stand tests. Supported by a documented increase in postflight capillary transport in the leg of a Gemini astronaut,[4] the authors hypothesize that finishers and non-finishers may be differentiated by their postflight rates of capillary filtration. Increased capillary filtration may be an

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adaptation to chronically decreased capillary transmural pressure in the caudal region during weightlessness. The capillaries may adjust to this lower pressure by increasing transcapillary hydraulic conductivity to maintain transcapillary flow. Upon return to Earth, this same hydraulic conductivity yields higher flow in response to the added hydrostatic pressure in the caudal region in standing posture. Investigation of the relative importance of this and the many other factors affecting POI is one objective of this study.

Fluid loading,[19] exercise and lower body negative pressure,[17] and midodrine[14] have been shown to be inconsistently effective as countermeasures for orthostatic intolerance. Anti-G suits, which constitute the only reliable countermeasure currently available[12] are heavy and uncomfortable for long-term wear by all crew members. An attractive alternative is centrifuge training, which imposes an artificial orthostatic stress on the body that might prevent cardiovascular de-conditioning in the first place, rather than counteract it. However, unlike the nearly constant gravity found on the surface of a planet or moon, a centrifuge of limited radius suitable for spaceflight creates a varying acceleration that scales with the square of the radial distance from its center of rotation. Therefore, determining the appropriate centrifuge speed to model and train for a specific constant gravity condition is the second objective of this investigation.

METHODS

Model Development

The model consists of seven compartments that represent the heart/lung and systemic arteries as well as the cephalic, thorax, abdomen, thigh, and calf venous segments. The compliances of the arterial compartments were constant, while the five venous compartments were assigned continuous compliance functions matched to experimental volume shift data obtained via impedance plethysmography of subjects ($n = 8$) riding on a centrifuge.[6] Cardiac performance was modeled with a Starling-like function. The model incorporated 35 independent parameters, including factors characterizing cardiac performance, variable posture dependent vascular resistance, intrathoracic pressure, heart rate, nonlinear and continuous venous compliance, and circulating blood volume, and 17 dependent parameters, including cardiac output and cardiac and vascular compartment pressures and volumes.

The model was adapted from that of Broskey and Sharp,[2] which was previously adapted from an original model developed by White and Blomqvist.[20] The most notable differences between the present model and the original are features mimicking the physiologic effects of orthostatic stress with posture change, including compliant venous compartments responsive to hydrostatic pressure. In the current model, venous compliance was modeled with a more physiologic continuous hyperbolic secant function, compared to the discontinuous segmented function used in the model of Broskey and Sharp. The model also differs from that of Broskey and Sharp in its inclusion of centrifugal forces to determine pressures within the vasculature, as well as variable TPR, heart rate, and stroke volume that varied as functions of posture, centrifugal acceleration, and time. Intrathoracic pressure changes in response to both posture and centrifugal acceleration were also included.

Finally, three unique sets of model parameter values were developed to represent astronauts in three classes: male finishers of postflight stand tests, male non-finishers and females (all non-finishers). The differences in modeled male and female cardiovascular systems, which were represented by differences in total blood volume, compartment heights, compliance magnitudes and distribution, TPR, heart rate and stroke volume, will be further specified in this section.

The current model retains the Starling-like function originally devised by White and Blomqvist[20] to determine the cardiac flow rate

$$F_2(P_1) = \frac{SK}{1 + \alpha \exp[-\beta(P_1 - P_e)]} \tag{1}$$

where P_1 is the pressure of the heart and lung compartment, S is the effectiveness of the heart pumping (which is set to $S = 1$ for this investigation, but $S < 1$ could be used to model aged or diseased cardiac muscle, incompetent valves and arrhythmia or cardiac atrophy due to spaceflight), α and β are both cardiac output coefficients, P_e is the intrapleural or extracardiac pressure (which impacts diastolic filling[11]), and K is the maximum achievable flow rate of the heart for a given operating condition

$$K = \mathrm{HR} \cdot \mathrm{SV}[C_{K1} + C_{K2} \cdot G] \tag{2}$$

where SV is stroke volume and HR is heart rate, both taken as a function of non-dimensional gravity, G, and C_{K1} and C_{K2} are astronaut-dependent constants.

Heart rates for each of the three modeled astronauts were taken from Waters *et al.*[18] The heart rate for each subject varied in the centrifuge or standing states

$$\mathrm{HR} = \mathrm{HR}_0 + G(\mathrm{HR}_t \cdot t + C_{\mathrm{HR}}) \tag{3}$$

where HR_0 is the leading initial heart rate term, HR_t represents the rate of change with time, and C_{HR} is the secondary initial heart rate constant associated with gravity. In the supine posture, the heart rates remained constant at 61.6, 67, and 64.9 beats per min for the finishing male, non-finishing male, and female, respectively.

Similarly, the stroke volume was also modeled with data from Waters *et al.*[18] The stroke volume varied according to gravitational level and was specific to each astronaut

$$\mathrm{SV} = \mathrm{SV}_0 + \mathrm{SV}_G \cdot G \tag{4}$$

where SV_0 is the leading initial stroke volume term and SV_G is the secondary volume constant associated with gravity. In the supine posture, stroke volume remained constant at 77.2, 79.2, and 77.2 mL for the finishing male, non-finishing male, and female, respectively.

The compliance of each venous compartment was given by

$$C_\mathrm{i} = C_{\mathrm{i},0}\left[N + (1-N)\,\mathrm{sec}\,h\left(A_\mathrm{i}\left(P_\mathrm{ig} - 4\right)\right)\right] \tag{5}$$

where $C_{\mathrm{i},0}$ is the peak compliance of compartment i, P_ig is the transmural pressure of the compartment with gravity, A_i is a parameter controlling the steepness of the compliance curve, and N is the ratio of asymptotic to peak compliance. Venous compliance magnitude and distribution was determined from compartmental volume shifts measured in male subjects undergoing variable radius and Gz level stresses on the NASA Ames centrifuge.[6] $C_{\mathrm{i},0}$ and A_i values for each venous compartment were found iteratively by matching these volume shifts, using calculated hydrostatic pressures for each compartment for supine and centrifuge conditions. N was set based on matching caudal volume shifts, which occur over large pressure changes, forcing the hyperbolic secant function to its asymptotic range. Compliance magnitude for the female astronauts was modeled by scaling $C_{\mathrm{i},0}$ with average female/male ratios of body compartment size calculated from Army and Navy measurements,[10] while A_i and N remained the same as for males.

Venous compartment heights were also scaled between female and males by average heights measured among Army and Navy personnel.[10] The values are shown in the model parameters table.

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

$$V_\mathrm{i} - V_{\mathrm{i},0} = \int_{P_0}^{P_\mathrm{ig}} C_\mathrm{i}\, dP_\mathrm{ig} \tag{6}$$

where V_i is the volume of each compartment i at the current pressure, $V_{\mathrm{i},0}$ and P_0 are the initial volume and pressure, respectively. In addition, total volume is conserved

$$V_\mathrm{blood} = \sum V_\mathrm{i} \tag{7}$$

where V_blood is the total blood volume. To calculate V_blood for each astronaut the total blood volume for the average male was scaled by the ratio of average weights between male and female Army and Navy personnel.[10] The blood volumes used were 5.0 and 4.50 L for male and female astronauts, respectively.

The vasculature flow is modeled as viscous

$$\frac{P_2 - P_3}{R_\mathrm{a}} = Q = F_1(P_1) = \frac{P_3 - P_1}{R_\mathrm{v}} \tag{8}$$

where P_1, P_2, and P_3 are pressures within the heart/lung compartment and the arterial and venous compartments at heart level, respectively, R_a is the arterial resistance and R_v is the venous resistance. However, when the pressure of the heart and lung compartment drops below the pressure of partial collapse, venous flow rate becomes

$$Q = F_1(P_1) = \frac{P_3 - P_\mathrm{c}}{R_\mathrm{v}} \quad \text{for} \quad P_1 < P_\mathrm{c} \tag{9}$$

where P_c is the pressure of partial collapse.

Simple functions were developed to model the changes in TPR measured during stand tests on earth.[3,18] The functions matched measured TPR in initial and final (end of stand test for finishers and time of presyncope for non-finishers) standing posture, with a linear increase with time during standing. Venous resistance, R_v, for all subjects was constant at 0.8 mmHg/L/min, while arterial resistances varied according to

$$R_\mathrm{a} = R_0 + G(R_\mathrm{t} \cdot t + C_\mathrm{R}) \tag{10}$$

where R_0 represents the majority of the initial arterial resistance, R_t is the arterial resistance rate of change with time, and C_R is a constant associated with gravity that accounts for the remainder of the initial arterial resistance. For supine posture, R_a was fixed at 23.84, 20.89, and 16.07 mmHg/L/min for the male finisher, male non-finisher, and female, respectively.

The system flow rate is the solution of (1) and (8)

$$F_1(P_1) = F_2(P_1) \tag{11}$$

which describes the intersection of the cardiac and vascular flow curves.

Sensitivity Study

The sensitivity of arterial pressure and cardiac output to system parameters was determined by White and Blomqvist[20]

$$\mathrm{Sen}(f, z) = \left(\frac{\partial \log f}{\partial \log z}\right)_0 \tag{12}$$

where f and z represent any combination of dependant to independent parameters, respectively. The subscript

Model parameters.

Parameter	Reference values				Units	Definition
	Group	Male finisher	Male non-finisher	Female non-finisher		
Independent Parameters						
t					min	Time into simulated stand test
α	7.809					Cardiac output coefficient
β	0.381				mmHg^{-1}	Cardiac output coefficient
P_e	−4				mmHg	Extracardiac (intrapleural) pressure, 0G: −4.1, 1Gsup: −2.5, 1Gstand: −6.3[13]
S	1					Effectiveness of heart pumping
K	Eq. (2)				L/min	Maximum value of F_2 when $S = 1$
C_{K1}		1.9372	1.2694	0.8172		Maximum heart pumping rate constant
C_{K2}		0.9352	5.9306	8.8257		Maximum heart pumping rate constant associated with gravity
HR	Eq. (3)				beats/min	Heart rate
HR_0	72				beats/min	Leading term for initial heart rate at beginning of stand test
HR_t		0	4.29	8.48	beats/min^2	Heart rate constant associated with gravity and time
C_{HR}		16	−5	−7	beats/min	Secondary heart rate constant associated with gravity
SV	Eq. (4)				mL	Cardiac stroke volume
SV_0		64.35	64.33	64.35	mL	Initial cardiac stroke volume
SV_G		−31.09	−30.85	−35.94	mL	Stroke volume constant associated with gravity
C_1	0.012				L/mmHg	Compliance of heart/lung compartment
C_2	0.00355				L/mmHg	Compliance of arterial compartment
C_{ceph}	Eq. (5)				L/mmHg	Compliance of partially inflated cephalic venous compartment
$C_{ceph,0}$		0.0629	0.06293	0.04855	L/mmHg	Maximum compliance of cephalic venous compartment
$A_{ceph,high}$	0.40026					Compliance steepness factor for cephalic veins for high pressure
$A_{ceph,low}$	0.26684					Compliance steepness factor for cephalic veins for low pressure
C_{thorax}	Eq. (5)				L/mmHg	Compliance of partially inflated thoracic venous compartment
$C_{thorax,0}$		0.1715	0.17147	0.13792	L/mmHg	Maximum compliance factor for thoracic venous compartment
C_{abs}	Eq. (5)				L/mmHg	Compliance of partially inflated abdominal venous compartment
$C_{abs,0}$		0.0912	0.09115	0.07105	L/mmHg	Maximum compliance factor for abs venous compartment
$A_{centr,high}$	0.29352					Compliance steepness factor for central veins for high pressure
$A_{centr,low}$	0.26400					Compliance steepness factor for central veins for low pressure
C_{thigh}	Eq. (5)				L/mmHg	Compliance of partially inflated veins of thigh venous compartment
$C_{thigh,0}$		0.0133	0.01332	0.01144	L/mmHg	Maximum compliance of thigh venous compartment
C_{calf}	Eq. (5)				L/mmHg	Compliance of partially inflated veins of the calf venous compartment
$C_{calf,0}$		0.0106	0.01055	0.00871	L/mmHg	Maximum compliance of calf venous compartment
$A_{caud,high}$	0.29352					Compliance steepness factor for caudal veins for high pressure
$A_{caud,low}$	0.26400					Compliance steepness factor for caudal veins for low pressure
N	0.01					Ratio of asymptotic to peak compliance
P_c	−2				mmHg	Pressure of venous collapse in heart/lung compartment $= P_e + 2$ mmHg

Model parameters. Continued.

	Reference values					
Parameter	Group	Male finisher	Male non-finisher	Female non-finisher	Units	Definition
R_v	0.8				mmHg/L/min	Venous resistance
R_a	Eq. (10)				mmHg/L/min	Arterial resistance
R_0		17.7	17.7	16.7	mmHg/L/min	Leading term for initial arterial resistance at beginning of stand test
R_t		0.9432	1.25	2.941	mmHg/L	Rate of change of arterial resistance with time
C_R		5.3	1	-0.7	mmHg/L/min	Secondary initial arterial resistance constant
V_{10}^*	0.852				L	Component of V_{10} independent of P_e
V_{10}		0.8491	0.8491	0.7642	L	Unstressed volume of blood in heart/lung compartment $= V_{10}^* - C_1 P_e$
V_{20}		0.4009	0.4009	0.3608	L	Unstressed volume in arterial compartment
V_{ceph0}		0.4245	0.4245	0.3821	L	Unstressed volume in cephalic veins
V_{thorax0}		0.6604	0.6604	0.5943	L	Unstressed volume in thoracic veins
V_{abs0}		0.8019	0.8019	0.7217	L	Unstressed volume in abdominal veins
V_{thigh0}		0.3019	0.3019	0.2717	L	Unstressed volume in veins of the thighs
V_{calf0}		0.2830	0.2830	0.2547	L	Unstressed volume in veins of the calves
V_{blood}		5.0	5.0	4.5	L	Total blood volume $= V_{\text{blood0}} + V_1 + V_2 + V_{\text{ceph}} + V_{\text{thorax}} + V_{\text{abdominal}} + V_{\text{thigh}} + V_{\text{calf}}$
V_{blood0}	0.4				L	Unstressed blood volume in non-capacitive regions
H_1	-3.5				cm	Height of heart/lung region above right atrium (RA)
H_2	0				cm	Height of arterial region above RA
H_{ceph}		29.7	29.7	27.2	cm	Height of cephalic region above RA
H_{thorax}	0				cm	Height of thoracic region above RA
H_{abs}		-27	-27	-24.7	cm	Height of abdominal region above RA
H_{thigh}		-60.2	-60.2	-55	cm	Height of thigh region above RA
H_{calf}		-109.4	-109.4	-100	cm	Height of calf region above RA
Dependent parameters						
Q	5				L/min	Cardiac flow rate, found by iteration where $F_1 = F_2$
P_1	0				mmHg	Pressure within heart/lung compartment, found by iteration where $F_1 = F_2$
P_2	100				mmHg	Pressure within arterial compartment $= P_1 + Q^*(R_a + R_v)$
P_{2g}	100				mmHg	Arterial pressure with gravity
P_3	4				mmHg	Combined venous pressure
$P_{\text{ceph g}}$	4				mmHg	Cephalic venous pressure with gravity
$P_{\text{thorax g}}$	4				mmHg	Thoracic venous pressure with gravity
$P_{\text{abs g}}$	4				mmHg	Abdominal venous pressure with gravity
$P_{\text{thigh g}}$	4				mmHg	Venous pressure of thigh with gravity
$P_{\text{calf g}}$	4				mmHg	Venous pressure of calf with gravity
V_1		0.8491	0.8491	0.7642	L	Volume of blood in heart/lung compartment
V_2		0.4009	0.4009	0.3608	L	Volume of blood in arterial compartment
V_{ceph}		0.4245	0.4245	0.3821	L	Volume of blood in cephalic venous compartment
V_{thorax}		0.6604	0.6604	0.5943	L	Volume of blood in thoracic venous compartment
V_{abs}		0.8019	0.8019	0.7217	L	Volume of blood in abdominal venous compartment
V_{thigh}		0.3019	0.3019	0.2717	L	Volume of blood in venous compartment of thighs
V_{calf}		0.2830	0.2830	0.2547	L	Volume of blood in venous compartment of calves

TABLE 1. Various astronaut sensitivity values for cardiac output Q (upper table) and arterial pressure P_{2g} (lower table) for the independent parameters in the model for differing postures and gravities.

Male, finisher

	α	β	S or K	R_{a}	R_{v}	C_1	C_2	C_{ceph}	C_{chest}	C_{abs}	C_{thigh}	C_{calf}
0G	−0.470	1.012	0.996	−0.004	0.000	0.000	−0.004	0.000	−0.004	0.000	0.000	0.000
1G sup	−0.606	0.509	0.524	−0.476	0.000	0.000	−0.476	0.000	−0.476	0.000	0.000	0.000
1G stand	−0.113	0.613	0.586	−0.414	0.000	−0.004	−0.414	0.398	0.402	−0.836	−0.004	−0.004
1G stand—100 mL	−0.145	0.381	0.468	−0.532	0.000	−0.005	−0.532	0.509	1.016	−1.076	−0.011	−0.011
0G	−0.050	0.111	0.109	0.104	0.005	0.000	0.000	0.000	0.000	0.000	0.000	0.000
1G sup	−0.064	0.053	0.055	0.050	0.004	0.000	−0.053	0.000	−0.053	0.000	0.000	0.000
1G stand	−0.010	0.068	0.065	0.061	0.004	−0.001	−0.049	0.048	0.049	−0.098	−0.001	−0.001
1G stand—100 mL	−0.014	0.040	0.050	0.047	0.003	−0.001	−0.061	0.060	0.120	−0.122	−0.001	−0.001

	A_{ceph}	A_{cent}	A_{caud}	V_{10star}	V_{20}	V_{ceph0}	V_{chest0}	V_{abs0}	V_{thigh0}	V_{calf0}	V_{blood}	P_{e}
0G	0.000	0.000	0.000	−0.370	−0.004	−0.004	−0.370	−0.370	−0.004	−0.004	**2.064**	0.724
1G sup	0.000	0.000	0.000	−0.481	−0.476	−0.476	−0.481	−0.481	−0.476	−0.476	**2.735**	0.118
1G stand	−0.410	0.398	0.398	−1.257	−0.414	−0.418	−0.832	−1.252	−0.410	−0.410	**6.093**	0.449
1G stand–100 ml	−0.532	0.000	0.509	−1.604	−0.537	−0.537	−1.070	−1.598	−0.532	−0.526	**7.841**	0.574
0G	0.000	0.000	0.000	−0.042	0.000	0.000	−0.042	−0.042	0.000	0.000	**0.245**	0.079
1G sup	0.000	0.000	0.000	−0.054	−0.053	−0.053	−0.054	−0.054	−0.053	−0.053	**0.327**	0.010
1G stand	−0.049	0.048	0.048	−0.147	−0.049	−0.050	−0.098	−0.146	−0.049	−0.049	**0.834**	0.047
1G stand–100 ml	−0.061	0.000	0.060	−0.180	−0.061	−0.061	−0.121	−0.179	−0.061	−0.060	**1.074**	0.060

Male, non-finisher

	α	β	S or K	R_{a}	R_{v}	C_1	C_2	C_{ceph}	C_{chest}	C_{abs}	C_{thigh}	C_{calf}
0G	−0.470	1.012	0.996	−0.004	0.000	0.000	−0.004	0.000	−0.004	0.000	0.000	0.000
1G sup	−0.606	0.509	0.524	−0.476	0.000	−0.476	0.000	0.000	0.000	0.000	0.000	0.000
1G stand	−0.151	0.321	0.448	−0.552	0.000	−0.006	−0.552	0.528	0.539	−1.116	−0.011	−0.011
1G stand—280 mL	−0.198	−0.183	0.285	−0.715	0.000	0.000	−0.715	0.705	1.415	−2.161	−0.708	−0.700
0G	−0.050	0.111	0.109	0.104	0.005	0.000	0.000	0.000	0.000	0.000	0.000	0.000
1G sup	−0.063	0.052	0.054	0.049	0.005	0.000	0.052	0.000	0.000	0.000	0.000	0.000
1G stand	−0.015	0.035	0.050	0.045	0.005	−0.001	0.065	0.064	0.065	−0.131	−0.001	−0.001
1G stand—280 mL	−0.015	−0.014	0.022	0.020	0.002	0.000	−0.054	0.055	0.113	−0.159	−0.054	−0.053

	A_{ceph}	A_{cent}	A_{caud}	V_{10star}	V_{20}	V_{ceph0}	V_{chest0}	V_{abs0}	V_{thigh0}	V_{calf0}	V_{blood}	P_{e}
0G	0.000	0.000	0.000	−0.370	−0.004	−0.004	−0.370	−0.370	−0.004	−0.004	**2.064**	0.724
1G sup	0.000	0.005	0.000	−0.481	−0.476	−0.476	−0.476	−0.481	−0.476	0.000	**2.735**	0.586
1G stand	−0.546	0.000	0.528	−1.657	−0.557	−0.557	−1.104	−1.116	−0.546	−0.546	**7.789**	0.597
1G stand—280 mL	−0.723	−1.418	0.015	−2.876	−1.433	−1.433	−2.154	−2.869	−1.418	−0.723	**11.702**	0.796
0G	0.000	0.000	0.000	−0.042	0.000	0.000	−0.042	−0.042	0.000	0.000	**0.245**	0.079
1G sup	0.000	0.001	0.000	−0.053	−0.052	−0.052	−0.052	−0.053	0.052	0.000	**0.322**	0.063
1G stand	−0.065	0.000	0.064	−0.192	−0.066	−0.066	−0.129	−0.131	−0.065	−0.065	**1.102**	0.065
1G stand—280 mL	−0.055	−0.106	0.001	−0.208	−0.107	−0.107	−0.158	−0.207	−0.106	−0.055	**1.181**	0.055

Female, non-finisher

	α	β	S or K	R_{a}	R_{v}	C_1	C_2	C_{ceph}	C_{chest}	C_{abs}	C_{thigh}	C_{calf}
0G	−0.499	1.021	0.996	−0.004	0.000	0.000	−0.004	0.000	0.000	0.000	0.000	0.000
1G sup	−0.629	0.971	0.995	−0.005	0.000	0.000	−0.005	0.000	0.000	0.000	0.000	0.000
1G stand	−0.155	0.274	0.435	−0.565	−0.006	−0.006	−0.565	0.541	0.552	−1.135	−0.012	−0.012
1G stand—160 mL	−0.197	−0.111	0.290	−0.710	0.000	0.000	−0.710	0.015	0.715	−1.430	−0.695	−0.007
0G	−0.048	0.101	0.098	0.094	0.005	0.000	0.000	0.000	0.000	0.000	0.000	0.000
1G sup	−0.060	0.095	0.098	0.093	0.005	0.000	−0.001	0.000	0.000	0.000	0.000	0.000
1G stand	−0.014	0.026	0.044	0.039	0.004	−0.001	−0.061	0.060	0.061	−0.121	−0.001	−0.001
1G stand—160 mL	−0.019	−0.011	0.028	0.025	0.003	0.000	−0.066	0.001	0.069	−0.131	−0.065	−0.001

TABLE 1. Continued.

	A_{ceph}	A_{cent}	A_{caud}	V_{10star}	V_{20}	V_{ceph0}	V_{chest0}	V_{abs0}	V_{thigh0}	V_{calf0}	V_{blood}	P_{e}
0G	0.000	0.000	0.000	−0.393	−0.004	−0.004	−0.393	−0.393	−0.004	−0.004	**2.535**	0.770
1G sup	0.000	0.000	0.000	−0.496	−0.005	−0.005	−0.496	−0.496	−0.005	−0.005	**3.267**	0.603
1G stand	−0.559	−0.012	0.541	−1.707	−0.570	−0.571	−1.135	−1.695	−0.565	−0.565	**8.454**	0.611
1G stand—160 mL	−0.710	−0.717	0.015	−2.849	−1.415	−1.415	−2.131	−2.138	−0.717	−0.710	**10.272**	0.790
0G	0.000	0.000	0.000	−0.040	0.000	0.000	−0.040	−0.040	0.000	0.000	**0.276**	0.076
1G sup	0.000	0.000	0.000	−0.050	−0.001	−0.001	−0.050	−0.050	−0.001	−0.001	**0.355**	0.059
1G stand	−0.060	−0.001	0.060	−0.180	−0.062	−0.062	−0.121	−0.179	−0.061	−0.061	**1.110**	0.060
1G stand—160 mL	−0.066	−0.067	0.001	−0.254	−0.130	−0.130	−0.193	−0.193	−0.067	−0.066	**1.226**	0.068

Maximum sensitivity for each case is indicated in bold.

zero represents that the calculation is made at a baseline condition. In this study, the derivatives were approximated by finite changes in the parameters. Sensitivity for a 5% change in each independent parameter is reported. For pressure terms, the absolute pressure was used as opposed to the gauge pressure. Cardiovascular sensitivities were determined for a 0G baseline representing astronauts fully adapted to spaceflight, then for conditions mimicking the return of these astronauts to earth, including supine and standing postures. For the standing posture, sensitivities were calculated at the beginning of the stand test, when no volume had been lost from the cardiovascular system, and at the end of the stand test, when the maximum volume loss had occurred for each of the modeled astronauts. For the non-finisher, the end of the stand test represents the state of the cardiovascular system at which presyncope is imminent. However, for the finisher, the end of the stand test represents a condition that may be far from producing presyncope.

Simulated Stand Test

Simulated stand tests were conducted to find the rate of blood volume loss for each of the modeled astronauts that would produce presyncope in the same amount of time (for non-finishers) or result in similar arterial pressure after 10 min of standing (for finishers) as measured in returning astronauts on Earth.[18] Delayed onset of presyncope for the reduced gravity conditions on the moon and Mars was found using a loss rate for each astronaut scaled by the gravity in each location. Cerebral arterial pressure, which was used as an indicator of presyncope (thresholds of 30 mmHg for males and 40 mmHg for females), was found by subtracting the hydrostatic pressure between the heart and brain from the aortic pressure (varying with constant gravity vs. centrifuge acceleration, and with the shorter distance from heart to brain for females). Hematocrit increases from initial values of 45% for males and 42% for females were estimated by assuming the blood volume lost due to capillary filtration was devoid of cells.

Gravitational Equivalence of Centrifugation

Equivalence of artificial gravity on a centrifuge to constant gravity was evaluated with focus on several different parameters. For all tests, the rate of capillary filtration was assumed to be proportional to the geometric mean of the transmural pressures within the venous regions. First, the modeled centrifuge spinning rate was found that produced presyncope in the same time as during actual 1G stand tests. Additional tests were performed with cerebral arterial pressure (CAP), central venous pressure (CVP), aortic pressure (AOP), and cardiac flow rate (Q), each at the end of the standing period on Earth (10 min for finishers and the time to presyncope for non-finishers), as the matching parameter. These tests were repeated to match simulated constant gravity results on Mars and the moon. Centrifuge arm lengths corresponding to the NASA Ames 20G facility—2.55 m from the axis to the short platform and 8.35 m for the long platform.

RESULTS

Sensitivity Study

The sensitivity analysis showed that total blood volume V_{blood} most strongly affected the cardiac flow rate Q as well as arterial pressure $P_{2\text{g}}$ regardless of posture and gravity (Table 1). The next most sensitive parameters for $P_{2\text{g}}$ for all astronauts in microgravity were cardiac performance parameters α, β, S, K, and P_{e} and arterial resistance R_{a}, followed by volumes V_{10}^{*}, V_{chest0}, and V_{abs0}. All other parameters had less than 10% of the sensitivity of V_{blood}. In 1G supine, compliances C_2 and C_{chest} and all volumes became important and P_{e} became unimportant for the male finisher. The same behavior was exhibited for the male non-finisher, except that C_{chest} and V_{calf0} did not become important and P_{e} remained important. In the female, the sensitive parameters in 1G supine remained the same as those for 0G. When all astronauts stood in 1G, the only parameters with sensitivity greater than

10% of V_{blood} were C_{abs}, V_{10}^{*}, V_{chest0}, and V_{abs0}. At the end of the stand test, C_{chest} and C_{abs} and V_{10}^{*}, V_{chest0}, and V_{abs0} were sensitive for the male finisher. For the male non-finisher, C_{abs}, V_{10}^{*}, V_{chest0}, and V_{abs0} sensitivities were greater than 10% of V_{blood}, and C_{chest}, A_{cent}, V_{20}, V_{ceph0}, and V_{thigh0} were nearly so. For the female, C_{abs}, V_{10}^{*}, V_{20}, V_{ceph0}, V_{chest0}, and V_{abs0} sensitivities were greater than 10% of V_{blood}.

Simulated Stand Test

Constant Gravity

For the simulated Earth stand test of male non-finishers, a capillary filtration rate of 40 mL/min (similar to that found by Broskey and Sharp[2]) was required to produce a predicted time to presyncope of about 7 min (with a fluid loss of 300 mL, Fig. 1),

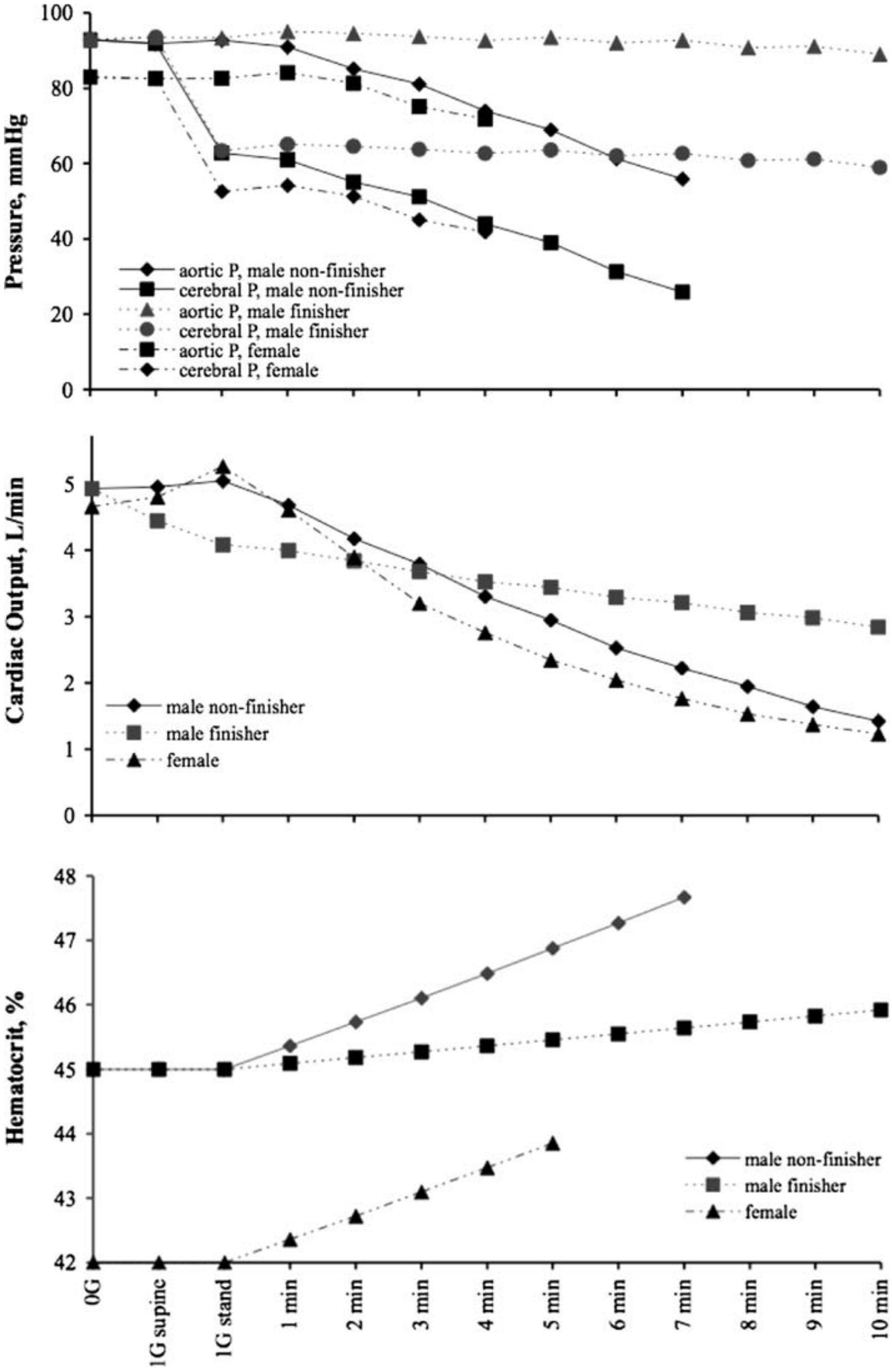

FIGURE 1. Arterial pressure, cardiac output, and hematocrit during simulated stand tests on Earth. Capillary filtration 40 mL/min during standing for non-finishers, 10 mL/min for finishers.

nearly identical to that of non-finishers in actual stand tests of returning astronauts.[3] The same capillary filtration rate caused simulated female non-finishers to become presyncopal in about 4 min with a fluid loss of 160 mL, which concurs with the available data for returning female astronauts.[18] For male finishers, the capillary filtration rate that produced a simulated arterial pressure matching that measured after 10 min of standing was 10 mL/min. These capillary filtration rates were scaled in proportion to gravity, 6.7 and 15 mL/min for non-finishers and 1.67 and 3.75 mL/min for finishers for the moon and Mars simulated stand tests, respectively. The results of these stand tests are shown in Figs. 2 and 3. An accumulated drop in arterial pressure sufficient to compromise cerebral perfusion

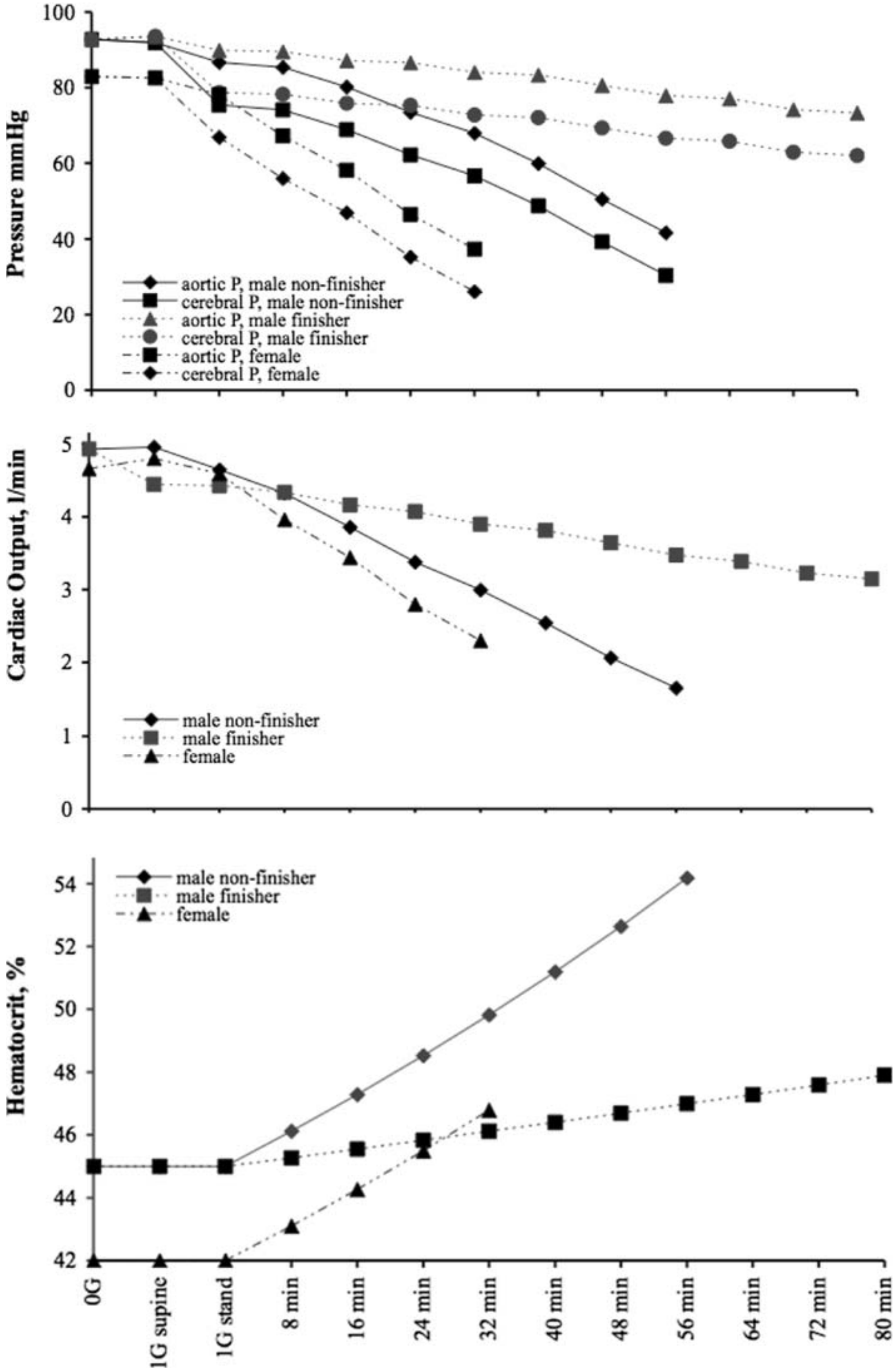

FIGURE 2. **Arterial pressure, cardiac output, and hematocrit during simulated stand test on Mars. Capillary filtration 15 mL/min during standing for non-finishers, 3.75 mL/min for finishers.**

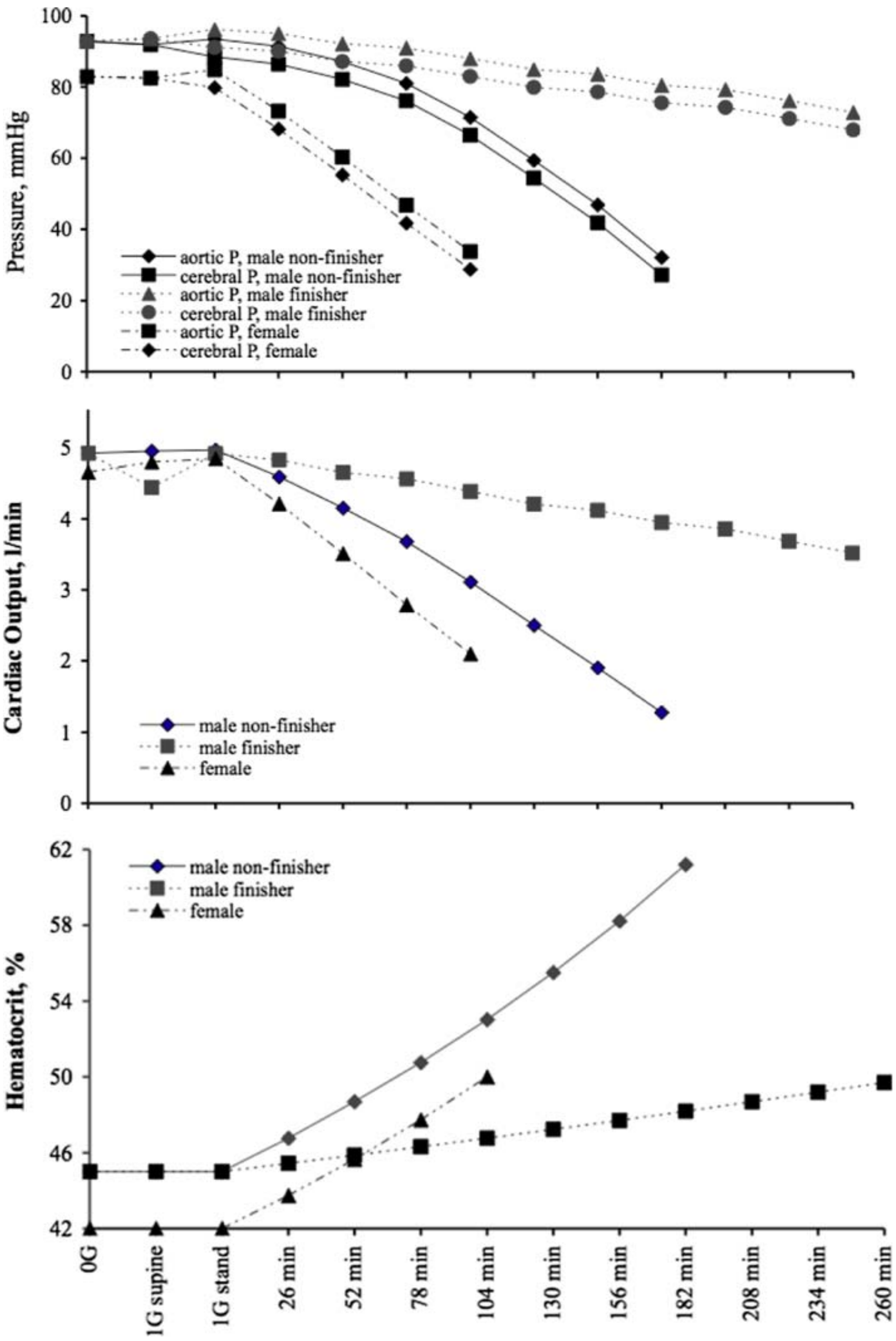

FIGURE 3. Arterial pressure, cardiac output, and hematocrit during simulated stand test on moon. Capillary filtration 6.67 mL/min during standing for non-finishers, 1.67 mL/min for finishers.

and, therefore, cause syncope was reached in male non-finishers in about 182 and 56 min with fluid losses of 1211 and 896 mL, and in female non-finishers in about 104 and 32 min with fluid losses of 692 and 512 mL for the moon and Mars, respectively. Cardiac outputs dropped to roughly 3 L/min for all astronauts during Earth stand tests, to roughly 2 L/min for non-finishers during Mars stand tests and even lower on the moon. Hematocrit rose within normal ranges on Earth, but to abnormal values for non-finishers on the moon and Mars.

Artificial Gravity on a Centrifuge

The centrifugal acceleration at heart level required to match the times to presyncope on the centrifuge to those during standing are given in Table 2. In all cases, the centrifugal acceleration is less than the corresponding constant gravity level. Estimates of centrifugal acceleration at heart level on the male finisher required to produce values of four important cardiovascular parameters (cardiac flow rate *Q*, central venous pressure CVP, cerebral arterial pressure CAP, and aortic pressure AOP) matching those for standing posture (before blood volume loss by capillary filtration) in constant gravity on Earth, moon, and Mars are shown in Fig. 4. For Earth and Mars, centrifuge accelerations greater than the constant gravity values were required to match CAP, but lower accelerations provided matches for CVP, AOP, and *Q*. For the moon, accelerations higher than 1/6 G were required to match all four parameters.

TABLE 2. Male finisher (f), male non-finisher (nf), and female G-loadings at heart level for equivalent times to presyncope on Earth, Mars, and the moon using data collected during studies on NASA Ames' 20 G centrifuge at short (SC, 2.55 m from the axis to the foot platform) and long (LC, 8.35 m) arm lengths, respectively.

	Earth, 1G	Mars, 3/8G	Moon, 1/6G
Male, f, LC	0.89G	0.33G	0.15G
Male, nf, LC	0.83G	0.31G	0.14G
Female, LC	0.72G	0.27G	0.12G
Male, f, SC	0.95G	0.36G	0.16G
Male, nf, SC	0.90G	0.34G	0.15G
Female, SC	0.85G	0.32G	0.14G

DISCUSSION

Sensitivity Study

The sensitivity analysis shows that blood pressure is most sensitive to blood volume, which decreases

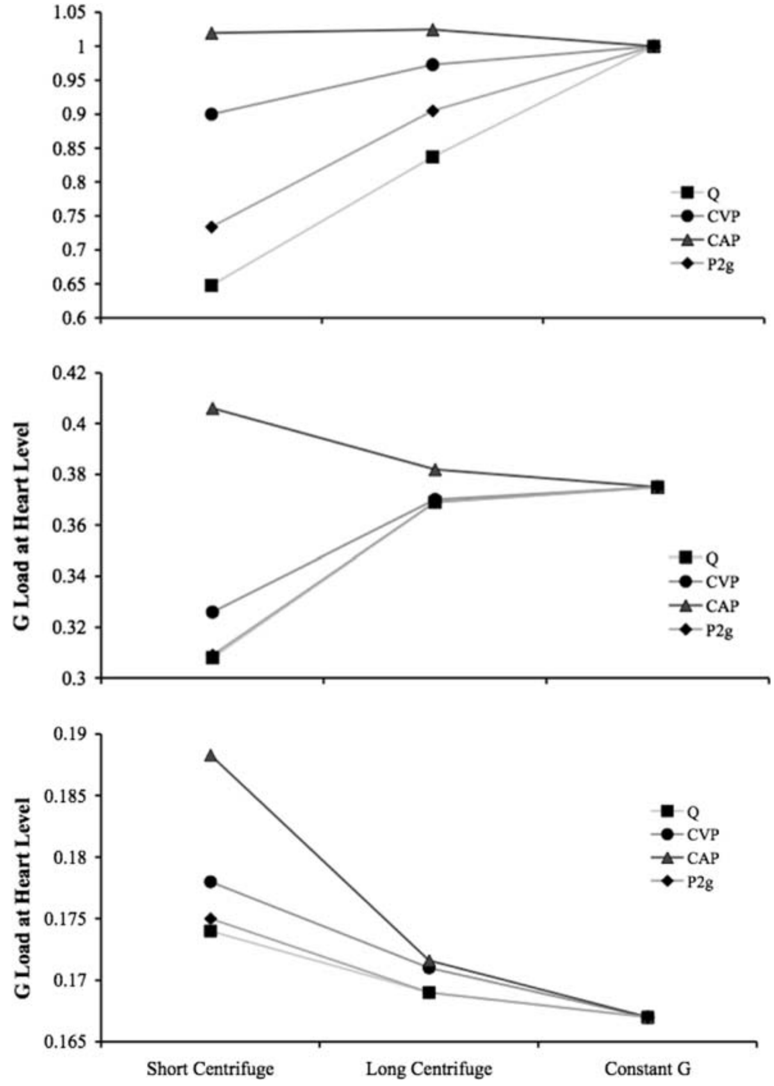

FIGURE 4. Acceleration at heart level for NASA short- and long-arm centrifuge studies required to produce selected cardiovascular parameters at values equivalent to constant gravity on Earth (upper), Mars (middle), and moon (lower).

during standing due to capillary filtration. All other parameters were less sensitive by about an order of magnitude or more. Venous compliance was shown to be more important than peripheral resistance and cardiac pumping parameters, which are subject to autonomic regulation and have been previously investigated for their association with POI. As an improvement over the model of Broskey and Sharp,[2] this model includes autonomic regulation of heart rate, stroke volume, and peripheral resistance in Eqs. (3), (4), and (10), however, the influences of these parameters are shown by the sensitivity study to be minor compared to capillary filtration.

Further, the sensitivity results revealed that central compliances, for which little data is available, were more important than caudal compliances, which were previously thought to have a strong role in producing POI. Note that not only are the caudal compliances smaller than the central compliances at equivalent pressure (see Model Parameters table), but in standing posture the higher pressure in the caudal region causes the actual caudal compliances to be even smaller. Therefore, fractional changes in caudal compliance contribute small volume shifts, which have a small influence on arterial pressure and POI.

Simulated Stand Tests

The simulated 1G stand tests found that a substantial difference in capillary transport rate could explain the differences in orthostatic tolerance between male finishers and non-finishers, which is in agreement with the greater hemoconcentration measured in presyncopal vs. non-presyncopal subjects in tilt and Lower Body Negative Pressure (LBNP) experiments.[7] The simulated stand tests in reduced gravity showed that POI can still occur in these environments, though after much longer standing times. While in this study presyncope was judged by arterial pressure dropping to a threshold, on the moon and Mars, cardiac output dropped to marginal levels and hematocrit increased dramatically. These changes may also cause symptoms of distress, perhaps earlier than the calculated times to presyncope.

Gender Differences

While the simulated dimensions, arterial resistance and distribution of compliance of non-finishing males and females differed slightly, these distinctions had a relatively small influence on time to presyncope compared to their differing thresholds of cerebral arterial pressure for presyncope. In every case, arterial blood pressure was found to be most sensitive to capillary filtration rate.

Equivalence of Centrifuge Training to Standing

The simulated centrifuge tests demonstrated that, although centrifugal forces produce a different distribution of hydrostatic stresses on the body than does constant gravity, centrifugation can produce presyncope in the same times as the corresponding constant gravity conditions. However, for the two centrifuge arm lengths used in this study, the values of other cardiovascular parameters (i.e., Q, CVP, CAP, and P_{2g}) were not simultaneously matched at the same rotational speeds.

CONCLUSIONS

The simulated stand tests confirm the sensitivity of cardiovascular orthostatic performance to blood volume, as well as the potential role of capillary filtration in explaining the delayed onset of presyncope. These simulations further suggest that increased capillary filtration may be largely responsible for the difference in times to presyncope between finishing and non-finishing males, and that the same increased capillary filtration rate, along with increased CAP threshold and lower initial arterial pressure, may explain the elevated orthostatic sensitivity of females.

The estimated times to presyncope for non-finishing astronauts were much longer for the lower constant gravity acceleration on the moon and Mars. These long delays are potentially hazardous because of the sustained diligence needed to recognize symptoms of POI so long after landing.

The simulated centrifuge tests suggest that training to reduce POI may be effective with centrifuge accelerations at heart level less than constant gravity levels, but response to centrifuge acceleration differs among several key indicators of cardiovascular performance. These differences diminish with increasing centrifuge arm length. Therefore, long arms are preferred to more exactly mimic the stimulation of baroreflex activity evoked by changing posture in a constant gravity environment.

Experimental studies are needed that focus on quantifying total and regional blood volumes throughout stand tests. From initial volume shifts, venous compliance can be deduced. From longer-term volume changes, regional capillary filtration can be quantified, which is perhaps the most pressing need to validate this mechanism of POI. In particular, more data is needed to quantify the hypothesized increase in filtration rates postflight compared to preflight, as well as the larger rate in non-finishers vs. finishers.

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