Computational model of cardiovascular response to centrifugation and lower body cycling exercise

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Title: Computational Model of Cardiovascular Response to Centrifugation and Lower-body Cycling Exercise

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Contributions to the study:
Dr. Diaz-Artiles is the main contributor to the article. She implemented the computational model, conducted to human experiments, analyzed the data, prepared figures, and drafted, revised, and approved the final manuscript. Prof. Heldt provided expertise concerning the cardiovascular modeling aspects and interpretation of the experimental data. He also edited, revised, and approved the final version of the manuscript. Prof. Young contributed with the overall supervision and management of the research project, including its relevance to artificial gravity for space travel, and edited, revised, and approved the final version of the manuscript.

Running Head: Cardiovascular Model of Centrifugation and Exercise

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ABSTRACT:
Short-radius centrifugation combined with exercise has been suggested as a potential countermeasure against spaceflight deconditioning. Both the long-term and acute physiological responses to such combination are incompletely understood. We developed and validated a computational model to study the acute cardiovascular response to centrifugation combined with lower-body ergometer exercise. The model consisted of 21 compartments, including the upper body, renal, splanchnic, and leg circulation, as well as a four-chamber heart and pulmonary circulation. It also included the effects of gravity gradient and ergometer exercise. Centrifugation and exercise profiles were simulated and compared to experimental data gathered on twelve subjects exposed to a range of gravitational levels (1G and 1.4G measured at the feet) and workload intensities (25-100W). The model was capable of reproducing cardiovascular changes (within ±1SD from the group-averaged behavior) due to both centrifugation and exercise, including dynamic responses during transitions between the different phases of the protocol. The model was then used to simulate the hemodynamic response of hypovolemic subjects (blood volume reduced by 5-15%) subjected to similar gravitational stress and exercise profiles, providing insights into the physiological responses of experimental conditions not tested before. Hypovolemic results are in agreement with the limited available data and the expected responses based on physiological principles, although additional experimental data are warranted to further validate our predictions, especially during the exercise phases. The model captures the cardiovascular response for a range of centrifugation and exercise profiles, and it shows promise in simulating additional conditions where data collection is difficult, expensive, or infeasible.

KEYWORDS:
Mathematical model, short-radius centrifuge; orthostatic intolerance; cardiovascular simulation; lower body ergometer exercise.

NEW & NOTEWORTHY:
Artificial gravity combined with exercise is a potential countermeasure for spaceflight deconditioning, but the long-term and acute cardiovascular response to such gravitational stress is still largely unknown. We provide a novel mathematical model of the cardiovascular system that incorporates gravitational stress generated by centrifugation and lower-body cycling exercise, and we validate it with experimental measurements from human subjects. Simulations of experimental conditions not used for model development corroborate the model’s predictive capabilities.
INTRODUCTION

Artificial gravity (AG) generated by centrifugation is a promising countermeasure to mitigate the detrimental effects of weightlessness during space missions (7). Previous ground-based studies have shown that exposure to centrifugation can improve cardiovascular responses to orthostatic stress (18, 35, 44, 55), especially if centrifugation is combined with exercise (20, 27–30, 51–53). Artificial gravity has also been proposed as a potential countermeasure to mitigate the recently discovered Spaceflight Associated Neuro-Ocular Syndrome (SANS) (6). Before implementing AG in space, however, additional research efforts are needed to determine the parameters that are most effective, including the angular velocity and radius of the centrifuge, and to characterize the cardiovascular response to these stressors under varying physiological baseline conditions (6). The expensive and time-consuming nature of these experimental studies with human subjects makes the use of computational tools a very attractive approach to systematically study human responses under these conditions.

Computational cardiovascular models can be used to describe and, more importantly, to predict, human responses in cases where data collection is difficult, expensive, or infeasible. Despite the complexity of the human body, computational approaches of various kinds and anatomical resolution have been successfully applied to a variety of applications, from very detailed three-dimensional models of selected regions, to low-dimensional models representing more aggregate system behavior (i.e. lumped-parameter models). The selection of the type of model is primarily driven by the objectives of the analysis as well as the availability of computational resources (46) and data to specify model parameters and validate the model behavior. In the present work we are interested in the overall, short-term, cardiovascular response to centrifugation combined with exercise and thus, the implementation of a lumped-parameter model seems the appropriate approach.

One of the first systematic approaches of quantitative, system-level modeling of cardiovascular regulation was developed by Guyton (21, 22). He was one of the first to apply a system engineering approach to quantify and analyze various aspects of cardiovascular function using mathematical and graphical techniques before computers became widely available. Since then, multiple models have been developed to study cardiovascular responses to gravitational stress, including head up tilt (HUT) (25, 26, 34), lower-body negative pressure (25, 37), standing-up (15, 38, 39), and centrifugation (54). However, none of these studies have evaluated the effects of centrifugation combined with exercise. The incorporation of the exercise response to the already very complex cardiovascular regulatory mechanisms brings additional physiological and methodological challenges (36) that we attempt to address in our modeling efforts.
We developed a lumped-parameter model of the cardiovascular system able to capture transient hemodynamic responses to lower-body ergometer exercise under gravitational stress generated by a short-radius centrifuge. The model was built on previous work developed to study short-term hemodynamic responses to centrifugation (54) and exercise (8), but not both mechanisms together at the same time. Our cardiovascular model includes the systemic circulation, four cardiac chambers, and the pulmonary circulation, divided in several parallel branches to account for the gravity gradient associated with short-radius centrifugation. The model also includes the two major short-term neural control mechanisms, the arterial baroreflex and the cardiopulmonary reflex, as well as important exercise mechanisms such as the muscle-pump effect. Experimental measurements collected during a human subject experiment at the Massachusetts Institute of Technology (MIT) short-radius centrifuge were used for validation purposes.

DESCRIPTION OF THE CARDIOVASCULAR MODEL

The cardiovascular system was represented using a lumped-parameter model in which the different vascular segments are represented using electric circuit analogs grouped in compartments. Extensive details of the model architecture and parameters have been published elsewhere (14) and are summarized in the Appendix. A general description of the most relevant features of the model is presented in the following paragraphs.

The model architecture is shown in Figure 1. It contains 21 compartments grouped into four main sections (head and arms, thorax, abdomen, and legs), representing the systemic circulation (15 vascular compartments including the arterial system, microcirculation, and the venous system), the cardiac chambers (4 cardiac compartments represented by time-varying elastance models), and the pulmonary circulation (2 additional compartments connected by a microvascular resistance, which we assumed to be linear).

Figure 2 shows the architecture of a generic compartment (25, 50). The lumped physical characteristics of each compartment are defined by a resistance $R_n$ and a capacitive element $C_n$ that relates the distending volume $V_{d,n}$ stored in the segment to transmural pressure $\Delta P_n = P_n - P_{ext,n}$. The pressure source $P_{ext,n}$ represents the external pressure acting on the vessels, such as intra-thoracic pressure, intra-abdominal pressure, or muscle-pump pressure. Additionally, the pressure source $P_{h,n}$ represents the hydrostatic pressure related to the gravitational orthostatic stress. Other parameters
associated with each compartment (not shown in **Figure 2**) include zero-pressure filling volume $V_{0,n}$, and the anatomical vertical length $l_{v,n}$ (superior-to-inferior extension of the vascular segment).

The flow in each compartment $q_n$ is calculated using the following constitutive relation:

$$q_n = \frac{P_{n-1} - P_n + P_{h,n}}{R_n}$$

where $P_{n-1}, P_n$ are the compartment pressures, $P_{h,n}$ is the hydrostatic pressure induced by centrifugation, and $R_n$ is the resistance of the $n^{th}$ compartment.

The transmural pressure in each compartment, defined as $P_n - P_{ext,n}$, depends on the distending volume $V_{d,n}$, and the compliance of the compartment $C_n$, through the following linear relationship (except for Compartments 11–splanchnic, 13–leg, and 14–abdominal; see **Figure 1** for compartment numbering scheme):

$$P_n - P_{ext,n} = \frac{V_{d,n}}{C_n}$$

Some compartments incorporate non-linear elements that affect their behavior. For example, the four cardiac chambers (left atrium, left ventricle, right atrium, right ventricle) are described using time-varying elastance models, and the generation of heartbeats is represented using an Integral Pulse Frequency Modulation (IPFM) model (3, 54). Thus, the contractile force of the myocardial wall is represented by the time-varying capacitors that cycle between a low capacitance (systolic) and a high capacitance (diastolic) state of the myocardium. The intra-thoracic pressure (i.e. external pressure in the thoracic compartments) modulates the filling status of the heart. Further details are included in the Appendix. Moreover, the heart compartments also incorporate unidirectional diodes that represent the cardiac valves and prevent reversal flow. Two vein compartments (Compartments 4–upper body and 13–leg) also include diodes to capture the unidirectional nature of the venous flow due to the presence of venous valves.

Non-linear pressure-volume relationships are also incorporated in some compartments (Compartments 11–splanchnic, 13–leg, and 14–abdominal) to capture their non-linear response when operating at high transmural pressures. In those compartments, the pressure-volume relationship is defined as:

$$V_{t,n} = V_{0,n} + \frac{2V_{max,n}}{\pi} \cdot \arctan \left( \frac{\pi C_{0,n} \cdot \Delta P_n}{2V_{max,n} \cdot \Delta P} \right) \text{ for } \Delta P > 0, \quad n = 11,13,14$$
where $V_{e,n}$ denotes the total volume, $V_{0,n}$ denotes the venous unstressed volume or zero-pressure filling volume, $V_{\text{max},n}$ denotes the distending volume limit ($V_{\text{max},11} = 1500$ mL, $V_{\text{max},13} = 1000$ mL, $V_{\text{max},11} = 650$ mL), $C_{0,n}$ denotes the vascular compliance at zero transmural pressure, and $\Delta P_n$ denotes the transmural pressure in the $n^{th}$ compartment.

The cardiovascular model was implemented in MATLAB Simulink. The distending volume is used as the state variable, yielding the following expression for each compartment based on volume conservation principles:

$$\frac{d}{dt} V_{d,n}(t) = q_{in,n} - q_{out,n}$$

where $q_{in,n}$ and $q_{out,n}$ correspond to the inward and outward flow in the $n^{th}$ compartment. The complete cardiovascular model is defined by a set of coupled-first order differential equations.

**Arterial baroreflex and cardiopulmonary control systems**

The arterial baroreceptors and the cardiopulmonary receptors are the two major neurally-mediated control systems that ensure short-term cardiovascular regulation in the presence of external disturbances such as orthostatic stress or exercise. They are represented in our model as set-point controllers that serve to minimize an error signal, namely the deviation of a specific local pressure from a pre-defined set-point value, by adjusting various effector mechanisms in a feedback configuration via autonomic pathways. To model the arterial baroreflex, we considered a single lumped baroreceptor in the carotid sinus, assumed to be located 25 cm cranial of the heart. Thus, the carotid sinus pressure, $P_{CS}$, is calculated as the aortic arch pressure $P_1$ minus the hydrostatic column acted upon by short-radius centrifugation. The error signal between the measured pressure and the arterial pressure set-point, $P_A^{sp}$, is fed into two linear time-invariant filters (sympathetic and parasympathetic (54)). The resultant signals are then scaled by effector-specific gain values and then applied to the effector variables. The arterial baroreflex effector variables include heart rate, right and left ventricular contractility, and the peripheral resistance and venous unstressed volume of the upper body, renal, splanchnic, and leg compartments.

The cardiopulmonary reflex is represented using a similar feedback control loop in which the measured variable is the right atrial transmural pressure, $\Delta P_{RA}$, and is compared to the cardiopulmonary set-point pressure, $P_{CP}^{sp}$. The gains of the sympathetic filter are also specific to each effector variable. The cardiopulmonary reflex effector variables include peripheral resistances and venous unstressed volumes of the upper body, renal, splanchnic, and leg compartments. Both contributions from the
arterial baroreflex and the cardiopulmonary reflex constitute the total neurally-mediated global reflex contribution to each effector variable.

**Centrifugation**

We aim to simulate the short-term cardiovascular responses to gravitational stress during short-radius centrifugation. Centrifugation is modeled by: 1) changes in the hydrostatic pressure in all systemic compartments; 2) changes in intrathoracic pressure due to the weight of the liver being pulled in the caudal direction, implemented as changes in the external pressures of the thoracic compartments; and 3) changes in total blood volume due to the increase in transcapillary fluid flow into the dependent vasculature. Short-radius centrifugation induces a gravity gradient along the long body axis in which the hydrostatic pressure depends on the angular velocity and the distance from the center of rotation. Compartments in the lower body are subjected to a higher hydrostatic pressure than compartments in the upper body. The compartmental nature of the model, particularly on the Gz axis, facilitates the representation of these hydrostatic changes along the body’s longitudinal axis. Important variables during centrifugation are angular velocity and distances of the CV compartments to the center of rotation (which are dependent of subjects’ anthropometry and positioning). The expressions in Table 1 define the gravitational stress imposed on the individual compartments during gradual exposure to short-radius centrifugation with angular velocity ranging from $\omega = 0$ to $\omega = \omega_{\text{max}}$. Additional details of these mathematical expressions and their implementation in the model are included in our previous publications (13, 14).

**Exercise**

Exercise causes circulatory adjustments that are essential to satisfy the metabolic needs of exercising muscles. These adjustments include local vasodilation in exercising muscle groups, sympathetic nervous system activation, an increase in cardiac output, and an increase in arterial blood pressure above the baseline level. In our modeling effort the effects of exercise are represented using the following four mechanisms:

**Decrease in leg arterial resistance.** Due to the higher metabolic demand during exercise, arterial resistance decreases locally in the exercising muscles to increase local blood flow to satisfy the local metabolic demand, and remove metabolic end products. In our modeling effort, we simulate lower-body cycling exercise by disconnecting the leg resistance from the control systems at the onset of exercise and manually adjusting it to match previously gathered experimental data (10) according to the following expression:
\[ R_{lc}(t) = R_{lc}^- + (R_{lf} - R_{lc}^-)(1 - e^{-t/\tau}) \]  

where \( R_{lc}^- \) is the leg vascular resistance immediately before the onset of an exercise phase, \( R_{lf} \) is the final leg vascular resistance for a given exercise intensity, and \( \tau \) is the time constant governing the changes in local vascular resistance.

**Leg muscle pump effect.** During exercise, muscles exert a pump effect by squeezing the veins while contracting, thus facilitating the return of blood to the heart. In our model, muscle pump effects are simulated by varying the external pressure at the venous leg compartment periodically, following a cycling cadence of 1 rev/sec (similar to the subjects’ experimental data). The leg external pressure due to the muscle pump effect, \( P_{pump}^{ext} \), is represented according to:

\[
P_{pump}^{ext} = \begin{cases} 
\frac{p_{pump}^{max}}{2}(1 - \cos(4\pi t)) & 0 \leq t \leq 1/4 \text{ sec} \\
\frac{p_{pump}^{max}}{2}(1 + \cos(4\pi(t - 1/2))) & 1/2 \leq t < 3/4 \text{ sec} \\
0 & 3/4 \leq t < 1 \text{ sec}
\end{cases}
\]  

where \( p_{pump}^{max} \) is the maximal leg external pressure and depends on the exercise intensity. In addition to the periodic muscle pump effect during cycling, an external muscle pump pressure \( P_{spin}^{ext} \), proportional to the centrifugal force, was added to the venous leg compartment when subjects were not cycling while they were being centrifuged (i.e. spin-up phase, AG-alone phases, and spin-down phase, see **Figure 3**). This pressure models the effects of continuous leg muscle activation when subjects are pushed against the pedals by centrifugal force (similar to the muscle pump caused by “active” standing).

**Increase in intra-abdominal pressure.** Abdominal pressure increases during exercise due to the contraction of abdominal muscles. This effect is represented as an increase in external pressure in the abdominal compartments (7, 8, 9, 10, 11, and 14), according to the following exponential function:

\[ P_{ext}^{abd} = p_{max}^{abd} (1 - e^{-t/\hat{\tau}}) \]  

where \( \hat{\tau} \) is a time constant on the order of a few seconds and \( p_{max}^{abd} \) is the maximal external pressure that depends on the intensity of the exercise.

**Increase in arterial blood pressure.** With increasing exercise intensity, arterial blood pressure progressively increases over baseline conditions, which cannot be explained on the basis a simple set-point feedback control system as implemented here. To capture the increased arterial blood pressure, we made the set-point reference pressure, \( P_A^{sp} \), an adjustable parameter that depends on the exercise intensity. Thus, \( P_A^{sp} \) is considered a tunable parameter to the model. Increases in \( P_A^{sp} \) increase
sympathetic activity through the arterial baroreceptor control systems previously described. Thus, consequences of increasing the set-point pressure $P_A^{sp}$ include increases in heart rate, ventricular contractility, total peripheral resistance (except in the working muscles), and venous tone.

Parameters

Most of the numerical values assigned to the model parameters have been estimated from the literature (24, 25). For each compartment, the parameter assignments include values for resistance $R$, compliance $C$, zero-pressure filling volume $V_{0,n}$, and anatomical vertical length $l_{v,n}$. The compartmental parameters and, in addition, the microvascular resistance values, pulmonary and cardiac parameters, as well as parameters related to the control systems are provided in Table 4 in the Appendix. The parameters related to exercise are specific to our individual simulation profile and are detailed below.

SIMULATION PROFILE AND EXPERIMENTAL DATA

We simulated a centrifugation profile identical to the one implemented in a human experiment conducted on the MIT centrifuge (10). The experiment was approved by the Committee on the Use of Humans as Experimental Subjects at MIT. Each subject gave written informed consent to participate in the study. Experimental methods and data analysis are fully described in a previous publication (10). In summary, twelve subjects were positioned in the right-side-down lateral decubitus position with their head positioned at the center of rotation of the MIT centrifuge. The radius of the centrifuge was limited to 1.4m to simulate the space limitations inherent to the short-radius centrifuge proposed for the International Space Station, as part of the “Artificial Gravity with Ergometric Exercise as the Countermeasure for Space Deconditioning in Humans” (AGREE) project (13). Thus, subjects adopted a crouched posture that was taken into account in our simulations by adjusting the leg anatomical vertical lengths $l_{v12}$ and $l_{v13}$. Subjects were exposed to different levels of centrifugation while performing ergometer exercise at three intensities (25W, 50W, and 100W). The protocol, shown in Figure 3, includes the following phases: baseline at rest (3 min), spin-up to the desired G-level (~100 sec), AG phase for subjects to get used to the new gravitational environment (~2 min), the exercise portion of the protocol, which includes three exercise intensities and transitions between them (15 min), another AG phase with no exercise for subjects to partially recover (2 min), and spin-down deceleration phase (1 min). The entire protocol was completed in 25 minutes. During the centrifugation runs, continuous, beat-to-beat cardiovascular data were collected using a non-invasive monitoring system (Nexfin monitor, Edwards Lifesciences Corporation, Irvine, CA). Collected variables include heart rate (HR), mean arterial pressure (MAP), systolic blood pressure (SBP), diastolic blood pressure (DBP), pulse pressure (PP), stroke volume (SV), cardiac output (CO), and total peripheral resistance (TPR).
Simulation approach

A comparatively small set of physiologically plausible parameters from our model were adjusted to simulate the centrifugation and exercise profiles described above. First, total blood volume was set to \( V_{\text{tot}} = 5175 \text{ ml} \) to closely represent our study population. This choice was based on an average of 75 ml of blood per kg of body mass (17, 25, 42) and our experimental subjects’ average weight (± standard deviation) of 69.3 ± 11.6 kg.

Second, the angular velocity, \( \omega(t) \), closely replicated the experimental protocol, increasing from 0 rpm to \( \omega_{\text{max}} \) during the spin-up phase, and decreasing back to 0 rpm during the spin-down phase, in both cases following quarter-sine profiles. The experimental AG conditions included 1G and 1.4G at the feet, which were the settings of the MIT centrifuge corresponding to a maximum angular velocity of 28.6 and 33.9 rpm, respectively. \( P_{\text{spin}} \) was also adjusted according to the centrifugation level.

Third, the three exercise-related parameters (\( P_{A}^{sp} \), \( P_{\text{max}}^{pump} \), \( R_{lf} \)) were manually adjusted at each workload stage to match the population-averaged MAP and TPR responses (as judged by visual inspections). The decreases in total vascular resistance were simulated by disconnecting the leg peripheral resistance \( R_{lc}(t) \) from the control systems at the onset of exercise, and matching the experimentally observed decreases by appropriately setting the resistance parameters of Eqn. (5). This process was repeated at every workload transition, adjusting the final leg resistance and the time constant to match the experimental data. Similarly, the arterial blood pressure set-point, \( P_{A}^{sp} \), and the external pressure due to leg muscle pump, \( P_{\text{max}}^{pump} \), were manually adjusted such that the simulated MAP matched the experimental data. The nominal \( P_{A}^{sp} \) was 93 mmHg; it was increased with increasing exercise intensity. The external pressure, \( P_{\text{max}}^{pump} \), was zero at rest and also increased with increasing exercise intensity. Finally, the maximal intra-abdominal pressure, \( P_{\text{max}}^{\text{abd}} \), was also increased with increasing exercise intensity in accordance with measurements from the literature (24, 25). For all parameters, transitions between exercise phases were defined by exponential functions with the appropriate time constants to match the experimental data. Table 2 summarizes all exercise input parameters used in our simulations.

RESULTS

Baseline Steady State Simulation
Results during steady-state simulations in supine position show that blood flow and volume distributions to the different vascular beds are within the range of the normal population (47). The distribution of CO to the upper body is 22% (normal range is 15%-29%), 20% to the kidney (18%-24%), 35% to the splanchnic compartment (24%-48%), and 22% to the lower body (14%-33%). Additional details about flow and volume distributions among the compartments are given in Table 5 in the Appendix.

Centrifugation Simulation

Figure 4 and Figure 5 show the simulated and experimental cardiovascular responses to centrifugation and ergometer exercise at 1G and 1.4G (measured at the feet), respectively. All major hemodynamic parameters generated by the model stayed within ± 1SD of the experimental data at almost all times throughout the entire protocol.

To simulate the exercise protocol, the simulated MAP and TPR responses were matched to the population-averaged experimental responses by adjusting the values of the pressure set-point $P_{A}^{SP}$, leg external pressure $P_{max}^{pump}$, and $R_{tc}$ leg arterial resistance were selected for each exercise level (see Table 2). The top graphs in Figure 4 and Figure 5 show that our matching approach captures MAP and TPR very closely. The nominal arterial set-point $P_{A}^{SP}$ was 93 mmHg, and this value was maintained until the beginning of exercise, when the arterial set-point increased according to the exercise intensity (see Table 2). Similarly, during the spin-up phase the simulated TPR responded appropriately to the gravitational stress created by centrifugation: at the beginning of the spin-up phase, the simulated resistance slightly decreased followed by a noticeable increase due to the control system reflexes. This behavior of the TPR is typical of active standing maneuvers (26, 43). At the beginning of the exercise (once the spin-up and AG phases were completed) the leg microvascular resistance was disconnected from the controls and adjusted to decrease such that the simulated TPR matched the experimental data. Thus, the $R_{tc}$ dynamics was composed of three transitions corresponding to the three workload intensities simulated, as shown in the figures.

The rest of the cardiovascular variables are considered outputs of the simulation. They largely reproduced the general trend of the experiment data, including baseline steady-state conditions as well as the dynamic changes during spin-up/spin-down and exercise transitions. The arterial baroreflex and the cardiopulmonary reflex responded properly to the cardiovascular stress created by centrifugation. In addition, the three exercise phases were very distinguishable from one another, and the time constants during transitions were particularly well matched. During the exercise portion of the protocol, the cyclic
muscle pump action is noticeable in most of the simulated cardiovascular variables, making the computational responses oscillate around their mean responses. Thus, during exercise, the simulated responses in Figure 4 and Figure 5 manifest themselves as “thicker” lines, due to the periodic external pressure imposed in the venous leg compartment simulating the effects of the cycling exercise.

The simulated heart rate response replicates the experimental data well during all phases of the protocol. Simulated SBP, DBP, SV, and CO are slightly underestimated, especially at higher workloads, though they match the general trends of the data and generally stay within ±1 SD of the experimental data. The PP simulations reproduce the experimental data for lower work rates (25W and 50W) but underestimate the experimental results for higher work rates (100W). The underestimation of the PP seemed to be driven by the underestimation of systolic pressures, particularly during the intensive exercise phase at 100W (~7% underestimation in both gravitational scenarios), causing the PP underestimation to reach 17% (1G) and 19% (1.4G) at this particular exercise phase. All in all, the systolic, diastolic, and mean ABP were maintained within 10% of experimental values. Table 3 summarizes the simulated and experimental averages of the CV variables during the different phases of the simulation: baseline, AG alone, exercise at 25W, exercise at 50W, and exercise at 100W. Averages were calculated using the last two minutes of each protocol period, in order to avoid the transient episodes between phases.

Case study: Centrifugation of Hypovolemic Subjects due to Microgravity Exposure

Having developed and validated the model for centrifugation and exercise, we can use this model to characterize the cardiovascular response in subjects with specific health conditions, or subjected to new gravitational stress configurations. Additionally, the model can also be used to help test hypotheses about the cardiovascular response in additional scenarios. Physiological reasoning can be used to predict in a qualitative manner specific responses driven by changes in certain parameters. However, the specific magnitude of a response, or degree of impact of particular parameter changes are harder to predict by reasoning alone, given the nonlinear and time-varying nature of the cardiovascular system. As an example, we chose to explore the cardiovascular response to hypovolemic conditions. This scenario is particularly relevant for human spaceflight, since astronauts lose approximately 10% of their blood volume when exposed to extended microgravity (5, 49), which has proven to be problematic when returning to a gravitational environment such as Earth (4, 33), or may become an issue in the future when microgravity adapted individuals are exposed to artificial gravity during spaceflight (12, 19, 44, 45). We conducted additional simulations using the same exercise protocol and the centrifugation
profile at 1G to investigate cardiovascular responses when blood volume was reduced by 5, 10, and 15% with respect to the euvoletic baseline (nominal $V_{tot}=5175 \text{ mL}$).

Results are shown in Figure 6 and provide quantitative information about the changes in cardiovascular variables to centrifugation combined with lower-body ergometer exercise. MAP decreases with decreasing levels of blood volume, despite the progressively larger increases in heart rate. The MAP reduction seems to be driven by reduction in SBP, especially during the no-exercise portions of the protocol (BL and AG) where DBP stays relatively constant across all blood volumes tested. PP, SV, and CO also decrease with reducing levels of blood volume. All changes are generally exacerbated at higher work rates, except for HR and TPR, where the responses at 100W across the different blood volume conditions do not differ greatly.

DISCUSSION

Several studies have investigated the short-term hemodynamics response of exercise in the upright and supine posture (1, 11), and as a potential countermeasure in ground-based bedrest studies (40). Our focus here is on the acute cardiovascular response to a gravitational stress that can be recreated in space and that is not constant along the major body axis. We developed a lumped-parameter model of the cardiovascular system to simulate the short-term hemodynamic responses to combined gravitational stress and exercise. In particular, gravitational stress was generated by centrifugation of subjects using a short-radius centrifuge, therefore generating a high gravity gradient along the long axis of the body. The model simulates the hydrostatic pressures among cardiovascular compartments caused by the gravity gradient. In addition, the effects of ergometer exercise were also incorporated in the model, including the increase in blood pressure, the muscle pump effect, the decrease in vascular resistance, and changes in intra-abdominal pressure. Finally, the model was programmed to recreate the 25-min exercise protocol experienced by 12 subjects in a previous human experiment conducted at MIT (10). Although there have been other studies investigating centrifugation combined with ergometer exercise (16, 27–29, 45, 48, 51), these studies have mainly focused on physiological responses before and after a specific intervention (e.g. bed rest or training protocol) and not during the centrifugation sessions. Thus, the cardiovascular data taken during the MIT centrifugation experiments were used to calibrate and evaluate the computational model. Thus, we are combining mathematical modeling and human experiments in a synergistic manner. On the one hand, experiments are necessary for specifying model parameters and for model validation; on the other hand, models allow for flexibility to investigate physiological mechanisms under consideration, enhance experimental data interpretation, and serve as a vehicle to test competing hypothesis.
Generally, the cardiovascular model matched the dynamic cardiovascular response during the 25-min exercise protocol quite well. It showed a slight tendency to underestimate some of the cardiovascular variables, particularly SV, and PP at higher workload intensities, and to a lesser extent, CO. These results could be better adjusted by modifying some of the numerous parameters that are built in the model. However, it is important to emphasize that the purpose of these simulations is to intentionally limit the number of inputs and not to exert the full flexibility of the model to reduce the error between the experimental and simulated responses. A small number of parameters, namely TPR and MBP, have been constrained to determine if the resulting simulations capture the physiologic response over a range of exercise levels and AG regimes. The multi-compartment model has more than 100 parameters and it can be manipulated to perfectly match the cardiovascular responses. However, the value of such an exercise is small, as most parameters will have negligible influence on the output and the resultant solution will therefore not be unique and will not provide much physiological insights.

Overall, the cardiovascular model developed in this research effort provides unique information about the cardiovascular responses to gravitational stress and exercise. Model results and comparisons during the baseline period are particularly interesting since they provide a good indication of the cardiovascular modeling performance without any stressor such as centrifugation or exercise. A finite number of hemodynamic compartments and the primary exercise mechanisms were included in the model. Although we recognize that exercise is a particularly complex activity from the physiological modeling point of view, our results show that our model included enough vascular and exercise mechanisms to attain suitable accuracy, at least within the selected ranges of AG and exercise intensity. As Reisner and Heldt pointed out (41), this refers to the “immortal problem of modeling”: creating a model simple enough to feasibly determine the outputs with enough accuracy, without including superfluous complexity that can make difficult the fundamental understanding of the model (i.e. how individual parts interact with each other).

To explore the physiological consequences of centrifugation we further studied quantitative responses to centrifugation and exercise in hypovolemic subjects, with reduction of 5, 10, and 15% of total blood volume. There is limited experimental data in the literature to perform a direct comparison between our simulations and hemodynamic responses from hypovolemic subjects subjected to short-radius centrifugation an exercise. Thus, we base our comparison to a similar study that used tilt tests maneuvers to study orthostatic stress. Linnarsson and his colleagues (35) investigated orthostatic tolerance in hypovolemic subjects after five days of bedrest. Subjects lost between 8-14% of blood
volume during the 5-day bed rest, and their short-term, post-bedrest HR, SYS, and DIA responses
during a tilt test (80º upright) changed approximately +29%, −15%, and −5% respectively, with respect
to pre-bed rest. Our data indicate that hypovolemic subjects presenting blood volume losses between 10-
15% will also experience increases in HR (+14 to 17%) and decreases in SYS (−10.5 to −15.6%) and
DIA (−2.8 to −5.7%). We expect to see less significant changes in a short-radius centrifuge due to the
presence of a strong gravity gradient that makes the gravitational stress less intense than being exposed
to constant 1G gravitational environment. Thus, our simulations seem to be in agreement with the
limited available data and the expected responses based on physiological principles. Additional
experiments are warranted to further validate the predicted values from our model, particularly the ones
involving exercise. However, these predictions are already providing insightful information about
experimental conditions not tested before.

Limitations

We chose to represent the cardiovascular behavior using a lumped-parameter model. This
approach is unable to simulate pulse wave propagation phenomena such as the changes in arterial
pressure waveform as it propagates through the arterial system (31, 50) and might therefore be
responsible for our underestimation of systolic blood pressure at higher centrifugation level and exercise
regimes. Despite this limitation our model was able to reproduce realistic responses at a lower
computational cost. Inertial effects were also not included in the model causing, for example, the
absence of the dichrotic notch typically present in the arterial and pulmonary arterial waveforms during
closure of the semilunar valves. Inertial effects become important when studying intra-beat changes
(within a cardiac cycle), which is not the case in the present study. Inertial effects have been estimated
to account for less than 1% of stroke volume and mean arterial pressure (9) and therefore they have been
neglected.

We have also not taken into account possible non-linear cardiac effects. Both systolic and
diastolic pressure-volume relationships were assumed to be linear, which is reasonable at normal filling
pressures, but these relationships become non-linear at higher filling pressures. Simulations of
pathologically high pressures were beyond of the scope of this work, and for the purpose of the
simulations presented here, the pressure-volume relationships were assumed linear. Additionally, the
unstressed volume was assumed to be static throughout the cardiac cycle and the same for the diastolic
and systolic pressure-volume relationships. Typically, the end-systolic unstressed volume is between
25-40% lower than its diastolic counterpart (2, 32), indicating a small but potentially significant
contribution to stroke volume, thus decreasing the underestimation seen in our simulations.
Viscoelastic stress-relaxation effects of the systemic veins were also not included in our modeling effort. This phenomenon refers to the intrinsic ability of the vascular walls to stretch slowly when the pressure rises and to contract slowly when the pressure falls (23, 26). This effect becomes important when studying very short-term (~30 s) dynamic blood pressure responses after exposure to passive head-up tilt, due to the altering of the time-course of venous pooling to the lower body and thus, limiting the blood pressure dip typically seen during active standing (26). In our work we focused on steady-state cardiovascular responses during active exposure to centrifugation and therefore these effects were also neglected. We have also not taken into account breathing-related changes in intrathoracic pressure. As the depth of breathing increases with increasing exercise, the lowering of intrathoracic pressure aids in venous return at higher exercise levels. We have also assumed that the resistance changes due to exercise are largely determined by the arteriolar vasodilation and that the muscle pump primarily affects the filling state of the leg veins.

Finally, we have already commented on the difficulty of assigning numerical values to all the parameters of the model. The degree to which our model reproduces the experimental data suggests that we have included all the major features with a reasonable degree of parameter accuracy. Sensitivity analysis techniques could elucidate the influence of each parameter on the model outputs to determine the subset of physiological parameters that dominate the model response. This could be further related to individual differences seen in hemodynamic responses to gravitational stress across specific population, such as astronauts coming back to Earth after being exposed to microgravity conditions.

Conclusion

We have developed a computational model of the cardiovascular system capable of reproducing hemodynamic responses during gravitational stress generated by a short-radius centrifuge and lower-body ergometer exercise. The model simulated both transient and steady-state responses that compare well with experimental data gathered on twelve subjects that underwent the same simulated protocol using the MIT short-radius centrifuge. We explored the capabilities of the model to generate new hypotheses and to quantify changes in cardiovascular responses due to variations in an individual parameter (i.e. total blood volume).
APPENDIX

A. Additional Details about the Cardiovascular Model

Most of the model equations have already been reported in a previous publication (14), but for completeness, we are including them in this Appendix.

Cardiac Model

The four cardiac chambers are simulated using time-varying elastance models (24, 25). The time-varying elastance in each one of the four cardiac chambers is represented using the equation below, where the time interval of diastolic relaxation $T_d^r$ is assumed to be one half of the systolic time interval $T_s$:

$$E(t) = \begin{cases} 
E_d + \frac{E_{es} - E_d}{2} \cdot \left( 1 - \cos \left( \frac{\pi t}{T_s} \right) \right) & 0 \leq t \leq T_s \\
E_d + \frac{E_{es} - E_d}{2} \cdot \left( 1 + \cos \left( 2\pi \frac{t}{T_s} \right) \right) & T_s < t \leq \frac{3}{2}T_s \\
E_d & \frac{3}{2}T_s < t 
\end{cases} \tag{8}$$

and $E_d$ and $E_{es}$ are the diastolic elastance and end-systolic elastances in each one of the four cardiac chambers, respectively. The timing parameters include the atrial and ventricular systole duration, $T_{S}^{a}$ and $T_{S}^{v}$, as well as the “P-R interval”, which we defined here as the delay between the onset of the atrial and ventricular contraction $T_{a-v}$. Their values are assumed to be proportional to the square root of the R-R interval length $T_{RR}$ (24, 25) and are defined as $T_{S}^{a}(s) = 0.2\sqrt{T_{RR}}$, $T_{S}^{v}(s) = 0.3\sqrt{T_{RR}}$, and $T_{a-v}(s) = 0.12\sqrt{T_{RR}}$

The cardiac pacemaker is represented using an Integral Pulse Frequency Modulation (IPFM) model (3, 24, 25, 54), according to:

$$M(t) = \int_{t_{k-1}}^{t} m(t)dt = \int_{t_{k-1}}^{t} (m_{0} + m_{r}(t))dt$$

where $M(t)$ mimics the behavior of the transmembrane potential in the sino-atrial node whose value at time $t$ depends on the cumulative automaticity $m_{0}$ (assumed constant), and the contribution of neural control input $m_{r}(t)$ (either sympathetic or parasympathetic activity) since the end of the last heartbeat (or cardiac excitation time $t_{k-1}$). A new heartbeat occurs at the time $t_{k}$ when the transmembrane potential $M(t)$ reaches a predefined threshold potential $\Gamma = 1$, and the time since the previous heartbeat is at least one fifth of the preceding cardiac cycle length:

$$\int_{t_{k-1}}^{t_{k}} m(t)dt = M(t_{k}) \geq \Gamma \quad \text{and} \quad t_{k} - t_{k-1} \geq 0.2(t_{k-1} - t_{k-2})$$
The function \( m(t) \) is defined as the inverse of the instantaneous R-R interval \( I(t) \):

\[
m(t) = \frac{1}{I(t)} = \frac{1}{I_0 + \Delta I_{AB}(t)}
\]

where \( I_0 \) is the nominal R-R interval, and \( \Delta I_{AB}(t) \) is the control input from the arterial baroreflex control system.

**Control Systems**

The baroreceptor control system is modeled using a negative feedback loop and an arterial pressure set-point \( P_A^{sp} \). Assuming one lumped baroreceptor located in the carotid sinus at 25 cm above the heart, the carotid sinus pressure \( P_{CS} \) (mmHg) is defined as:

\[
P_{CS} = P_1 - \frac{1}{2} \cdot \rho \cdot \omega^2(t) \cdot ((25 + d)^2 - d^2)
\]

where \( d \) is the distance between the head and the center of rotation measured in cm, \( \rho \) is the blood density in \( \frac{\text{mmHg}}{\text{cm}^2} \), and \( \omega(t) \) is the angular velocity of the centrifuge in rad/s. The feedback error signal \( e_{AB}(t) \) is calculated as follows:

\[
e_{AB}(t) = 18 \cdot \arctan \left( \frac{P_{CS} - P_A^{sp}}{18} \right)
\]

The cardiopulmonary reflex is also modeled using a negative feedback loop and a pressure set-point \( P_{CP}^{sp} \). The variable measured is the transmural right atrial pressure \( \Delta P_{RA} \) and the error signal \( e_{CP}(t) \) is calculated as follows:

\[
e_{CP}(t) = 5 \cdot \arctan \left( \frac{\Delta P_{RA} - P_{CP}^{sp}}{5} \right)
\]

The sympathetic and parasympathetic control systems are modeled as two linear time-invariant (LTI) filters. The transfer functions for the sympathetic \( s(s) \) and parasympathetic \( p(s) \) filters are:

\[
s(s) = \frac{1}{42s^2} e^{-2s} + \frac{1}{75s^2} e^{-5s} + \frac{1}{300s^2} e^{-30s}
\]

\[
p(s) = 1
\]
Orthostatic stress causes a decrease in intravascular volume due to an increase in transcapillary fluid flow to the dependent vasculature. This phenomenon can be represented using additional RC compartments (24, 25, 54). The transcapillary flow is solved analytically based on the orthostatic stress profile using the equations described in the following section. The solution of the equations depends on two parameters: the time constant \( \tau = RC = 4.6 \, \text{min} \) (24, 25), and the maximum interstitial volume change \( V_{\text{max}} = P_hC \), given in Table 1. The transcapillary flow is then subtracted from the venous return at the selected compartments where this phenomenon is significant: splanchnic venous (compartment 11), leg venous (compartment 13), and abdominal venous (compartment 14). The fractions of interstitial volume and interstitial flow assigned to each compartment are defined below:

\[
V^n(t) = \frac{p^n_{h,\text{max}}}{\sum_i p^i_{h,\text{max}}} \cdot V(t) \tag{14}
\]

\[
q^n(t) = \frac{p^n_{h,\text{max}}}{\sum_i p^i_{h,\text{max}}} \cdot q(t) \tag{15}
\]

where \( p^n_{h,\text{max}} \) is the maximum hydrostatic pressure in the \( n \)th compartment; and \( \sum_i p^i_{h,\text{max}} \) is the sum of the maximum hydrostatic pressures of the three compartments (11, 13, and 14).

**Analytical Solutions for the Transcapillary Flow and the Interstitial Fluid Volume**

The following equations provide an analytical solution for the intercapillary flow and interstitial volume change during gravitational stress.

**Region I:** Gradual increase in orthostatic stress over a period of length \( \Delta t \).

\[
q(t) = \frac{V_{\text{max}}}{\Delta t} \cdot (1 - e^{-\frac{t}{\tau}}) \tag{16}
\]

\[
V(t) = V_{\text{max}} \cdot \left( t \frac{\tau}{\Delta t} - \frac{t}{\tau} \left( 1 - e^{-\frac{t}{\tau}} \right) \right) \tag{17}
\]

**Region II:** Full gravitational stress during period of duration \( T_{\text{tilt}} \).

\[
q(t) = \frac{V_{\text{max}}}{\Delta t} \cdot (1 - e^{-\frac{\Delta t}{\tau}}) \cdot e^{-\frac{t-\Delta t}{\tau}} \tag{18}
\]

\[
V(t) = V_{\text{max}} \cdot \left( 1 - e^{-\frac{\Delta t}{\tau}} \right) e^{-\frac{t-\Delta t}{\tau}} \tag{19}
\]

**Region III:** Gradual decline in gravitational stress over a period of length \( \Delta t \).

\[
q(t) = \frac{V_{\text{max}}}{\Delta t} \cdot \left( 1 + \left( 1 - e^{-\frac{\Delta t}{\tau}} \right) e^{-\frac{T_{\text{tilt}}}{\tau}} \right) e^{-\frac{t-(\Delta t+T_{\text{tilt}})}{\tau}} - \frac{V_{\text{max}}}{\Delta t} \tag{20}
\]
Region IV: Post-orthostatic stress recovery of unspecified length.

\[ q(t) = -\frac{V_{\text{max}}}{\Delta t} \left(1 - e^{-\frac{\Delta t}{\tau}}\right) \left(1 - e^{-\frac{T_{\text{tilt}} + \Delta t}{\tau}}\right) e^{-\frac{t-(2\Delta t + T_{\text{tilt}})}{\tau}} \]  
(22)

\[ V(t) = V_{\text{max}} \cdot \frac{\tau}{\Delta t} \left(1 - e^{-\frac{\Delta t}{\tau}}\right) \left(1 - e^{-\frac{T_{\text{tilt}} + \Delta t}{\tau}}\right) e^{-\frac{t-(\Delta t + T_{\text{tilt}})}{\tau}} \]  
(23)

Initial Conditions

The following 23 non-linear algebraic equations are used to find the initial conditions, and they describe the blood flow in the compartments assuming that the system is in steady state (54). The first equation equates the right ventricular stroke volume and the left ventricular stroke volume, and the last equation is based on the conservation of volume equating the difference between the total volume and the unstressed volume, and the distending volume in each compartment.

\[ C_{td}(P_{\text{lv}} - P_{\text{th}}) - C_{ls}(P_{\text{lv}} - P_{\text{th}}) = C_{rd}(P_{\text{rv}} - P_{\text{th}}) - C_{rs}(P_{\text{rv}} - P_{\text{th}}) \]  
(24)

\[ C_{td}(P_{\text{lv}} - P_{\text{th}}) - C_{ls}(P_{\text{lv}} - P_{\text{th}}) = \frac{T_{v}^{\prime} \cdot P_{\text{lv}}}{R_{1}} \]  
(25)

\[ T_{v}^{\prime} \cdot \frac{P_{\text{lv}}}{R_{1}} = I_{0} \cdot \left(\frac{P_{1} - P_{2}}{R_{2}} + \frac{P_{1} - P_{6}}{R_{6}}\right) \]  
(26)

\[ I_{0} \cdot \frac{P_{1} - P_{2}}{R_{2}} = I_{0} \cdot \frac{P_{2} - P_{3}}{R_{3}} \]  
(27)

\[ I_{0} \cdot \frac{P_{2} - P_{3}}{R_{3}} = I_{0} \cdot \frac{P_{3} - P_{4}}{R_{ub}} \]  
(28)

\[ I_{0} \cdot \frac{P_{3} - P_{4}}{R_{ub}} = I_{0} \cdot \frac{P_{4} - P_{5}}{R_{4}} \]  
(29)

\[ I_{0} \cdot \frac{P_{4} - P_{5}}{R_{4}} = I_{0} \cdot \frac{P_{5} - P_{\text{ra}}}{R_{5}} \]  
(30)

\[ I_{0} \cdot \frac{P_{5} - P_{\text{ra}}}{R_{5}} = I_{0} \cdot \frac{P_{6} - P_{7}}{R_{7}} \]  
(31)

\[ I_{0} \cdot \frac{P_{6} - P_{7}}{R_{7}} = I_{0} \cdot \left(\frac{P_{7} - P_{8}}{R_{8}} + \frac{P_{7} - P_{10}}{R_{10}} + \frac{P_{7} - P_{12}}{R_{12}}\right) \]  
(32)

\[ I_{0} \cdot \frac{P_{7} - P_{8}}{R_{8}} = I_{0} \cdot \frac{P_{9} - P_{9}}{R_{rc}} \]  
(33)
\[ I_0 \cdot \frac{P_8 - P_0}{R_{rc}} = I_0 \cdot \frac{P_9 - P_{14}}{R_9} \]  
\[ (34) \]

\[ I_0 \cdot \frac{P_7 - P_{10}}{R_{10}} = I_0 \cdot \frac{P_{10} - P_{11}}{R_{sc}} \]  
\[ (35) \]

\[ I_0 \cdot \frac{P_{10} - P_{11}}{R_{sc}} = I_0 \cdot \frac{P_{11} - P_{14}}{R_{11}} \]  
\[ (36) \]

\[ I_0 \cdot \frac{P_7 - P_{12}}{R_{12}} = I_0 \cdot \frac{P_{12} - P_{13}}{R_{tc}} \]  
\[ (37) \]

\[ I_0 \cdot \frac{P_{12} - P_{13}}{R_{tc}} = I_0 \cdot \frac{P_{13} - P_{14}}{R_{13}} \]  
\[ (38) \]

\[ I_0 \cdot \frac{P_{14} - P_{15}}{R_{14}} = I_0 \cdot \left( \frac{P_9 - P_{14}}{R_9} + \frac{P_{11} - P_{14}}{R_{11}} + \frac{P_{13} - P_{14}}{R_{13}} \right) \]  
\[ (39) \]

\[ I_0 \cdot \frac{P_{14} - P_{15}}{R_{14}} = I_0 \cdot \frac{P_{15} - P_{ra}}{R_{15}} \]  
\[ (40) \]

\[ I_0 \cdot \left( \frac{P_5 - P_{ra}}{R_5} + \frac{P_{15} - P_{ra}}{R_{15}} \right) = T_d^v \cdot \frac{P_{ra} - P_{rvd}}{R_{tri}} \]  
\[ (41) \]

\[ T_d^v \cdot \frac{P_{ra} - P_{rvd}}{R_{tri}} = T_s^v \cdot \frac{P_{rvd} - P_{pa}}{R_{ro}} \]  
\[ (42) \]

\[ T_s^v \cdot \frac{P_{rvd} - P_{pa}}{R_{ro}} = I_0 \cdot \frac{P_{pa} - P_{pv}}{R_{pv}} \]  
\[ (43) \]

\[ I_0 \cdot \frac{P_{pa} - P_{pv}}{R_{pv}} = I_0 \cdot \frac{P_{pv} - P_{ia}}{R_{ti}} \]  
\[ (44) \]

\[ I_0 \cdot \frac{P_{pv} - P_{ia}}{R_{ti}} = T_d^v \cdot \frac{P_{ia} - P_{lvd}}{R_{mit}} \]  
\[ (45) \]

\[ V_{total} - V_{total}^0 = \sum_{j \in \{1,2,\ldots,10\}} C_j \cdot \Delta P_j + \sum_{k \in \{11,13,14\}} \left[ \frac{2V_{max}}{\pi} \cdot \arctan \left( \frac{\pi C_{0k}}{2V_{max}} \cdot \Delta P_k \right) \right] \]  
\[ (46) \]

B. Parameters of the Cardiovascular Model

(Insert Table 4)

C. Baseline Steady State Flows and Volume Distributions

(Insert Table 5)
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**FIGURE CAPTIONS**

**Figure 1.** Circuit representation of the 21-compartment cardiovascular model, composed of 4 sections: head and arms, thorax, abdomen, and legs. Systemic compartments include proximal aorta (1), brachiocephalic arteries (2), upper body precapillary (3) and postcapillary (4) compartments, superior vena cava (5), thoracic aorta (6), abdominal aorta (7), renal precapillary (8) and postcapillary (9) compartments, splanchnic precapillary (10) and postcapillary (11) compartments, leg precapillary (12) and postcapillary (13) compartments, abdominal veins (14), and thoracic inferior vena cava (15). Four microvascular resistances are also included: upper body $R_{ub}$, kidneys $R_{rc}$, splanchnic $R_{sc}$, and legs $R_{lc}$.

The right heart and left heart include variable capacitors and diodes representing the heart valves that prevent reversal flow. The pulmonary circulation is represented by two compartments (pre and post capillary components) connected by a microvascular resistor. Two vein compartments (Compartments 4–upper body and 13–leg) also include diodes to capture the unidirectional nature of the venous flow due to the presence of venous valves.

**Figure 2.** Single representation of the $n^{th}$ compartment, where $R_n$ is the resistance, $C_n$ is the (incremental) vascular compliance ($C_n$ is defined as $dV_n/d\Delta P_n$), $P_n$ is the compartment pressure, $q_n$ is the flow rate; $P_{hn}$ is the hydrostatic pressure; and $P_{ext,n}$ is the external pressure (e.g. intra-thoracic pressure, intra-abdominal pressure, muscle pump pressure). The arrows over the compliance (represented by the electric symbol of a capacitor) and pressure sources (represented by open circles) indicate the variable nature of these elements, either as a function of filling status (capacitors) or as a function of time (pressure sources).

**Figure 3.** Exercise protocol conducted by twelve subjects on the MIT short-radius centrifuge. The protocol consisted of the following phases: baseline (3 min), spin-up phase to the desired G-level (~100 sec), AG phase with only centrifugation (~2min), AG & Exercise phase (15 min), AG phase with no exercise for subjects to partially recover (2 min), and spin-down phase (1 min). We simulated an identical profile with our computational model and used the experimental data for validation purposes.

**Figure 4.** Simulated (black line) and experimental (grey line, mean ± SD including 12 subjects) cardiovascular responses to centrifugation at 1G (measured at the feet) and ergometer exercise in a short-radius centrifuge.
Figure 5. Simulated (black line) and experimental (grey line, mean ± SD including 12 subjects) cardiovascular responses to centrifugation at 1.4G (measured at the feet) and ergometer exercise in a short-radius centrifuge.

Figure 6. Simulated cardiovascular responses to centrifugation at 1G (measured at the feet) and ergometer exercise varying blood volume conditions. Data are reported for all protocol phases: baseline (BL), centrifugation alone (AG), and centrifugation combined with exercise (25W, 50W, and 100W). Blood volume levels include baseline blood volume ($V_{total} = 5175$ ml) and blood volume reductions of 5%, 10%, and 15%.
Table 1: Mathematical expressions capturing orthostatic stress during short-radius centrifugation through three mechanisms: 1) changes in hydrostatic pressure (term included in all systemic compartments), 2) changes in intrathoracic pressure (due to the weight of the liver being pulled down in the thoracic compartment; term included in compartments within the thorax region), and 3) changes in total blood volume (due to the increase in transeapillary fluid flow into the dependent vasculature)

| **Gravitational Effect** | **Short-radius Centrifugation** |
|--------------------------|---------------------------------|
| Hydrostatic pressure     | \( P_{h,n} = \frac{1}{2} \rho \omega^2(t)(R_{0,n}^2 - R_{i,n}^2) \) |
| Intrathoracic pressure   | \( P_{th}(t) = P_{th0} - 3.5 \frac{(r + d)^2 \cdot \omega_{max}^2}{g^2} \cdot \omega^2(t) \) |
| Maximum Interstitial Volume Change | \( V_{max} = 300ml \cdot \frac{(r + d) \cdot \omega_{max}^2}{g \cdot \sin(85^\circ)} \) |

where \( P_{h,n}(t) \) is the hydrostatic pressure, \( \rho \) is the density of the blood, \( \omega(t) \) is the angular velocity of the centrifuge, \( P_{th}(t) \) is the intrathoracic pressure, \( P_{th0} \) is the nominal intrathoracic pressure without orthostatic stress (−4 mmHg), \( \omega_{max} \) is the maximum and final angular velocity achieved, \( r = 55 \text{ cm} \) is the distance of the thoracic compartment to the center of rotation of the centrifuge, \( d \) is the distance from the head of the subject to the center of rotation of the centrifuge (\( d = 0 \text{ cm} \)), \( V_{max} \) is the maximum interstitial volume change (from intravascular volume to the interstitial space), \( R_{i,n} \) is the inner radius of the compartment under consideration, \( R_{0,n} \) is the outer radius of the compartment under consideration, which is defined as the sum of the effective length of the compartment and the inner radius. Note: The effective length of each compartment is defined as one half of its anatomical vertical length \( l_{v,n} \), except for the leg compartments, where the effective length is assumed to be one third of the anatomical vertical length.
Table 2: Exercise parameters during the different phases of the “1G” and “1.4G” simulations. Manipulated parameters include $P_A^{sp}$: set-point reference pressure for the arterial baroreceptor control system (mmHg); $R_{lc}$: leg microvascular resistance (Peripheral Resistance Units (PRU) or mmHg/ml/min.); $P_{pump}^{max}$: maximal leg external pressure (mmHg); and $P_{max}^{abd}$: maximal intra-abdominal pressure (mmHg). $P_A^{sp}$ and $P_{pump}^{max}$ were adjusted to match the experimental Mean Arterial Pressure (MAP) data, and $R_{lc}$ was adjusted to match the experimental total peripheral resistance (TPR) data. $P_{max}^{abd}$ was adjusted based on the literature.

| Simulation phase       | Arterial set-point $P_A^{sp}$ (mmHg) | Leg Arterial Resistance $R_{lc}$ (PRU) | Leg external pressure $P_{pump}^{max}$ due to muscle pump (mmHg) | Intra-abdominal pressure $P_{max}^{abd}$ (mmHg) |
|------------------------|--------------------------------------|----------------------------------------|---------------------------------------------------------------|-----------------------------------------------|
| AG level (measured at the feet) |                                      |                                        |                                                               |                                               |
| Baseline               | 1G 93                                | 1G 3.9                                | 1G 0                                                           | 1G 2                                          |
| AG after Spin-up       | 1G 93                                | 1G 3.9                                | 1G 20**                                                       | 1G 2                                          |
| Exercise: 25W          | 1G 120                               | 1G 1.15*                              | 1G 40***                                                      | 1G 2.5                                        |
| Exercise: 50W          | 1G 135                               | 1G 0.75*                              | 1G 50***                                                      | 1G 6                                          |
| Exercise: 100W         | 1G 205                               | 1G 0.54*                              | 1G 60***                                                      | 1G 10                                         |
| AG before Spin-down    | 1G 105                               | 1G 2.4*                               | 1G 20**                                                       | 1G 30**                                       |
| Rest                   | 1G 105                               | 1G 2.4*                               | 1G 0                                                           | 1G 0                                          |

*resistance disconnected from controls
**constant
***periodic 1 sec
Table 3: Simulated (Sim) and experimental (Exp, values are mean ± SD) average of cardiovascular variables during the different phases of the protocol at the two G-levels investigated: 1G and 1.4G (measured at the feet). For both simulated and experimental data, averages were calculated including the last 2 minutes of each period.

| Variable | Baseline | AG | AG + Exercise 25W | AG + Exercise 50W | AG + Exercise 100W |
|----------|----------|----|------------------|-------------------|-------------------|
|          | 1G       | 1.4G | 1G       | 1.4G       | 1G       | 1.4G       | 1G       | 1.4G       | 1G       | 1.4G       |
| CO (l/min) | 5.9±1.2 | 6.1±1.4 | 5.8±1.3 | 6.0±1.3 | 8.7±2.3 | 9.5±2.2 | 9.8±1.5 | 10.6±2.3 | 10.9±1.5 | 12.1±2.3 |
| SV (ml)  | 87.9±14.0 | 96.2±14.0 | 83.2±11.9 | 91.0±15.4 | 84.5±14.3 | 98.2±14.3 | 90.0±14.1 | 98.8±20.8 | 97.7±14.1 | 107.9±14.1 |
| HR (hpm) | 67.3±10.0 | 64.1±10.0 | 67.7±9.2 | 64.5±9.2 | 67.7±9.2 | 69.3±11.9 | 96.2±9.2 | 97.0±10.5 | 100.0±10.5 | 101.6±10.5 |
| SBP (mmHg)| 116.9±6.5 | 116.6±6.5 | 115.4±11.6 | 116.5±11.6 | 116.4±11.9 | 121.7±11.9 | 124.3±11.5 | 128.1±13.6 | 128.6±11.5 | 129.3±13.6 |
| MBP (mmHg)| 92.9±4.9 | 90.4±4.9 | 92.8±8.3 | 90.5±8.3 | 93.5±8.3 | 92.8±9.7 | 100.8±11.1 | 98.6±11.1 | 103.2±11.1 | 103.2±11.0 |
| DBP (mmHg)| 67.8±4.3 | 73.2±4.3 | 68.9±6.9 | 74.2±6.9 | 69.2±6.9 | 74.5±7.4 | 74.9±7.5 | 80.0±7.5 | 75.1±7.5 | 81.7±7.5 |
| PP (mmHg)| 49.1±6.8 | 43.4±6.8 | 46.5±9.1 | 42.4±9.1 | 47.2±7.6 | 49.5±7.6 | 48.2±10.6 | 53.5±9.7 | 54.9±9.7 | 57.4±9.7 |
| TPR (PRU)| 0.86±0.2 | 0.93±0.2 | 0.86±0.2 | 0.98±0.3 | 0.86±0.2 | 0.86±0.2 | 0.62±0.2 | 0.58±0.2 | 0.59±0.1 | 0.59±0.1 |
|           |          |      |          |          |          |          |          |          |          |          |
Table 4: Values of the cardiovascular model parameters

| Resistance (PRU) | Unstressed volume (mL) | Compliance (mL/mm Hg) | Anatomical vertical length (cm) | Elastances Cardiac Model (mm Hg/ml) | Regulatory Control Systems | Additional Parameters |
|------------------|------------------------|-----------------------|---------------------------------|-------------------------------------|---------------------------|----------------------|
| $R_1$=0.007      | $V_{0.1}$=21           | $C_1$=0.28            | $l_{v,1}$=10.0                  | $E_{extra}=0.74$                    | $p_{A}=93$ mm Hg          | $P_{th}=4$ mm Hg     |
| $R_2$=0.003      | $V_{0.2}$=5             | $C_2$=0.13            | $l_{v,2}$=4.5                   | $E_{d,ra}=0.3$                      | $G_{AS}^{Ra,hr}=9$        | $V_{tot}=5175$ mL    |
| $R_3$=0.014      | $V_{0.3}$=200           | $C_3$=0.2             | $l_{v,3}$=20.0                  | $E_{extra}=1.3$                     | $G_{A,P}=9$               | $HR_{nom}=67$ beats/min |
| $R_4$=0.11       | $V_{0.4}$=645           | $C_4$=7.0             | $l_{v,4}$=20.0                  | $E_{d,ra}=0.05$                     | $G_{CS}^{As}=0.007$       | $BW=69$ Kg           |
| $R_5$=0.028      | $V_{0.5}$=16            | $C_5$=1.3             | $l_{v,5}$=14.5                  | $E_{es,la}=0.61$                    | $G_{AS}^{CS}=0.022$       |                      |
| $R_6$=0.011      | $V_{0.6}$=16            | $C_6$=0.1             | $l_{v,6}$=16.0                  | $E_{d,la}=0.5$                      | $G_{AS}^{CS}=0.005$       |                      |
| $R_7$=0.010      | $V_{0.7}$=10             | $C_7$=0.1             | $l_{v,7}$=14.5                  | $E_{es,lb}=2.5$                     | $G_{AS}^{CS}=0.05$        |                      |
| $R_8$=0.10       | $V_{0.8}$=20            | $C_8$=0.21            | $l_{v,8}$=0                     | $E_{d,lb}=0.11$                     | $G_{AS}^{CS}=0.05$        |                      |
| $R_9$=0.11       | $V_{0.9}$=30            | $C_9$=5.0             | $l_{v,9}$=0                     |                                      | $G_{AS}^{CS}=0.05$        |                      |
| $R_{10}$=0.07    | $V_{1.0}$=300           | $C_{10}$=0.2          | $l_{v,10}$=10.0                 |                                      | $G_{AS}^{CS}=5$           |                      |
| $R_{11}$=0.07    | $V_{1.1}$=1146          | $C_{11}$=0.5          | $l_{v,11}$=10.0                 |                                      | $G_{AS}^{CS}=2$           |                      |
| $R_{12}$=0.09    | $V_{1.2}$=200           | $C_{12}$=0.2          | $l_{v,12}$=85                   |                                      | $G_{AS}^{CS}=13$          |                      |
| $R_{13}$=0.10    | $V_{1.3}$=716           | $C_{13}$=20           | $l_{v,13}$=85                   |                                      | $G_{AS}^{CS}=7$           |                      |
| $R_{14}$=0.019   | $V_{1.4}$=79            | $C_{14}$=1.3          | $l_{v,14}$=14.5                 | $P_{CP}=6$ mm Hg                     | $G_{CS}^{PS}=0.05$        |                      |
| $R_{15}$=0.008   | $V_{1.5}$=33            | $C_{15}$=0.5          | $l_{v,15}$=6                    |                                      | $G_{CS}^{PS}=0.05$        |                      |
| $R_{16}$=0.006   | $V_{1.6}$=14            | $C_{16}$=3.4          |                                      |                                      | $G_{CS}^{PS}=0.05$        |                      |
| $R_{17}$=0.006   | $V_{1.7}$=46            | $C_{17}$=9.0          |                                      |                                      | $G_{CS}^{PS}=0.05$        |                      |
| $R_{18}$=0.07    | $V_{1.8}$=160           | $C_{18}$=1.5          |                                      |                                      | $G_{CS}^{PS}=0.05$        |                      |
| $R_{19}$=0.006   | $V_{1.9}$=430           | $C_{19}$=3.4          |                                      |                                      | $G_{CS}^{PS}=13$          |                      |
| $R_{20}$=0.010   | $V_{2.0}$=46            | $C_{20}$=3.4          |                                      |                                      | $G_{CS}^{PS}=3$           |                      |
| $R_{21}$=4.0     | $V_{2.1}$=24            | $C_{21}$=9.0          |                                      |                                      | $G_{CS}^{PS}=64$          |                      |
| $R_{22}$=4.2     | $V_{2.2}$=55            | $C_{22}$=3.4          |                                      |                                      | $G_{CS}^{PS}=30$          |                      |
| $R_{23}$=2.4     |                        |                       |                                      |                                      |                           |                      |
| $R_{24}=3.9$     |                        |                       |                                      |                                      |                           |                      |

$R$: resistances; $V_0$: unstressed volumes; $C$: compliances; $l_\nu$: anatomical vertical lengths; $E$: elastances; $P$: pressures; $G$: gains factors; $V$: volumes; $HR$: heart rate; $BW$: body weight. Abbreviations: ra, right atrium; tri, tricuspid valve; rv, right ventricle; pa, pulmonary arteries; pc, pulmonary circulation; pv, pulmonary veins; la, left atrium; mit, mitral valve; lv, left ventricle; ub, upper body; rc, renal circulation, sc, splanchnic circulation; lc, leg circulation; es, end-systolic elastance; d, diastolic elastance; A, arterial baroreflex; CP, cardiopulmonary reflex; sp, set-point; S, sympathetic, P, parasympathetic; R-R, R-R interval; $th_0$, nominal intra-thoracic.
Table 5: Flow and Volume parameters in each of the compartments during steady-state simulation in supine position.

| Upper Body Circulation | Heart Circulation | Thoracic and Abdominal Circulation | Splanchnic Circulation | Renal Circulation | Leg Circulation |
|------------------------|-------------------|-----------------------------------|------------------------|------------------|----------------|
| Flow (l/min) | Volume (ml) | Flow (l/min) | Volume (ml) | Flow (l/min) | Volume (ml) | Flow (l/min) | Volume (ml) | Flow (l/min) | Volume (ml) |
| Q₁ = 1.34 | V₂ = 17.6 | Q₁ra = 5.85 | V₁ra = 31.8 | Q₁ = 4.56 | V₀ = 25.6 | Q₁₀ = 2.07 | V₀₁₀ = 317.8 | Q₁₁ = 1.19 | V₀₁₁ = 38.8 |
| Q₂ = 1.33 | V₃ = 218.5 | Q₂rv = 5.86 | V₂rv = 110.5 | Q₂ = 4.55 | V₁ = 19.1 | Q₂₁₁ = 2.06 | V₁₁₁ = 1382.7 | Q₂₁₂ = 1.18 | V₁₁₂ = 52.2 |
| Q₃ = 1.31 | V₄ = 682.9 | Q₃v = 5.88 | V₃v = 54.5 | Q₃₁₁ = 4.52 | V₀₁₁ = 81.9 | Q₃₁₁₀ = 2.06 | Q₀₁₁₀ = 1.19 | Q₁₁₁₀ = 1.28 |
| Q₅ = 1.32 | V₅ = 24.8 | Q₅pc = 5.85 | V₅pc = 153.8 | Q₅₁₅₁ = 4.53 | V₁₅₁ = 36.4 |
| Q₆ = 0.92 | V₆ = 48.1 | Q₆₁₅₀ = 4.53 |

Q<sub>n</sub>, flow going into the compartment n; Q<sub>no</sub>, flow going out the compartment n; ra, right atrium; rv, right ventricle; la, left atrium; lv, left ventricle;
