1    **TITLE PAGE**
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4      Cycling Exercise
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30     model, conducted to human experiments, analyzed the data, prepared figures, and drafted,
31     revised, and approved the final manuscript. Prof. Heldt provided expertise concerning the
32     cardiovascular modeling aspects and interpretation of the experimental data. He also edited,
33     revised, and approved the final version of the manuscript. Prof. Young contributed with the
34     overall supervision and management of the research project, including its relevance to artificial
35     gravity for space travel, and edited, revised, and approved he final version of the manuscript.
36
37   - **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.

**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.

2

81    **INTRODUCTION**

82          Artificial gravity (AG) generated by centrifugation is a promising countermeasure to mitigate

83    the detrimental effects of weightlessness during space missions (7). Previous ground-based studies have

84    shown that exposure to centrifugation can improve cardiovascular responses to orthostatic stress (18, 35,

85    44, 55), especially if centrifugation is combined with exercise (20, 27–30, 51–53). Artificial gravity has

86    also been proposed as a potential countermeasure to mitigate the recently discovered Spaceflight

87    Associated Neuro-Ocular Syndrome (SANS) (6). Before implementing AG in space, however,

88    additional research efforts are needed to determine the parameters that are most effective, including the

89    angular velocity and radius of the centrifuge, and to characterize the cardiovascular response to these

90    stressors under varying physiological baseline conditions (6). The expensive and time-consuming nature

91    of these experimental studies with human subjects makes the use of computational tools a very

92    attractive approach to systematically study human responses under these conditions.

93

94          Computational cardiovascular models can be used to describe and, more importantly, to predict,

95    human responses in cases where data collection is difficult, expensive, or infeasible. Despite the

96    complexity of the human body, computational approaches of various kinds and anatomical resolution

97    have been successfully applied to a variety of applications, from very detailed three-dimensional models

98    of selected regions, to low-dimensional models representing more aggregate system behavior (i.e.

99    lumped-parameter models). The selection of the type of model is primarily driven by the objectives of

100   the analysis as well as the availability of computational resources (46) and data to specify model

101   parameters and validate the model behavior. In the present work we are interested in the overall, short-

102   term, cardiovascular response to centrifugation combined with exercise and thus, the implementation of

103   a lumped-parameter model seems the appropriate approach.

104

105          One of the first systematic approaches of quantitative, system-level modeling of cardiovascular

106   regulation was developed by Guyton (21, 22). He was one of the first to apply a system engineering

107   approach to quantify and analyze various aspects of cardiovascular function using mathematical and

108   graphical techniques before computers became widely available. Since then, multiple models have been

109   developed to study cardiovascular responses to gravitational stress, including head up tilt (HUT) (25,

110   26, 34), lower-body negative pressure (25, 37), standing-up (15, 38, 39), and centrifugation (54).

111   However, none of these studies have evaluated the effects of centrifugation combined with exercise. The

112   incorporation of the exercise response to the already very complex cardiovascular regulatory

113   mechanisms brings additional physiological and methodological challenges (36) that we attempt to

114   address in our modeling efforts.

3

115

116     We developed a lumped-parameter model of the cardiovascular system able to capture transient
117 hemodynamic responses to lower-body ergometer exercise under gravitational stress generated by a
118 short-radius centrifuge. The model was built on previous work developed to study short-term
119 hemodynamic responses to centrifugation (54) and exercise (8), but not both mechanisms together at the
120 same time. Our cardiovascular model includes the systemic circulation, four cardiac chambers, and the
121 pulmonary circulation, divided in several parallel branches to account for the gravity gradient associated
122 with short-radius centrifugation. The model also includes the two major short-term neural control
123 mechanisms, the arterial baroreflex and the cardiopulmonary reflex, as well as important exercise
124 mechanisms such as the muscle-pump effect. Experimental measurements collected during a human
125 subject experiment at the Massachusetts Institute of Technology (MIT) short-radius centrifuge were
126 used for validation purposes.

127

128 **DESCRIPTION OF THE CARDIOVASCULAR MODEL**

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

134

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

141

142     **Figure 2** shows the architecture of a generic compartment (25, 50). The lumped physical
143 characteristics of each compartment are defined by a resistance $R_n$ and a capacitive element $C_n$ that
144 relates the distending volume $V_{d,n}$ stored in the segment to transmural pressure $\Delta P_n = P_n - P_{ext,n}$. The
145 pressure source $P_{ext,n}$ represents the external pressure acting on the vessels, such as intra-thoracic
146 pressure, intra-abdominal pressure, or muscle-pump pressure. Additionally, the pressure source $P_{h,n}$
147 represents the hydrostatic pressure related to the gravitational orthostatic stress. Other parameters

4

148     associated with each compartment (not shown in **Figure 2**) include zero-pressure filling volume $V_{0,n}$,

149     and the anatomical vertical length $l_{v,n}$ (superior-to-inferior extension of the vascular segment).

150

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

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

152     where $P_{n-1}, P_n$ are the compartment pressures, $P_{h,n}$ is the hydrostatic pressure induced by

153     centrifugation, and $R_n$ is the resistance of the $n^{\text{th}}$ compartment.

154

155         The transmural pressure in each compartment, defined as $P_n - P_{ext,n}$ , depends on the

156     distending volume $V_{d,n}$, and the compliance of the compartment $C_n$, through the following linear

157     relationship (except for Compartments 11–splanchnic, 13–leg, and 14–abdominal; see **Figure 1** for

158     compartment numbering scheme):

$$P_n - P_{ext,n} = \frac{V_{d,n}}{C_n} \tag{2}$$

159

160         Some compartments incorporate non-linear elements that affect their behavior. For example, the

161     four cardiac chambers (left atrium, left ventricle, right atrium, right ventricle) are described using time-

162     varying elastance models, and the generation of heartbeats is represented using an Integral Pulse

163     Frequency Modulation (IPFM) model (3, 54). Thus, the contractile force of the myocardial wall is

164     represented by the time-varying capacitors that cycle between a low capacitance (systolic) and a high

165     capacitance (diastolic) state of the myocardium. The intra-thoracic pressure (i.e. external pressure in the

166     thoracic compartments) modulates the filling status of the heart. Further details are included in the

167     Appendix. Moreover, the heart compartments also incorporate unidirectional diodes that represent the

168     cardiac valves and prevent reversal flow. Two vein compartments (Compartments 4–upper body and

169     13–leg) also include diodes to capture the unidirectional nature of the venous flow due to the presence

170     of venous valves.

171

172         Non-linear pressure-volume relationships are also incorporated in some compartments

173     (Compartments 11–splanchnic, 13–leg, and 14–abdominal) to capture their non-linear response when

174     operating at high transmural pressures. In those compartments, the pressure-volume relationship is

175     defined as:

$$V_{t,n} = V_{0,n} + \frac{2V_{max,n}}{\pi} \cdot arctan\left(\frac{\pi C_{0,n}}{2V_{max,n}} \cdot \Delta P_n\right) \ \ for \ \Delta P > 0, \ \ \ \ n = 11,13,14 \tag{3}$$

5

176     where $V_{t,n}$ denotes the total volume, $V_{0,n}$ denotes the venous unstressed volume or zero-pressure filling

177     volume, $V_{max,n}$ denotes the distending volume limit ( $V_{max,11}$ =1500 mL, $V_{max,13}$ =1000 mL,

178     $V_{max,11}$=650 mL), $C_{0,n}$ denotes the vascular compliance at zero transmural pressure, and $\Delta P_n$ denotes

179     the transmural pressure in the nth compartment.

180

181         The cardiovascular model was implemented in MATLAB Simulink. The distending volume is

182     used as the state variable, yielding the following expression for each compartment based on volume

183     conservation principles:

$$\frac{d}{dt}V_{d,n}(t) = q_{in_n} - q_{out_n} \tag{4}$$

184     where $q_{in_n}$ and $q_{out_n}$ correspond to the inward and outward flow in the nth compartment. The complete

185     cardiovascular model is defined by a set of coupled-first order differential equations.

186

187     *Arterial baroreflex and cardiopulmonary control systems*

188         The arterial baroreceptors and the cardiopulmonary receptors are the two major neurally-

189     mediated control systems that ensure short-term cardiovascular regulation in the presence of external

190     disturbances such as orthostatic stress or exercise. They are represented in our model as set-point

191     controllers that serve to minimize an error signal, namely the deviation of a specific local pressure from

192     a pre-defined set-point value, by adjusting various effector mechanisms in a feedback configuration via

193     autonomic pathways. To model the arterial baroreflex, we considered a single lumped baroreceptor in

194     the carotid sinus, assumed to be located 25 cm cranial of the heart. Thus, the carotid sinus pressure, $P_{CS}$,

195     is calculated as the aortic arch pressure $P_1$ minus the hydrostatic column acted upon by short-radius

196     centrifugation. The error signal between the measured pressure and the arterial pressure set-point, $P_A^{sp}$,

197     is fed into two linear time-invariant filters (sympathetic and parasympathetic (54)). The resultant signals

198     are then scaled by effector-specific gain values and then applied to the effector variables. The arterial

199     baroreflex effector variables include heart rate, right and left ventricular contractility, and the peripheral

200     resistance and venous unstressed volume of the upper body, renal, splanchnic, and leg compartments.

201

202         The cardiopulmonary reflex is represented using a similar feedback control loop in which the

203     measured variable is the right atrial transmural pressure, $\Delta P_{RA}$, and is compared to the cardiopulmonary

204     set-point pressure, $P_{CP}^{sp}$. The gains of the sympathetic filter are also specific to each effector variable.

205     The cardiopulmonary reflex effector variables include peripheral resistances and venous unstressed

206     volumes of the upper body, renal, splanchnic, and leg compartments. Both contributions from the

6

207    arterial baroreflex and the cardiopulmonary reflex constitute the total neurally-mediated global reflex
208    contribution to each effector variable.

209

210    *Centrifugation*

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

227

228    *Exercise*

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

234

235    **Decrease in leg arterial resistance.** Due to the higher metabolic demand during exercise, arterial
236    resistance decreases locally in the exercising muscles to increase local blood flow to satisfy the local
237    metabolic demand, and remove metabolic end products. In our modeling effort, we simulate lower-body
238    cycling exercise by disconnecting the leg resistance from the control systems at the onset of exercise
239    and manually adjusting it to match previously gathered experimental data (10) according to the
240    following expression:

7

$$R_{lc}(t) = R_{lc}^- + \left(R_{lf} - R_{lc}^-\right)\left(1 - e^{-t/\tau}\right) \tag{5}$$

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, $P_{ext}^{pump}$, is represented according to:

$$P_{ext}^{pump} = \begin{cases} P_{max}^{pump}\dfrac{1}{2}(1 - \cos(4\pi t)) & 0 \leq t \leq 1/4 \ sec \\ P_{max}^{pump} & 1/4 \leq t < 1/2 \ sec \\ P_{max}^{pump}\dfrac{1}{2}(1 + \cos(4\pi(t - 1/2))) & 1/2 \leq t < 3/4 \ sec \\ 0 & 3/4 \leq t < 1 \ sec \end{cases} \tag{6}$$

where $P_{max}^{pump}$ 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 $P_{spin}$, 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:

$$P_{ext}^{abd} = P_{max}^{abd}\left(1 - e^{-t/\hat{\tau}}\right) \tag{7}$$

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

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268　sympathetic activity through the arterial baroreceptor control systems previously described. Thus,

269　consequences of increasing the set-point pressure $P_A^{sp}$ include increases in heart rate, ventricular

270　contractility, total peripheral resistance (except in the working muscles), and venous tone.

271

272　*Parameters*

273　　　　Most of the numerical values assigned to the model parameters have been estimated from the

274　literature (24, 25). For each compartment, the parameter assignments include values for resistance R,

275　compliance C, zero-pressure filling volume $V_{0,n}$, and anatomical vertical length $l_{v,n}$. The compartmental

276　parameters and, in addition, the microvascular resistance values, pulmonary and cardiac parameters, as

277　well as parameters related to the control systems are provided in **Table 4** in the Appendix. The

278　parameters related to exercise are specific to our individual simulation profile and are detailed below.

279

280　**SIMULATION PROFILE AND EXPERIMENTAL DATA**

281　　　　We simulated a centrifugation profile identical to the one implemented in a human experiment

282　conducted on the MIT centrifuge (10). The experiment was approved by the Committee on the Use of

283　Humans as Experimental Subjects at MIT. Each subject gave written informed consent to participate in

284　the study. Experimental methods and data analysis are fully described in a previous publication (10). In

285　summary, twelve subjects were positioned in the right-side-down lateral decubitus position with their

286　head positioned at the center of rotation of the MIT centrifuge. The radius of the centrifuge was limited

287　to 1.4m to simulate the space limitations inherent to the short-radius centrifuge proposed for the

288　International Space Station, as part of the "Artificial Gravity with Ergometric Exercise as the

289　Countermeasure for Space Deconditioning in Humans" (AGREE) project (13). Thus, subjects adopted a

290　crouched posture that was taken into account in our simulations by adjusting the leg anatomical vertical

291　lengths $l_{v12}$ and $l_{v13}$. Subjects were exposed to different levels of centrifugation while performing

292　ergometer exercise at three intensities (25W, 50W, and 100W). The protocol, shown in **Figure 3,**

293　includes the following phases: baseline at rest (3 min), spin-up to the desired G-level (~100 sec), AG

294　phase for subjects to get used to the new gravitational environment (~2 min), the exercise portion of the

295　protocol, which includes three exercise intensities and transitions between them (15 min), another AG

296　phase with no exercise for subjects to partially recover (2 min), and spin-down deceleration phase (1

297　min). The entire protocol was completed in 25 minutes. During the centrifugation runs, continuous,

298　beat-to-beat cardiovascular data were collected using a non-invasive monitoring system (Nexfin

299　monitor, Edwards Lifesciences Corporation, Irvine, CA). Collected variables include heart rate (HR),

300　mean arterial pressure (MAP), systolic blood pressure (SBP), diastolic blood pressure (DBP), pulse

301　pressure (PP), stroke volume (SV), cardiac output (CO), and total peripheral resistance (TPR).

9

302

303    *Simulation approach*

304         A comparatively small set of physiologically plausible parameters from our model were

305    adjusted to simulate the centrifugation and exercise profiles described above. First, total blood volume

306    was set to $V_{tot} = 5175$ ml to closely represent our study population. This choice was based on an

307    average of 75 ml of blood per kg of body mass (17, 25, 42) and our experimental subjects' average

308    weight (± standard deviation) of $69.3 \pm 11.6$ kg.

309         Second, the angular velocity, $\omega(t)$, closely replicated the experimental protocol, increasing

310    from 0 rpm to $\omega_{max}$ during the spin-up phase, and decreasing back to 0 rpm during the spin-down

311    phase, in both cases following quarter-sine profiles. The experimental AG conditions included 1G and

312    1.4G at the feet, which were the settings of the MIT centrifuge corresponding to a maximum angular

313    velocity of 28.6 and 33.9 rpm, respectively. $P_{spin}$ was also adjusted according to the centrifugation

314    level.

315         Third, the three exercise-related parameters ($P_A^{sp}$, $P_{max}^{pump}$, $R_{lf}$) were manually adjusted at each

316    workload stage to match the population-averaged MAP and TPR responses (as judged by visual

317    inspections). The decreases in total vascular resistance were simulated by disconnecting the leg

318    peripheral resistance $R_{lc}(t)$ from the control systems at the onset of exercise, and matching the

319    experimentally observed decreases by appropriately setting the resistance parameters of Eqn. (5). This

320    process was repeated at every workload transition, adjusting the final leg resistance and the time

321    constant to match the experimental data. Similarly, the arterial blood pressure set-point, $P_A^{sp}$, and the

322    external pressure due to leg muscle pump, $P_{max}^{pump}$, were manually adjusted such that the simulated MAP

323    matched the experimental data. The nominal $P_A^{sp}$ was 93 mmHg; it was increased with increasing

324    exercise intensity. The external pressure, $P_{max}^{pump}$, was zero at rest and also increased with increasing

325    exercise intensity. Finally, the maximal intra-abdominal pressure, $P_{max,}^{abd}$ was also increased with

326    increasing exercise intensity in accordance with measurements from the literature (24, 25). For all

327    parameters, transitions between exercise phases were defined by exponential functions with the

328    appropriate time constants to match the experimental data. **Table 2** summarizes all exercise input

329    parameters used in our simulations.

330

331

332    **RESULTS**

333    *Baseline Steady State Simulation*

10

334    Results during steady-state simulations in supine position show that blood flow and volume
335    distributions to the different vascular beds are within the range of the normal population (47). The
336    distribution of CO to the upper body is 22% (normal range is 15%-29%), 20% to the kidney (18%-
337    24%), 35% to the splanchnic compartment (24%-48%), and 22% to the lower body (14%-33%).
338    Additional details about flow and volume distributions among the compartments are given in **Table 5** in
339    the Appendix.

340

341    *Centrifugation Simulation*

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

346

347    To simulate the exercise protocol, the simulated MAP and TPR responses were matched to the
348    population-averaged experimental responses by adjusting the values of the pressure set-point $P_A^{sp}$, leg
349    external pressure $P_{max}^{pump}$ , and $R_{lc}$ leg arterial resistance were selected for each exercise level (see **Table**
350    **2**). The top graphs in **Figure 4** and **Figure 5** show that our matching approach captures MAP and TPR
351    very closely. The nominal arterial set-point $P_A^{sp}$ was 93 mmHg, and this value was maintained until the
352    beginning of exercise, when the arterial set-point increased according to the exercise intensity (see
353    **Table 2**). Similarly, during the spin-up phase the simulated TPR responded appropriately to the
354    gravitational stress created by centrifugation: at the beginning of the spin-up phase, the simulated
355    resistance slightly decreased followed by a noticeable increase due to the control system reflexes. This
356    behavior of the TPR is typical of active standing maneuvers (26, 43). At the beginning of the exercise
357    (once the spin-up and AG phases were completed) the leg microvascular resistance was disconnected
358    from the controls and adjusted to decrease such that the simulated TPR matched the experimental data.
359    Thus, the $R_{lc}$ dynamics was composed of three transitions corresponding to the three workload
360    intensities simulated, as shown in the figures.

361

362    The rest of the cardiovascular variables are considered outputs of the simulation. They largely
363    reproduced the general trend of the experiment data, including baseline steady-state conditions as well
364    as the dynamic changes during spin-up/spin-down and exercise transitions. The arterial baroreflex and
365    the cardiopulmonary reflex responded properly to the cardiovascular stress created by centrifugation. In
366    addition, the three exercise phases were very distinguishable from one another, and the time constants
367    during transitions were particularly well matched. During the exercise portion of the protocol, the cyclic

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368 muscle pump action is noticeable in most of the simulated cardiovascular variables, making the
369 computational responses oscillate around their mean responses. Thus, during exercise, the simulated
370 responses in **Figure 4** and **Figure 5** manifest themselves as "thicker" lines, due to the periodic external
371 pressure imposed in the venous leg compartment simulating the effects of the cycling exercise
372
373        The simulated heart rate response replicates the experimental data well during all phases of the
374 protocol. Simulated SBP, DBP, SV, and CO are slightly underestimated, especially at higher workloads,
375 though they match the general trends of the data and generally stay within ±1 SD of the experimental
376 data. The PP simulations reproduce the experimental data for lower work rates (25W and 50W) but
377 underestimate the experimental results for higher work rates (100W). The underestimation of the PP
378 seemed to be driven by the underestimation of systolic pressures, particularly during the intensive
379 exercise phase at 100W (~7% underestimation in both gravitational scenarios), causing the PP
380 underestimation to reach 17% (1G) and 19% (1.4G) at this particular exercise phase. All in all, the
381 systolic, diastolic, and mean ABP were maintained within 10% of experimental values. **Table 3**
382 summarizes the simulated and experimental averages of the CV variables during the different phases of
383 the simulation: baseline, AG alone, exercise at 25W, exercise at 50W, and exercise at 100W. Averages
384 were calculated using the last two minutes of each protocol period, in order to avoid the transient
385 episodes between phases.
386
387 *Case study: Centrifugation of Hypovolemic Subjects due to Microgravity Exposure*
388        Having developed and validated the model for centrifugation and exercise, we can use this
389 model to characterize the cardiovascular response in subjects with specific health conditions, or
390 subjected to new gravitational stress configurations. Additionally, the model can also be used to help
391 test hypotheses about the cardiovascular response in additional scenarios. Physiological reasoning can
392 be used to predict in a qualitative manner specific responses driven by changes in certain parameters.
393 However, the specific magnitude of a response, or degree of impact of particular parameter changes are
394 harder to predict by reasoning alone, given the nonlinear and time-varying nature of the cardiovascular
395 system. As an example, we chose to explore the cardiovascular response to hypovolemic conditions.
396 This scenario is particularly relevant for human spaceflight, since astronauts lose approximately 10% of
397 their blood volume when exposed to extended microgravity (5, 49), which has proven to be problematic
398 when returning to a gravitational environment such as Earth (4, 33), or may become an issue in the
399 future when microgravity adapted individuals are exposed to artificial gravity during spaceflight (12, 19,
400 44, 45). We conducted additional simulations using the same exercise protocol and the centrifugation

12

401     profile at 1G to investigate cardiovascular responses when blood volume was reduced by 5, 10, and 15%

402     with respect to the euvolemic baseline (nominal $V_{tot}$=5175 $mL$).

403

404     Results are shown in **Figure 6** and provide quantitative information about the changes in cardiovascular

405     variables to centrifugation combined with lower-body ergometer exercise. MAP decreases with

406     decreasing levels of blood volume, despite the progressively larger increases in heart rate. The MAP

407     reduction seems to be driven by reduction in SBP, especially during the no-exercise portions of the

408     protocol (BL and AG) where DBP stays relatively constant across all blood volumes tested. PP, SV, and

409     CO also decrease with reducing levels of blood volume. All changes are generally exacerbated at higher

410     work rates, except for HR and TPR, where the responses at 100W across the different blood volume

411     conditions do not differ greatly.

412

413     **DISCUSSION**

414         Several studies have investigated the short-term hemodynamics response of exercise in the

415     upright and supine posture (1, 11), and as a potential countermeasure in ground-based bedrest studies

416     (40). Our focus here is on the acute cardiovascular response to a gravitational stress that can be

417     recreated in space and that is not constant along the major body axis. We developed a lumped-parameter

418     model of the cardiovascular system to simulate the short-term hemodynamic responses to combined

419     gravitational stress and exercise. In particular, gravitational stress was generated by centrifugation of

420     subjects using a short-radius centrifuge, therefore generating a high gravity gradient along the long axis

421     of the body. The model simulates the hydrostatic pressures among cardiovascular compartments caused

422     by the gravity gradient. In addition, the effects of ergometer exercise were also incorporated in the

423     model, including the increase in blood pressure, the muscle pump effect, the decrease in vascular

424     resistance, and changes in intra-abdominal pressure. Finally, the model was programmed to recreate the

425     25-min exercise protocol experienced by 12 subjects in a previous human experiment conducted at MIT

426     (10). Although there have been other studies investigating centrifugation combined with ergometer

427     exercise (16, 27–29, 45, 48, 51), these studies have mainly focused on physiological responses *before*

428     and *after* a specific intervention (e.g. bed rest or training protocol) and not *during* the centrifugation

429     sessions. Thus, the cardiovascular data taken during the MIT centrifugation experiments were used to

430     calibrate and evaluate the computational model. Thus, we are combining mathematical modeling and

431     human experiments in a synergistic manner. On the one hand, experiments are necessary for specifying

432     model parameters and for model validation; on the other hand, models allow for flexibility to investigate

433     physiological mechanisms under consideration, enhance experimental data interpretation, and serve as a

434     vehicle to test competing hypothesis.

13

435

436        Generally, the cardiovascular model matched the dynamic cardiovascular response during the
437    25-min exercise protocol quite well. It showed a slight tendency to underestimate some of the
438    cardiovascular variables, particularly SV, and PP at higher workload intensities, and to a lesser extent,
439    CO. These results could be better adjusted by modifying some of the numerous parameters that are built
440    in the model. However, it is important to emphasize that the purpose of these simulations is to
441    intentionally limit the number of inputs and not to exert the full flexibility of the model to reduce the
442    error between the experimental and simulated responses. A small number of parameters, namely TPR
443    and MBP, have been constrained to determine if the resulting simulations capture the physiologic
444    response over a range of exercise levels and AG regimes. The multi-compartment model has more than
445    100 parameters and it can be manipulated to perfectly match the cardiovascular responses. However, the
446    value of such an exercise is small, as most parameters will have negligible influence on the output and
447    the resultant solution will therefore not be unique and will not provide much physiological insights.

448

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

461

462        To explore the physiological consequences of centrifugation we further studied quantitative
463    responses to centrifugation and exercise in hypovolemic subjects, with reduction of 5, 10, and 15% of
464    total blood volume. There is limited experimental data in the literature to perform a direct comparison
465    between our simulations and hemodynamic responses from hypovolemic subjects subjected to short-
466    radius centrifugation an exercise. Thus, we base our comparison to a similar study that used tilt tests
467    maneuvers to study orthostatic stress. Linnarsson and his colleagues (35) investigated orthostatic
468    tolerance in hypovolemic subjects after five days of bedrest. Subjects lost between 8-14% of blood

14

469    volume during the 5-day bed rest, and their short-term, post-bedrest HR, SYS, and DIA responses

470    during a tilt test (80º upright) changed approximately +29%, −15%, and −5% respectively, with respect

471    to pre-bed rest. Our data indicate that hypovolemic subjects presenting blood volume losses between 10-

472    15% will also experience increases in HR (+14 to 17%) and decreases in SYS (−10.5 to −15.6%) and

473    DIA (−2.8 to −5.7%). We expect to see less significant changes in a short-radius centrifuge due to the

474    presence of a strong gravity gradient that makes the gravitational stress less intense than being exposed

475    to constant 1G gravitational environment. Thus, our simulations seem to be in agreement with the

476    limited available data and the expected responses based on physiological principles. Additional

477    experiments are warranted to further validate the predicted values from our model, particularly the ones

478    involving exercise. However, these predictions are already providing insightful information about

479    experimental conditions not tested before.

480

481    *Limitations*

482       We chose to represent the cardiovascular behavior using a lumped-parameter model. This

483    approach is unable to simulate pulse wave propagation phenomena such as the changes in arterial

484    pressure waveform as it propagates through the arterial system (31, 50) and might therefore be

485    responsible for our underestimation of systolic blood pressure at higher centrifugation level and exercise

486    regimes. Despite this limitation our model was able to reproduce realistic responses at a lower

487    computational cost. Inertial effects were also not included in the model causing, for example, the

488    absence of the dichrotic notch typically present in the arterial and pulmonary arterial waveforms during

489    closure of the semilunar valves. Inertial effects become important when studying intra-beat changes

490    (within a cardiac cycle), which is not the case in the present study. Inertial effects have been estimated

491    to account for less than 1% of stroke volume and mean arterial pressure (9) and therefore they have been

492    neglected.

493       We have also not taken into account possible non-linear cardiac effects. Both systolic and

494    diastolic pressure-volume relationships were assumed to be linear, which is reasonable at normal filling

495    pressures, but these relationships become non-linear at higher filling pressures. Simulations of

496    pathologically high pressures were beyond of the scope of this work, and for the purpose of the

497    simulations presented here, the pressure-volume relationships were assumed linear. Additionally, the

498    unstressed volume was assumed to be static throughout the cardiac cycle and the same for the diastolic

499    and systolic pressure-volume relationships. Typically, the end-systolic unstressed volume is between

500    25-40% lower than its diastolic counterpart (2, 32), indicating a small but potentially significant

501    contribution to stroke volume, thus decreasing the underestimation seen in our simulations.

15

502    Viscoelastic stress-relaxation effects of the systemic veins were also not included in our

503    modeling effort. This phenomenon refers to the intrinsic ability of the vascular walls to stretch slowly

504    when the pressure rises and to contract slowly when the pressure falls (23, 26). This effect becomes

505    important when studying very short-term (~30 s) dynamic blood pressure responses after exposure to

506    passive head-up tilt, due to the altering of the time-course of venous pooling to the lower body and thus,

507    limiting the blood pressure dip typically seen during active standing (26). In our work we focused on

508    steady-state cardiovascular responses during active exposure to centrifugation and therefore these

509    effects were also neglected. We have also not taken into account breathing-related changes in

510    intrathoracic pressure. As the depth of breathing increases with increasing exercise, the lowering of

511    intrathoracic pressure aids in venous return at higher exercise levels. We have also assumed that the

512    resistance changes due to exercise are largely determined by the arteriolar vasodilation and that the

513    muscle pump primarily affects the filling state of the leg veins.

514    Finally, we have already commented on the difficulty of assigning numerical values to all the

515    parameters of the model. The degree to which our model reproduces the experimental data suggests that

516    we have included all the major features with a reasonable degree of parameter accuracy. Sensitivity

517    analysis techniques could elucidate the influence of each parameter on the model outputs to determine

518    the subset of physiological parameters that dominate the model response. This could be further related

519    to individual differences seen in hemodynamic responses to gravitational stress across specific

520    population, such as astronauts coming back to Earth after being exposed to microgravity conditions.

521

522    *Conclusion*

523    We have developed a computational model of the cardiovascular system capable of reproducing

524    hemodynamic responses during gravitational stress generated by a short-radius centrifuge and lower-

525    body ergometer exercise. The model simulated both transient and steady-state responses that compare

526    well with experimental data gathered on twelve subjects that underwent the same simulated protocol

527    using the MIT short-radius centrifuge. We explored the capabilities of the model to generate new

528    hypotheses and to quantify changes in cardiovascular responses due to variations in an individual

529    parameter (i.e. total blood volume).

530

**APPENDIX**

**A. Additional Details about the Cardiovascular Model**

533  Most of the model equations have already been reported in a previous publication (14), but for

534  completeness, we are including them in this Appendix.

535

536  *Cardiac Model*

537  The four cardiac chambers are simulated using time-varying elastance models (24, 25). The

538  time-varying elastance in each one of the four cardiac chambers is represented using the equation below,

539  where the time interval of diastolic relaxation $T_d^r$ is assumed to be one half of the systolic time interval

540  $T_s$:

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

541  and $E_d$ and $E_{es}$ are the diastolic elastance and end-systolic elastances in each one of the four cardiac

542  chambers, respectively. The timing parameters include the atrial and ventricular systole duration, $T_S^a$

543  and $T_S^v$, as well as the "P-R interval", which we defined here as the delay between the onset of the atrial

544  and ventricular contraction $T_{a-v}$. Their values are assumed to be proportional to the square root of the

545  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

546  $T_{a-v}(s) = 0.12\sqrt{T_{RR}}$

547

548  The cardiac pacemaker is represented using an Integral Pulse Frequency Modulation (IPFM)

549  model (3, 24, 25, 54), according to:

$$M(t) = \int_{t_k-1}^{t} m(t)dt = \int_{t_k-1}^{t} (m_0 + m_r(t))dt$$

550  where $M(t)$ mimics the behavior of the transmembrane potential in the sino-atrial node whose value at

551  time $t$ depends on the cumulative automaticity $m_0$ (assumed constant), and the contribution of neural

552  control input $m_r(t)$ (either sympathetic or parasympathetic activity) since the end of the last heartbeat

553  (or cardiac excitation time $t_k - 1$). A new heartbeat occurs at the time $t_k$ when the transmembrane

554  potential $M(t)$ reaches a predefined threshold potential $\Gamma = 1$, and the time since the previous heartbeat

555  is at least one fifth of the preceding cardiac cycle length:

556  $$\int_{t_k-1}^{t_k} m(t)dt = M(t_k) \ge \Gamma \quad \text{and} \quad t_k - t_{k-1} \ge 0.2(t_{k-1} - t_{k-2})$$

17

557

558

559    The function $m(t)$ is defined as the inverse of the instantaneous R-R interval $I(t)$:

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

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

561    control system.

562

563    *Control Systems*

564    The baroreceptor control system is modeled using a negative feedback loop and an arterial

565    pressure set-point $P_A^{sp}$. Assuming one lumped baroreceptor located in the carotid sinus at 25 cm above

566    the heart, the carotid sinus pressure $P_{CS}$ (mmHg) is defined as:

$$P_{CS} = P_1 - \frac{1}{2} \cdot \rho \cdot \omega^2(t) \cdot ((25 + d)^2 - d^2) \tag{9}$$

567    where $d$ is the distance between the head and the center of rotation measured in cm, $\rho$ is the blood

568    density in $\frac{mmHg}{1/_{s^2}cm^2}$, and $\omega(t)$ is the angular velocity of the centrifuge in rad/s. The feedback error signal

569    $e_{AB}(t)$ is calculated as follows:

$$e_{AB}(t) = 18 \cdot arctan\left(\frac{P_{CS} - P_A^{sp}}{18}\right) \tag{10}$$

570

571    The cardiopulmonary reflex is also modeled using a negative feedback loop and a pressure set-

572    point $P_{CP}^{sp}$. The variable measured is the transmural right atrial pressure $\Delta P_{RA}$.and the error signal

573    $e_{CP}(t)$ is calculated as follows:

$$e_{CP}(t) = 5 \cdot arctan\left(\frac{\Delta P_{RA} - P_{CP}^{sp}}{5}\right) \tag{11}$$

574

575    The sympathetic and parasympathetic control systems are modeled as two linear time-invariant

576    (LTI) filters. The transfer functions for the sympathetic $s(s)$ and parasympathetic $p(s)$ filters are:

$$s(s) = \frac{1}{42s^2}e^{-2s} + \frac{1}{75s^2}e^{-5s} + \frac{1}{300s^2}e^{-30s} \tag{12}$$

577

$$p(s) = 1 \tag{13}$$

578

579    *Transcapillary Flow and the Interstitial Fluid Volume*

18

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

$$V^n(t) = \frac{P^n_{h,max}}{\sum_i P^i_{h,max}} \cdot V(t) \tag{14}$$

589

$$q^n(t) = \frac{P^n_{h,max}}{\sum_i P^i_{h,max}} \cdot q(t) \tag{15}$$

590

591    where $P^n_{h,max}$ is the maximum hydrostatic pressure in the nth compartment; and $\sum_i P^i_{h,max}$ is the sum of
592    the maximum hydrostatic pressures of the three compartments (11, 13, and 14).

593

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

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

597

598    <u>Region I</u>: Gradual increase in orthostatic stress over a period of length $\Delta t$.

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

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

599    <u>Region II</u>: Full gravitational stress during period of duration $T_{tilt}$.

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

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

600    <u>Region III</u>: Gradual decline in gravitational stress over a period of length $\Delta t$.

$$q(t) = \frac{V_{max}}{\Delta t} \cdot \left( 1 + \left( 1 - e^{-\frac{\Delta t}{\tau}} \right) e^{-\frac{T_{tilt}}{\tau}} \right) \cdot e^{-\frac{t-(\Delta t + T_{tilt})}{\tau}} - \frac{V_{max}}{\Delta t} \tag{20}$$

19

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

$$+ V_{max} \cdot \frac{\tau}{\Delta t} \cdot \left(1 + \left(1 - e^{-\frac{\Delta t}{\tau}}\right) e^{-\frac{T_{tilt}}{\tau}}\right) \cdot \left(1 - e^{-\frac{t - (\Delta t + T_{tilt})}{\Delta t}}\right) \quad (21)$$

601    <u>Region IV</u>: Post-orthostatic stress recovery of unspecified length.

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

$$V(t) = V_{max} \cdot \frac{\tau}{\Delta t} \cdot \left(1 - e^{-\frac{\Delta t}{\tau}}\right) \cdot \left(1 - e^{-\frac{T_{tilt} + \Delta t}{\tau}}\right) \cdot e^{-\frac{t - (2\Delta t + T_{tilt})}{\tau}} \quad (23)$$

602

603    *Initial Conditions*

604          The following 23 non-linear algebraic equations are used to find the initial conditions, and they

605    describe the blood flow in the compartments assuming that the system is in steady state (54). The first

606    equation equates the right ventricular stroke volume and the left ventricular stroke volume, and the last

607    equation is based on the conservation of volume equating the difference between the total volume and

608    the unstressed volume, and the distending volume in each compartment.

609

$$C_{ld}(P_{lvd} - P_{th}) - C_{ls}(P_{lvs} - P_{th}) = C_{rd}(P_{rvd} - P_{th}) - C_{rs}(P_{rvs} - P_{th}) \quad (24)$$

$$C_{ld}(P_{lvd} - P_{th}) - C_{ls}(P_{lvs} - P_{th}) = T_s^v \cdot \frac{P_{lvd}}{R_1} \quad (25)$$

$$T_s^v \cdot \frac{P_{lvd}}{R_1} = I_0 \cdot \left(\frac{P_1 - P_2}{R_2} + \frac{P_1 - P_6}{R_6}\right) \quad (26)$$

$$I_0 \cdot \frac{P_1 - P_2}{R_2} = I_0 \cdot \frac{P_2 - P_3}{R_3} \quad (27)$$

$$I_0 \cdot \frac{P_2 - P_3}{R_3} = I_0 \cdot \frac{P_3 - P_4}{R_{ub}} \quad (28)$$

$$I_0 \cdot \frac{P_3 - P_4}{R_{ub}} = I_0 \cdot \frac{P_4 - P_5}{R_4} \quad (29)$$

$$I_0 \cdot \frac{P_4 - P_5}{R_4} = I_0 \cdot \frac{P_5 - P_{ra}}{R_5} \quad (30)$$

$$I_0 \cdot \frac{P_1 - P_6}{R_6} = I_0 \cdot \frac{P_6 - P_7}{R_7} \quad (31)$$

$$I_0 \cdot \frac{P_6 - P_7}{R_7} = I_0 \cdot \left(\frac{P_7 - P_8}{R_8} + \frac{P_7 - P_{10}}{R_{10}} + \frac{P_7 - P_{12}}{R_{12}}\right) \quad (32)$$

$$I_0 \cdot \frac{P_7 - P_8}{R_8} = I_0 \cdot \frac{P_8 - P_9}{R_{rc}} \quad (33)$$

20

$$I_0 \cdot \frac{P_8 - P_9}{R_{rc}} = I_0 \cdot \frac{P_9 - P_{14}}{R_9} \tag{34}$$

$$I_0 \cdot \frac{P_7 - P_{10}}{R_{10}} = I_0 \cdot \frac{P_{10} - P_{11}}{R_{sc}} \tag{35}$$

$$I_0 \cdot \frac{P_{10} - P_{11}}{R_{sc}} = I_0 \cdot \frac{P_{11} - P_{14}}{R_{11}} \tag{36}$$

$$I_0 \cdot \frac{P_7 - P_{12}}{R_{12}} = I_0 \cdot \frac{P_{12} - P_{13}}{R_{lc}} \tag{37}$$

$$I_0 \cdot \frac{P_{12} - P_{13}}{R_{lc}} = I_0 \cdot \frac{P_{13} - P_{14}}{R_{13}} \tag{38}$$

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

$$I_0 \cdot \frac{P_{14} - P_{15}}{R_{14}} = I_0 \cdot \frac{P_{15} - P_{ra}}{R_{15}} \tag{40}$$

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

$$T_d^v \cdot \frac{P_{ra} - P_{rvd}}{R_{tri}} = T_s^v \cdot \frac{P_{rvd} - P_{pa}}{R_{ro}} \tag{42}$$

$$T_s^v \cdot \frac{P_{rvd} - P_{pa}}{R_{ro}} = I_0 \cdot \frac{P_{pa} - P_{pv}}{R_{pv}} \tag{43}$$

$$I_0 \cdot \frac{P_{pa} - P_{pv}}{R_{pv}} = I_0 \cdot \frac{P_{pv} - P_{la}}{R_{li}} \tag{44}$$

$$I_0 \cdot \frac{P_{pv} - P_{la}}{R_{li}} = T_d^v \cdot \frac{P_{la} - P_{lvd}}{R_{mit}} \tag{45}$$

$$V_{total} - V_{total}^0 = \sum_{\substack{j \in \left\{ \begin{smallmatrix} 1,2,\dots,10, \\ 12,15,ra,rv, \\ pa,pv,la,lv \end{smallmatrix} \right\}}} C_j \cdot \Delta P_j + \sum_{k \in \{11,13,14\}} \left[ \frac{2V_{maxk}}{\pi} \cdot arctan\left( \frac{\pi C_{0k}}{2V_{maxk}} \cdot \Delta P_k \right) \right] \tag{46}$$

610

611

612

**B.  Parameters of the Cardiovascular Model**

614

(Insert **Table 4**)

616

**C.  Baseline Steady State Flows and Volume Distributions**

618

(Insert **Table 5**)

21

620

621

**ACKNOWLEDEMENTS**

We thank the subjects who kindly participated in the experimental study conducted at the Massachusetts Institute of Technology.

**DISCLOSURES**

No conflicts of interest, financial or otherwise, are declared by the authors.

633

634

635

636    **REFERENCES**

637    1.    **Ade CJ**, **Broxterman RM**, **Barstow TJ**. Effects of body posture and exercise training on
638          cardiorespiratory responses to exercise. *Respir Physiol Neurobiol* 188: 39–48, 2013.

639    2.    **Alexander J**, **Sunagawa K**, **Chang N**, **Sagawa K**. Instantaneous pressure-volume relation of
640          the ejecting canine left atrium. *Circ Res* 61: 209–219, 1987.

641    3.    **de Boer RW**, **Karemaker JM**, **Stracke J**. Description of the Heart_Rate Variability Data in
642          Accordance With a Physiological Model for the Genesis of Heartbeats. *Phychophysiology* 22:
643          147–155, 1985.

644    4.    **Buckey JC**, **Lane LD**, **Levine BD**, **Watenpaugh DE**, **Wright SJ**, **Moore WE**, **Gaffney FA**,
645          **Blomqvist CG**. Orthostatic intolerance after spaceflight. *J Appl Physiol* 81: 7–18, 1996.

646    5.    **Charles BJ**, **Lathers CM**. Cardiovascular Adaption to Spaceflight. *J Clin Pharmacol* 31: 1010–
647          1023, 1991.

648    6.    **Clément G**. International roadmap for artificial gravity research. *npj Microgravity* 3: 29, 2017.

649    7.    **Clement GR**, **Bukley AP**, **Paloski WH**. Artificial gravity as a countermeasure for mitigating
650          physiological deconditioning during long-duration space missions. *Front Syst Neurosci* 9: 92,
651          2015.

652    8.    **Croston RC**, **Rummel J a.**, **Kay FJ**. Computer model of cardiovascular control system
653          responses to exercise. *J. Dyn. Syst. Meas. Control* (1973). doi: 10.1115/1.3426719.

654    9.    **Defares JG**, **Osborn JJ**, **Hara HH**. Theoretical synthesis of the cardiovascular system. Study I:
655          The controlled system. *Acta Physiol Pharmacol Neerl* 12: 189–265, 1963.

656    10.   **Diaz-Artiles A**, **Heldt T**, **Young LR**. Short-Term Cardiovascular Response to Short-Radius
657          Centrifugation With and Without Ergometer Exercise. *Front Physiol* 9: 1492, 2018.

658    11.   **Diaz-Artiles A**, **Navarro Tichell P**, **Perez F**. Cardiopulmonary Responses to Sub-Maximal
659          Ergometer Exercise in a Hypo-Gravity Analog Using Head-Down Tilt and Head-Up Tilt. *Front*
660          *Physiol* 10: 1–15, 2019.

661    12.   **Diaz A**, **Heldt T**, **Young LR**. Cardiovascular responses to artificial gravity combined with
662          exercise. In: *2015 IEEE Aerospace Conference Proceedings*. Big Sky, MT: 2015.

663    13.   **Diaz A**, **Trigg C**, **Young LR**. Combining ergometer exercise and artificial gravity in a compact-
664          radius centrifuge. *Acta Astronaut* 113: 80–88, 2015.

665    14.   **Diaz Artiles A**, **Heldt T**, **Young LR**. Effects of artificial gravity on the cardiovascular system:
666          Computational approach. *Acta Astronaut* 126: 395–410, 2016.

667    15.   **Ellwein LM**, **Tran HT**, **Zapata C**, **Novak V**, **Olufsen MS**. Sensitivity Analysis and Model
668          Assessment: Mathematical Models for Arterial Blood Flow and Blood Pressure. *Cardiovasc Eng*
669          8: 94–108, 2008.

670    16.   **Evans JM**, **Stenger MB**, **Moore FB**, **Hinghofer-Szalkay H**, **Rössler A**, **Patwardhan AR**,
671          **Brown DR**, **Ziegler MG**, **Knapp CF**. Centrifuge training increases presyncopal orthostatic
672          tolerance in ambulatory men. *Aviat Sp Environ Med* 75: 850–858, 2004.

673    17.   **Gibson BYJG**, **Evans WA**. Clinical studies of the blood volume. II. The relation of plasma and
674          total blood volume to venous pressure, blood velocity rate, physical measurements, age and sex
675          in ninety normal humans. *J Clin Invest* 16: 317–328, 1937.

676    18.   **Goswami N**, **Bruner M**, **Xu D**, **Bareille MP**, **Beck A**, **Hinghofer-Szalkay H**, **Blaber AP**.

23

677      Short-arm human centrifugation with 0.4g at eye and 0.75g at heart level provides similar
678      cerebrovascular and cardiovascular responses to standing. *Eur J Appl Physiol* 115: 1569–1575,
679      2015.

680  19.  **Goswami N**, **Evans J**, **Schneider S**, **Von Der Wiesche M**, **Mulder E**, **Rössler A**, **Hinghofer-**
681      **Szalkay H**, **Blaber AP**. Effects of individualized centrifugation training on orthostatic tolerance
682      in men and women. *PLoS One* 10, 2015.

683  20.  **Greenleaf JE**, **Gundo DP**, **Watenpaugh DE**, **Mulenburg GM**, **Mckenzie MA**, **Looft-Wilson**
684      **R**, **Hargens AR**. Cycle-Powered Short Radius (1.9 m) Centrifuge : Effect of Exercise Versus
685      Passive Acceleration on Heart Rate in Humans. In: *NASA Technical Memorandum 110433*.
686      Moffett Field, California: 1997, p. 1–14.

687  21.  **Guyton A**, **AW L**, **Kaufmann B**. Effect of Mean Circulatory Filling Pressure and Other
688      Circulatory Factors on Cardiac Output. *Am J Physiol* 180: 463–468, 1955.

689  22.  **Guyton AC**, **Coleman TG**, **Granger HJ**. Circulation: overall regulation. *Annu Rev Physiol* 34:
690      13–46, 1972.

691  23.  **Guyton AC**, **Jones CE**, **Coleman TG**. *Circulatory Physiology: Cardiac Output and Its*
692      *Regulation*. 2nd Ed. Philadelphia: WB Saunders, 1973.

693  24.  **Heldt T**, **Mukkamala R**, **Moody GB**, **Mark RG**. CVSim: An Open-Source Cardiovascular
694      Simulator for Teaching and Research. *Open Pacing Electrophysiol Ther J* 3: 45–54, 2010.

695  25.  **Heldt T**, **Shim EB**, **Kamm RD**, **Mark RG**. Computational modeling of cardiovascular response
696      to orthostatic stress. *J Appl Physiol* 92: 1239–1254, 2002.

697  26.  **van Heusden K**, **Gisolf J**, **Stok WJ**, **Dijkstra S**, **Karemaker JM**. Mathematical modeling of
698      gravitational effects on the circulation: importance of the time course of venous pooling and
699      blood volume changes in the lungs. *AJP Hear Circ Physiol* 291: H2152–H2165, 2006.

700  27.  **Iwasaki K-I**, **Shiozawa T**, **Kamiya A**, **Michikami D**, **Hirayanagi K**, **Yajima K**, **Iwase S**,
701      **Mano T**. Hypergravity exercise against bed rest induced changes in cardiac autonomic control.
702      *Eur J Appl Physiol* 94: 285–291, 2005.

703  28.  **Iwase S**. Effectiveness of centrifuge-induced artificial gravity with ergometric exercise as a
704      countermeasure during simulated microgravity exposure in humans. *Acta Astronaut* 57: 75–80,
705      2005.

706  29.  **Iwase S**, **Fu Q**, **Narita K**, **Morimoto E**, **Takada H**, **Mano T**. Effects of graded load of artificial
707      gravity on cardiovascular functions in humans. *Environ Med* 46: 29–32, 2002.

708  30.  **Katayama K**, **Sato K**, **Akima H**. Acceleration with Exercise during Head-Down Bed Rest
709      Preserves Upright Exercise Responses. *Aviat Sp Environ Med* 75: 1029–1035, 2004.

710  31.  **Kokalari I**, **Karaja T**, **Guerrisi M**. Review on lumped parameter method for modeling the
711      blood flow in systemic arteries. *J Biomed Sci Eng* 6: 92–99, 2013.

712  32.  **Lau V-K**, **Sagawa K**, **Suga H**. Instantaneous pressure-volume relationship of right atrium
713      during isovolumic in canine heart. *Am J Physiol - Hear Circ Physiol* 236: H672–H679, 1979.

714  33.  **Lee SMC**, **Feiveson AH**, **Stein S**, **Stenger MB**, **Platts SH**. Orthostatic Intolerance After ISS
715      and Space Shuttle Missions. *Aerosp Med Hum Perform* 86: 54–67, 2015.

716  34.  **Lim E**, **Chan GSH**, **Dokos S**, **Ng SC**, **Latif L a**, **Vandenberghe S**, **Karunanithi M**, **Lovell**
717      **NH**. A cardiovascular mathematical model of graded head-up tilt. *PLoS One* 8: e77357, 2013.

24

718   35.   **Linnarsson D**, **Hughson RL**, **Fraser KS**, **Clément G**, **Karlsson LL**, **Mulder E**, **Paloski WH**,
719         **Rittweger J**, **Wuyts FL**, **Zange J**. Effects of an artificial gravity countermeasure on orthostatic
720         tolerance, blood volumes and aerobic power after short-term bed rest (BR-AG1). *J Appl Physiol*
721         118: 29–35, 2015.

722   36.   **Melchior FM**, **Srinivasan RS**, **Charles JB**. Mathematical modeling of human cardiovascular
723         system for simulation of orthostatic response. *Am J Physiol* 262: H1920–H1933, 1992.

724   37.   **Melchior FM**, **Srinivasan RS**, **Thullier PH**, **Clère JM**. Simulation of cardiovascular response
725         to lower body negative pressure from 0 to -40 mmHg. *J Appl Physiol* 77: 630–640, 1994.

726   38.   **Olufsen M**, **Tran H**, **Ottesen J**. Modeling cerebral blood flow control during posture change
727         from sitting to standing. *Cardiovasc Eng* 4: 47–58, 2004.

728   39.   **Olufsen MS**, **Ottesen JT**, **Tran HT**, **Ellwein LM**, **Lipsitz L a**, **Novak V**. Blood pressure and
729         blood flow variation during postural change from sitting to standing: model development and
730         validation. *J Appl Physiol* 99: 1523–1537, 2005.

731   40.   **Ploutz-Snyder LL**, **Downs M**, **Goetchius E**, **Crowell B**, **English KL**, **Ploutz-Snyder R**, **Ryder
732         J**, **Dillon EL**, **Sheffield-Moore M**, **Scott JM**. Exercise Training Mitigates Multi-System
733         Deconditioning during Bed Rest. 2018.

734   41.   **Reisner AT**, **Heldt T**. A computational model of hemorrhage and dehydration suggests a
735         pathophysiological mechanism: Starling-mediated protein trapping. *AJP Hear Circ Physiol* 304:
736         H620–H631, 2013.

737   42.   **Sjöstrand T**. Volume and Distribution of Blood and Their Significance in Regulating the
738         Circulation. *Physiol Rev* 33: 202–228, 1953.

739   43.   **Sprangers RL**, **Wesseling KH**, **Imholz AL**, **Imholz BP**, **Wieling W**. Initial blood pressure fall
740         on stand up and exercise explained by changes in total peripheral resistance. *J Appl Physiol* 70:
741         523–530, 1991.

742   44.   **Stenger MB**, **Evans JM**, **Knapp CF**, **Lee SMC**, **Phillips TR**, **Perez SA**, **Moore AD**, **Paloski
743         WH**, **Platts SH**. Artificial gravity training reduces bed rest-induced cardiovascular
744         deconditioning. *Eur J Appl Physiol* 112: 605–616, 2012.

745   45.   **Stenger MB**, **Evans JM**, **Patwardhan AR**, **Moore FB**, **Hinghofer-Szalkay H**, **Rössler A**,
746         **Ziegler MG**, **Knapp CF**. Artificial gravity training improves orthostatic tolerance in ambulatory
747         men and women. *Acta Astronaut* 60: 267–272, 2007.

748   46.   **Taelman L**, **Degroote J**, **Verdonck P**, **Vierendeels J**, **Segers P**. Modeling hemodynamics in
749         vascular networks using a geometrical multiscale approach: numerical aspects. *Ann Biomed Eng*
750         41: 1445–58, 2013.

751   47.   **W Leggett R**, **Williams L**. A Proposed Blood Circulation Model for Reference Man. 1995.

752   48.   **Wang YC**, **Yang C Bin**, **Wu YH**, **Gao Y**, **Lu DY**, **Shi F**, **Wei XM**, **Sun XQ**. Artificial gravity
753         with ergometric exercise as a countermeasure against cardiovascular deconditioning during 4
754         days of head-down bed rest in humans. *Eur J Appl Physiol* 111: 2315–2325, 2011.

755   49.   **Watenpaugh DE**. Fluid volume control during short-term space flight and implications for
756         human performance. *J Exp Biol* 204: 3209–3215, 2001.

757   50.   **Westerhof N**, **Lankhaar J-W**, **Westerhof BE**. The arterial Windkessel. *Med Biol Eng Comput*
758         47: 131–141, 2009.

759   51.   **Yang C Bin**, **Zhang S**, **Zhang Y**, **Wang B**, **Yao Y-J**, **Wang YC**, **Wu YH**, **Liang W Bin**, **Sun**

25

760       **XQ**. Combined short-arm centrifuge and aerobic exercise training improves cardiovascular
761       function and physical working capacity in humans. *Med Sci Monit* 16: 575–583, 2010.

762   52.   **Yang Y**, **Baker M**, **Graf S**, **Larson J**, **Caiozzo VJ**. Hypergravity resistance exercise: the use of
763       artificial gravity as potential countermeasure to microgravity. *J Appl Physiol* 103: 1879–87,
764       2007.

765   53.   **Yang Y**, **Kaplan A**, **Pierre M**, **Adams G**, **Cavanagh P**, **Takahashi C**, **Kreitenberg A**, **Hicks**
766       **J**, **Keyak J**, **Caiozzo V**. Space cycle: a human-powered centrifuge that can be used for
767       hypergravity resistance training. [Online]. *Aviat Sp Environ Med* 78: 2–9, 2007.
768       http://www.ncbi.nlm.nih.gov/pubmed/17225475.

769   54.   **Zamanian SA**. Modeling and Simulating Human Cardiovascular Response to Acceleration. MS
770       Thesis, Massachusetts Institute of Technology: 2007.

771   55.   **Zhang Q**, **Evans JM**, **Stenger MB**, **Moore FB**, **Knapp CF**. Autonomic Cardiovascular
772       Responses to Orthostatic Stress After a Short Artificial Gravity Exposure. *Aerosp Med Hum*
773       *Perform* 88: 827–833, 2017.

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**FIGURE CAPTIONS**
776
777 **Figure 1**. Circuit representation of the 21-compartment cardiovascular model, composed of 4 sections:

778 head and arms, thorax, abdomen, and legs. Systemic compartments include proximal aorta (1),

779 brachiocephalic arteries (2), upper body precapillary (3) and postcapillary (4) compartments, superior

780 vena cava (5), thoracic aorta (6), abdominal aorta (7), renal precapillary (8) and postcapillary (9)

781 compartments, splanchnic precapillary (10) and postcapillary (11) compartments, leg precapillary (12)

782 and postcapillary (13) compartments, abdominal veins (14), and thoracic inferior vena cava (15). Four

783 microvascular resistances are also included: upper body $\boldsymbol{R_{ub}}$, kidneys $\boldsymbol{R_{rc}}$, splanchnic $\boldsymbol{R_{sc}}$, and legs $\boldsymbol{R_{lc}}$.

784 The right heart and left heart include variable capacitors and diodes representing the heart valves that

785 prevent reversal flow. The pulmonary circulation is represented by two compartments (pre and post

786 capillary components) connected by a microvascular resistor. Two vein compartments (Compartments

787 4–upper body and 13–leg) also include diodes to capture the unidirectional nature of the venous flow

788 due to the presence of venous valves.

789 **Figure 2**. Single representation of the $n^{\text{th}}$ compartment, where $\boldsymbol{R_n}$ is the resistance, $\boldsymbol{C_n}$ is the

790 (incremental) vascular compliance ($\boldsymbol{C_n}$ is defined as $\boldsymbol{dV_n/d\Delta P_n}$), $\boldsymbol{P_n}$ is the compartment pressure, $\boldsymbol{q_n}$

791 is the flow rate; $\boldsymbol{P_{h,n}}$ is the hydrostatic pressure; and $\boldsymbol{P_{ext,n}}$ is the external pressure (e.g. intra-thoracic

792 pressure, intra-abdominal pressure, muscle pump pressure). The arrows over the compliance

793 (represented by the electric symbol of a capacitor) and pressure sources (represented by open circles)

794 indicate the variable nature of these elements, either as a function of filling status (capacitors) or as a

795 function of time (pressure sources).

796 **Figure 3.** Exercise protocol conducted by twelve subjects on the MIT short-radius centrifuge. The

797 protocol consisted of the following phases: baseline (3 min), spin-up phase to the desired G-level (~100

798 sec), AG phase with only centrifugation (~2min), AG & Exercise phase (15 min), AG phase with no

799 exercise for subjects to partially recover (2 min), and spin-down phase (1 min). We simulated an

800 identical profile with our computational model and used the experimental data for validation purposes.

801 Figure adapted from (10).

802 **Figure 4.** Simulated (black line) and experimental (grey line, mean ± SD including 12 subjects)

803 cardiovascular responses to centrifugation at 1G (measured at the feet) and ergometer exercise in a

804 short-radius centrifuge.

27

805    **Figure 5.** Simulated (black line) and experimental (grey line, mean ± SD including 12 subjects)

806    cardiovascular responses to centrifugation at 1.4G (measured at the feet) and ergometer exercise in a

807    short-radius centrifuge.

808    **Figure 6.** Simulated cardiovascular responses to centrifugation at 1G (measured at the feet) and

809    ergometer exercise varying blood volume conditions. Data are reported for all protocol phases: baseline

810    (BL), centrifugation alone (AG), and centrifugation combined with exercise (25W, 50W, and 100W).

811    Blood volume levels include baseline blood volume (**$V_{total}$ = 5175 ml**) and blood volume reductions

812    of 5%, 10%, and 15%.

813

814    **TABLES**
815
816    **Table 1**: Mathematical expressions capturing orthostatic stress during short-radius centrifugation
817    through three mechanisms: 1) changes in hydrostatic pressure (term included in all systemic
818    compartments), 2) changes in intrathoracic pressure (due to the weight of the liver being pulled down in
819    the thoracic compartment; term included in compartments within the thorax region), and 3) changes in
820    total blood volume (due to the increase in transcapillary fluid flow into the dependent vasculature)

| Gravitational Effect | Short-radius Centrifugation |
|---|---|
| Hydrostatic pressure | $P_{h,n} = \frac{1}{2}\rho\omega^2(t)\left(R_{0,n}^2 - R_{i,n}^2\right)$ |
| Intrathoracic pressure | $P_{th}(t) = P_{th_0} - 3.5\dfrac{(r+d)^2 \cdot \omega_{max}^2}{g^2} \cdot \omega^2(t)$ |
| Maximum Interstitial Volume Change | $V_{max} = 300ml \cdot \dfrac{(r+d) \cdot \omega_{max}^2}{\text{g} \cdot \sin(85°)}$ |

821
822    where $P_{h,n}(t)$ is the hydrostatic pressure, $\rho$ is the density of the blood, $\omega(t)$ is the angular velocity of the
823    centrifuge, $P_{th}(t)$ is the intrathoracic pressure, $P_{th_0}$ is the nominal intrathoracic pressure without orthostatic stress
824    ($-4$ mmHg), $\omega_{max}$ is the maximum and final angular velocity achieved, $r = 55\ cm$ is the distance of the thoracic
825    compartment to the center of rotation of the centrifuge, $d$ is the distance from the head of the subject to the center
826    of rotation of the centrifuge ($d = 0\ cm$), $V_{max}$ is the maximum interstitial volume change (from intravascular
827    volume to the interstitial space), $R_{i,n}$ is the inner radio of the compartment under consideration (the distance
828    between the superior end of the compartment and the center of rotation), and $R_{0,n}$ is the outer radius of the
829    compartment under consideration, which is defined as the sum of the effective length of the compartment and the
830    inner radius. Note: The effective length of each compartment is defined as one half of its anatomical vertical
831    length $l_{v,n}$, except for the leg compartments, where the effective length is assumed to be one third of the
832    anatomical vertical length.
833

29

834  **Table 2:** Exercise parameters during the different phases of the "1G" and "1.4G" simulations.

835  Manipulated parameters include $P_A^{sp}$: set-point reference pressure for the arterial baroreceptor control

836  system (mmHg); $R_{lc}$ : leg microvascular resistance (Peripheral Resistance Units (PRU) or

837  mmHg/ml/min.)); $P_{max}^{pump}$: maximal leg external pressure (mmHg); and $P_{max}^{abd}$: maximal intra-abdominal

838  pressure (mmHg). $P_A^{sp}$ and $P_{max}^{pump}$ were adjusted to match the experimental Mean Arterial Pressure

839  (MAP) data, and $R_{lc}$ was adjusted to match the experimental total peripheral resistance (TPR) data.

840  $P_{max}^{abd}$ was adjusted based on the literature.

841

| Simulation phase | Arterial set-point $P_A^{sp}$ (mmHg) | | Leg Arterial Resistance $R_{lc}$ (PRU) | | Leg external pressure $P_{max}^{pump}$ due to muscle pump (mmHg) | | Intra-abdominal pressure $P_{max}^{abd}$ (mmHg) | |
|---|---|---|---|---|---|---|---|---|
| AG level (measured at the feet) | 1G | 1.4G | 1G | 1.4G | 1G | 1.4G | 1G | 1.4G |
| Baseline | 93 | 93 | 3.9 | 3.9 | 0 | 0 | 2 | 2 |
| AG after Spin-up | 93 | 93 | 3.9 | 3.9 | 20[**] | 30[**] | 2 | 2 |
| Exercise: 25W | 120 | 125 | 1.15[*] | 1[*] | 40[***] | 65[***] | 2.5 | 2.5 |
| Exercise: 50W | 135 | 140 | 0.75[*] | 0.75[*] | 50[***] | 75[***] | 6 | 6 |
| Exercise: 100W | 205 | 225 | 0.54[*] | 0.54[*] | 60[***] | 90[***] | 10 | 10 |
| AG before Spin-down | 105 | 105 | 2.4[*] | 2.4[*] | 20[**] | 30[**] | | |
| Rest | 105 | 105 | | | 0 | 0 | | |

842  [*]resistance disconnected from controls
843  [**]constant
844  [***]periodic 1 sec
845
846
847
848
849

30

**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.

| CV Variable | Baseline 1G | | Baseline 1.4G | | AG 1G | | AG 1.4G | | AG +Exercise 25W 1G | | AG +Exercise 25W 1.4G | | AG + Exercise 50W 1G | | AG + Exercise 50W 1.4G | | AG + Exercise 100W 1G | | AG + Exercise 100W 1.4G | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Sim | Exp | Sim | Exp | Sim | Exp | Sim | Exp | Sim | Exp | Sim | Exp | Sim | Exp | Sim | Exp | Sim | Exp | Sim | Exp |
| CO (l/min) | 5.9 | 6.1±1.2 | 5.9 | 6.5±1.1 | 5.8 | 5.8±1.3 | 6.0 | 6.7±1.3 | 8.7 | 9.5±2.2 | 9.8 | 10.9±1.5 | 10.6 | 12.1±2.3 | 11.6 | 13.2±2.3 | 13.2 | 15.8±2.8 | 14.5 | 16.7±2.5 |
| SV (ml) | 87.9 | 96.2±14.0 | 87.9 | 101.0±11.9 | 83.2 | 91.0±15.4 | 84.5 | 98.2±14.3 | 90.0 | 98.8±20.8 | 97.7 | 107.9±14.1 | 96.7 | 110.5±19.2 | 104.6 | 115.5±17.8 | 98.5 | 114.8±17.4 | 106.4 | 120.3±20.3 |
| HR (bpm) | 67.3 | 64.1±9.0 | 67.3 | 64.9±10.0 | 67.7 | 64.5±9.2 | 67.7 | 69.3±11.9 | 96.2 | 97.0±10.5 | 100.0 | 101.6±12.8 | 109.3 | 110.3±12.4 | 110.6 | 114.4±14.2 | 133.7 | 138.1±17.6 | 136.3 | 140.2±17.4 |
| SBP (mmHg) | 116.9 | 116.6±6.5 | 116.9 | 123.4±9.7 | 115.4 | 116.5±11.6 | 116.4 | 121.7±11.9 | 124.3 | 128.1±13.6 | 128.6 | 136.6±11.5 | 129.3 | 138.1±14.2 | 135.3 | 151.0±16.7 | 140.4 | 151.0±17.5 | 147.5 | 158.7±19.9 |
| MBP (mmHg) | 92.9 | 90.4±4.9 | 92.9 | 94.4±7.4 | 92.8 | 90.5±8.3 | 93.5 | 92.8±9.7 | 100.8 | 98.6±10.3 | 103.2 | 103.2±11.1 | 104.1 | 101.8±10.6 | 108.3 | 108.1±10.4 | 115.0 | 110.7±12.9 | 120.3 | 113.8±14.7 |
| DBP (mmHg) | 67.8 | 73.2±4.3 | 67.8 | 75.8±6.7 | 68.9 | 74.2±6.9 | 69.2 | 74.5±8.8 | 74.9 | 80.0±8.6 | 75.1 | 81.7±9.2 | 76.4 | 80.7±7.4 | 78.4 | 84.7±7.7 | 86.6 | 86.0±9.8 | 89.7 | 87.2±11.2 |
| PP (mmHg) | 49.1 | 43.4±6.8 | 49.1 | 47.6±5.8 | 46.5 | 42.4±9.1 | 47.2 | 47.2±7.6 | 49.5 | 48.2±10.6 | 53.5 | 54.9±6.3 | 52.8 | 57.4±9.7 | 57.0 | 66.3±11.1 | 53.7 | 65.0±10.2 | 57.8 | 71.5±10.3 |
| TPR (PRU) | 0.86 | 0.93±0.2 | 0.86 | 0.90±0.2 | 0.86 | 0.98±0.3 | 0.86 | 0.86±0.2 | 0.62 | 0.66±0.2 | 0.58 | 0.59±0.1 | 0.49 | 0.53±0.1 | 0.49 | 0.52±0.1 | 0.40 | 0.44±0.1 | 0.40 | 0.44±0.1 |

31

**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 | $E_{es,ra}$=0.74 | $P_A^{sp}$=93 $mm\,Hg$ | $P_{th_0}$=-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 | $G_{R-R}^{A,S}$=9 | $V_{tot}$=5175 $mL$ |
| $R_3$=0.014 | $V_{0,3}$=200 | $C_3$=0.2 | $l_{v,3}$=20.0 | $E_{es,rv}$=1.3 | $G_{R-R}^{A,P}$=9 | $HR_{nom}$=67 $beats/min$ |
| $R_4$=0.11 | $V_{0,4}$=645 | $C_4$=7.0 | $l_{v,4}$=20.0 | $E_{d,rv}$=0.05 | $G_{C_{lv}}^{A,S}$=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 | $G_{C_{rv}}^{A,S}$=0.022 | |
| $R_6$=0.011 | $V_{0,6}$=16 | $C_6$=0.1 | $l_{v,6}$=16.0 | $E_{d,la}$=0.5 | $G_{R_{ub}}^{A,S}$=-0.05 | |
| $R_7$=0.010 | $V_{0,7}$=10 | $C_7$=0.1 | $l_{v,7}$=14.5 | $E_{es,lv}$=2.5 | $G_{R_{rc}}^{A,S}$=-0.05 | |
| $R_8$=0.10 | $V_{0,8}$=20 | $C_8$=0.21 | $l_{v,8}$=0 | $E_{d,lv}$=0.11 | $G_{R_{sc}}^{A,S}$=-0.05 | |
| $R_9$=0.11 | $V_{0,9}$=30 | $C_9$=5.0 | $l_{v,9}$=0 | | $G_{R_{lc}}^{A,S}$=-0.05 | |
| $R_{10}$=0.07 | $V_{0,10}$=300 | $C_{10}$=0.2 | $l_{v,10}$=10.0 | | $G_{V_{ub}}^{A,S}$=5 | |
| $R_{11}$=0.07 | $V_{0,11}$=1146 | $C_{11}$=50 | $l_{v,11}$=10.0 | | $G_{V_{rc}}^{A,S}$=2 | |
| $R_{12}$=0.09 | $V_{0,12}$=200 | $C_{12}$=0.2 | $l_{v,12}$=85 | | $G_{V_{sc}}^{A,S}$=13 | |
| $R_{13}$=0.10 | $V_{0,13}$=716 | $C_{13}$=20 | $l_{v,13}$=85 | | $G_{V_{lc}}^{A,S}$=7 | |
| $R_{14}$=0.019 | $V_{0,14}$=79 | $C_{14}$=1.3 | $l_{v,14}$=14.5 | | $P_{CP}^{sp}$=6 $mm\,Hg$ | |
| $R_{15}$=0.008 | $V_{0,15}$=33 | $C_{15}$=0.5 | $l_{v,15}$=6 | | $G_{R_{ub}}^{CP,S}$=-0.05 | |
| $R_{tri}$=0.006 | $V_{0,ra}$=14 | $C_{pa}$=3.4 | | | $G_{R_{rc}}^{CP,S}$=-0.05 | |
| $R_{pa}$=0.006 | $V_{0,rv}$=46 | $C_{pv}$=9.0 | | | $G_{R_{sc}}^{CP,S}$=-0.05 | |
| $R_{pc}$=0.07 | $V_{0,pa}$=160 | | | | $G_{R_{lc}}^{CP,S}$=-0.05 | |
| $R_{pv}$=0.006 | $V_{0,pv}$=430 | | | | $G_{V_{ub}}^{CP,S}$=13 | |
| $R_{mit}$=0.010 | $V_{0,la}$=24 | | | | $G_{V_{rc}}^{CP,S}$=3 | |
| $R_{ub}$=4.0 | $V_{0,lv}$=55 | | | | $G_{V_{sc}}^{CP,S}$=64 | |
| $R_{rc}$=4.2 | | | | | $G_{V_{lc}}^{CP,S}$=30 | |
| $R_{sc}$=2.4 | | | | | | |
| $R_{lc}$=3.9 | | | | | | |

$R$: resistances; $V_0$: unstressed volumes; $C$: compliances; $l_v$: 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.
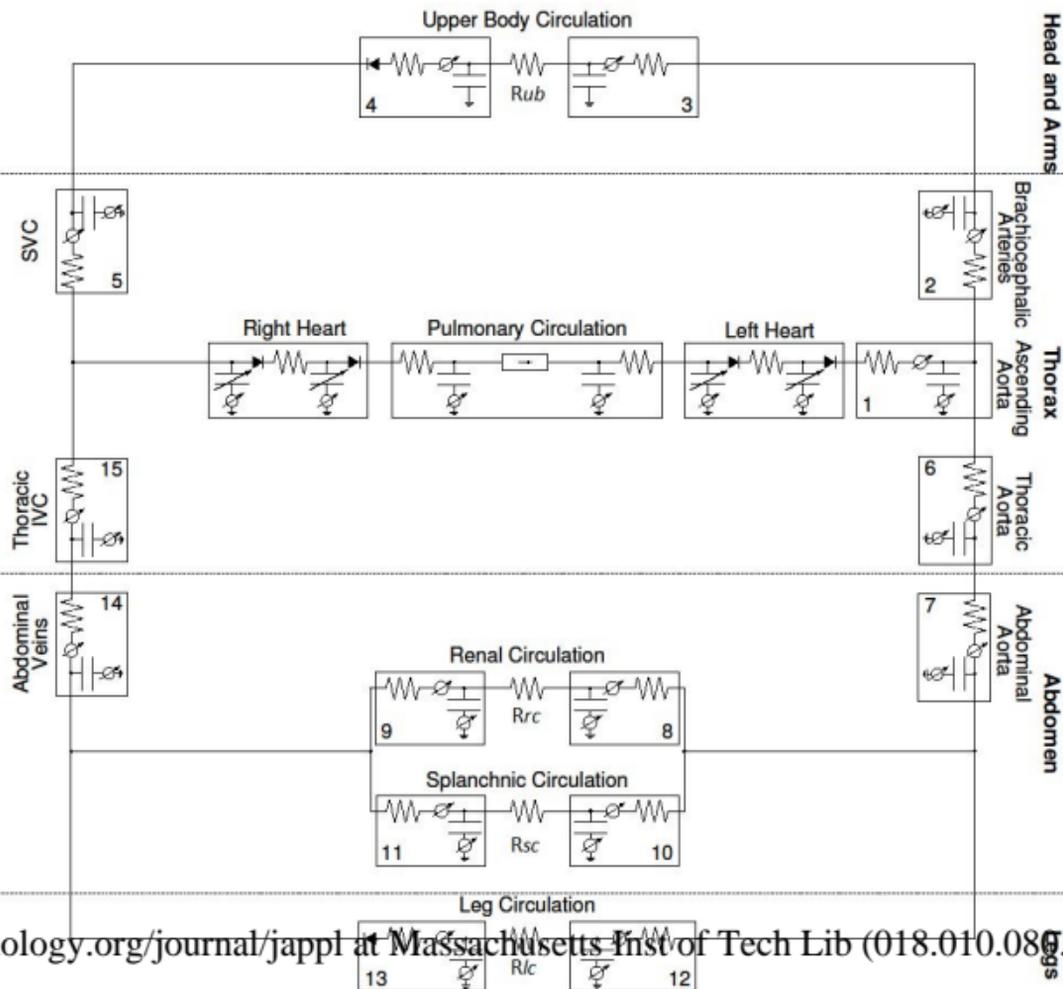
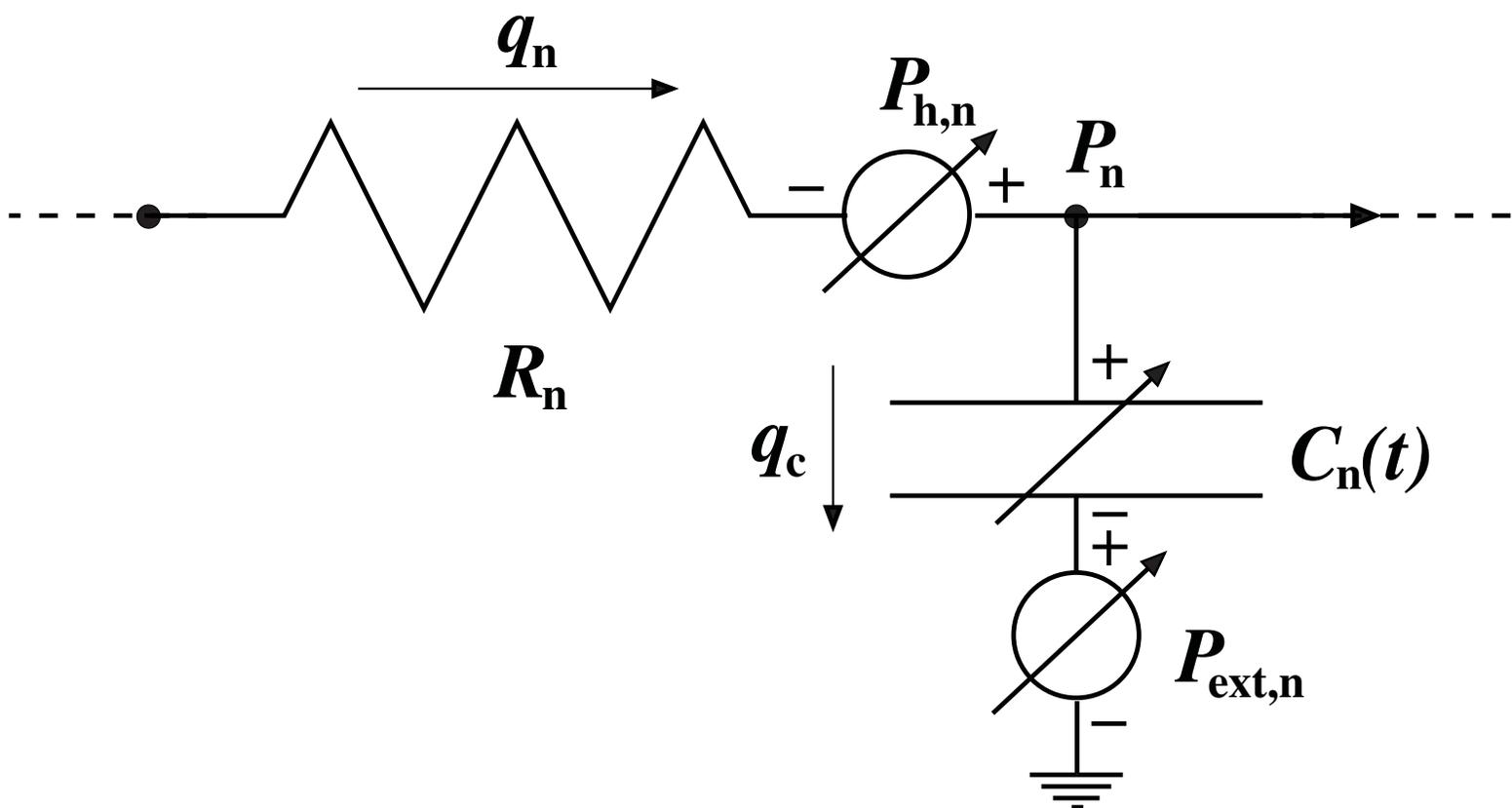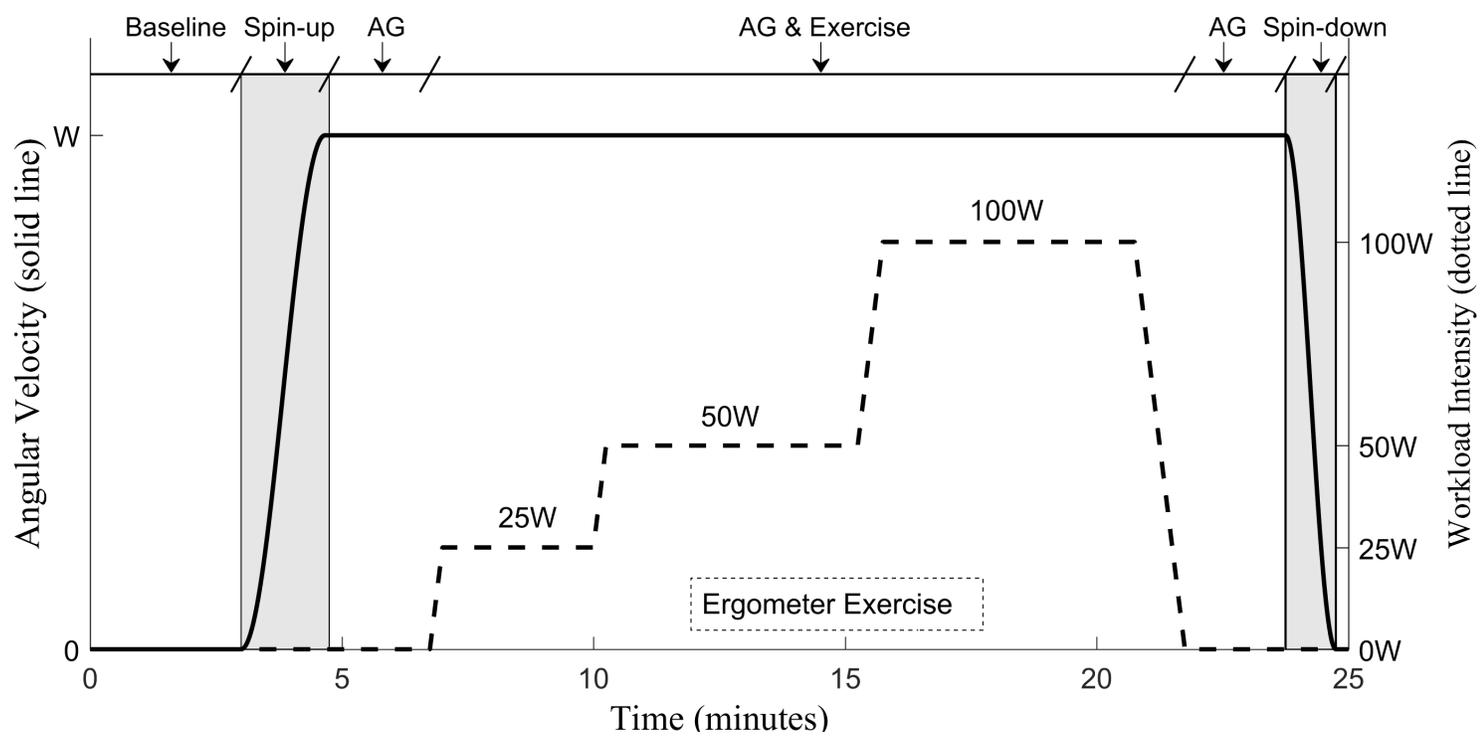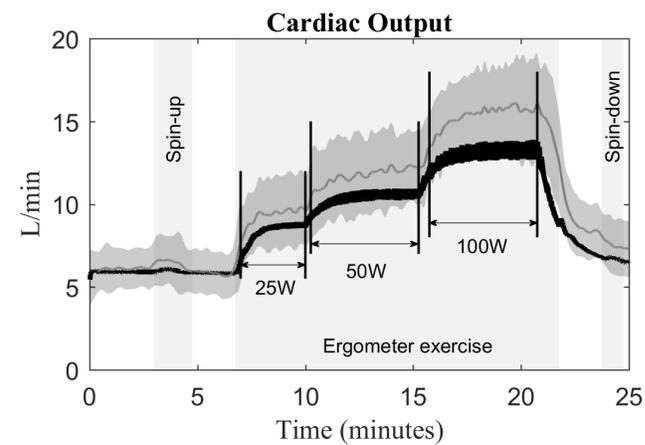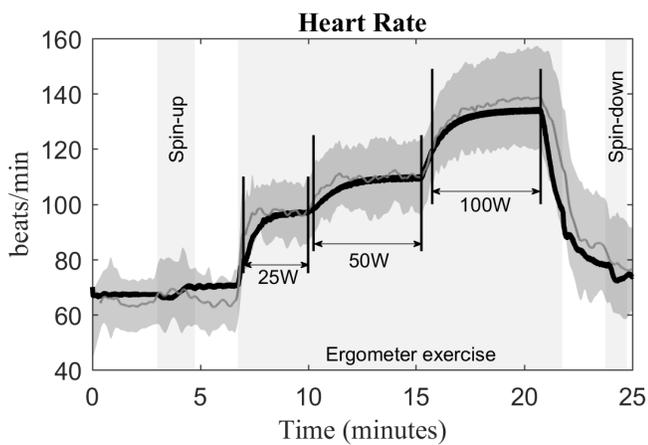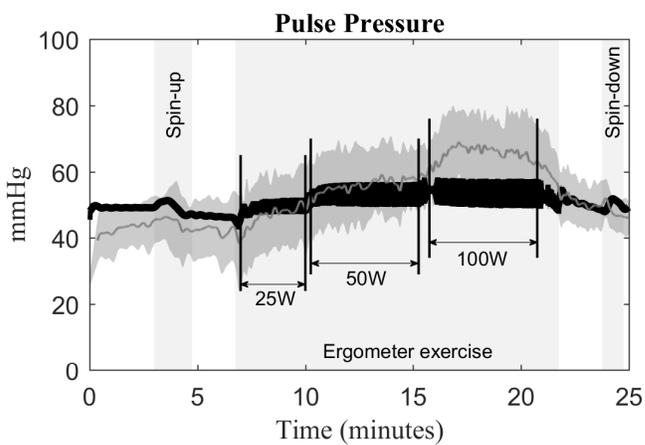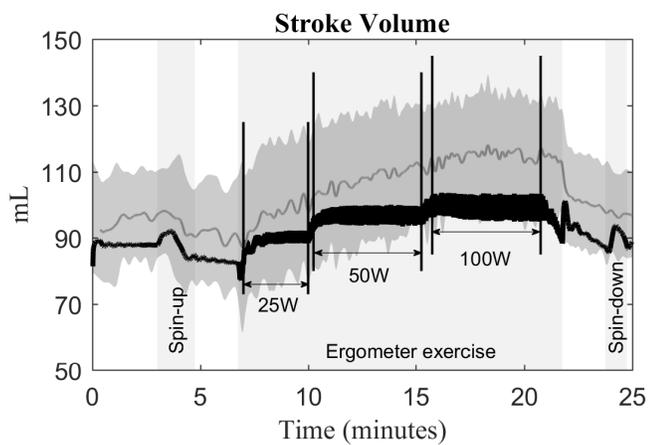**Table 5:** Flow and Volume parameters in each of the compartments during steady-state simulation in supine position.
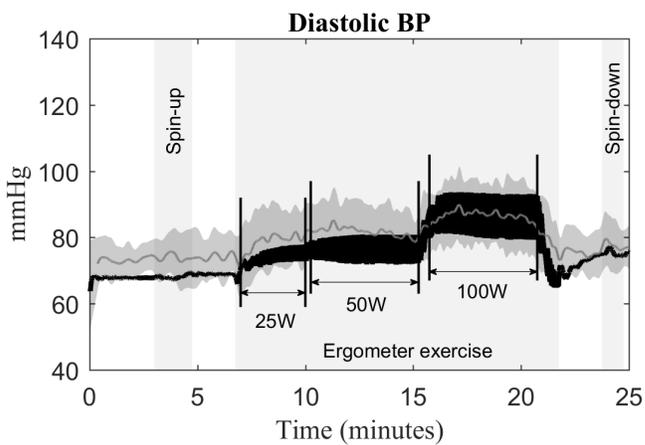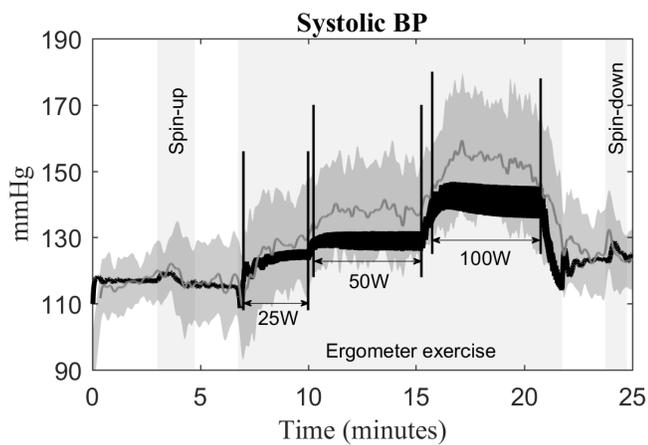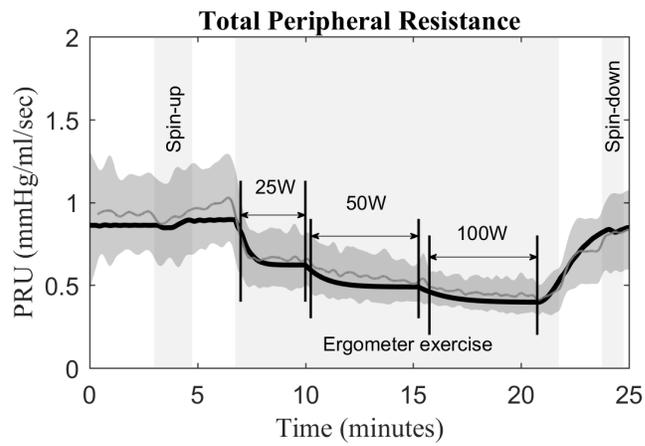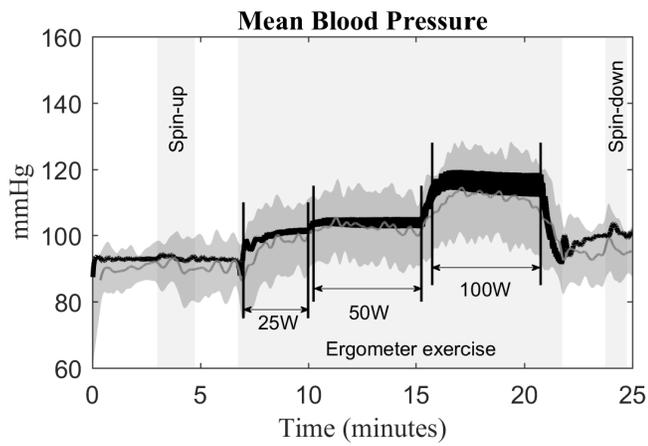
| Upper Body Circulation | | Heart Circulation | | Thoracic and Abdominal Circulation | | Splanchnic Circulation | | Renal Circulation | | Leg Circulation | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Flow (l/min) | Volume (ml) | Flow (l/min) | Volume (ml) | Flow (l/min) | Volume (ml) | Flow (l/min) | Volume (ml) | Flow (l/min) | Volume (ml) | Flow (l/min) | Volume (ml) |
| $Q_{2i} = 1.34$ | $V_2 = 17.6$ | $Q_{rai} = 5.85$ | $V_{ra} = 31.8$ | $Q_{6i} = 4.56$ | $V_6 = 25.6$ | $Q_{10i} = 2.07$ | $V_{10} = 317.8$ | $Q_{8i} = 1.19$ | $V_8 = 38.8$ | $Q_{12i} = 1.29$ | $V_{12} = 217.9$ |
| $Q_{3i} = 1.33$ | $V_3 = 218.5$ | $Q_{rvi} = 5.86$ | $V_{rv} = 110.5$ | $Q_{7i} = 4.55$ | $V_7 = 19.1$ | $Q_{11i} = 2.06$ | $V_{11} = 1382.7$ | $Q_{9i} = 1.18$ | $V_9 = 52.2$ | $Q_{13i} = 1.28$ | $V_{13} = 845.9$ |
| $Q_{4i} = 1.31$ | $V_4 = 682.9$ | $Q_{rvo} = 5.88$ | $V_{la} = 54.5$ | $Q_{14i} = 4.52$ | $V_{14} = 81.9$ | $Q_{11o} = 2.06$ | | $Q_{9o} = 1.19$ | | $Q_{13o} = 1.28$ | |
| $Q_{5i} = 1.31$ | $V_5 = 24.8$ | $Q_{pc} = 5.85$ | $V_{lv} = 153.8$ | $Q_{15i} = 4.53$ | $V_{15} = 36.4$ | | | | | | |
| $Q_{5o} = 1.32$ | | $Q_{lai} = 5.91$ | $V_1 = 48.1$ | $Q_{15o} = 4.53$ | | | | | | | |
| | | $Q_{lvi} = 5.92$ | | | | | | | | | |
| | | $Q_{lvo} = 5.91$ | | | | | | | | | |

870 $Q_{ni}$, flow going into the compartment $n$; $Q_{no}$, flow going out the compartment $n$; ra, right atrium; rv, right
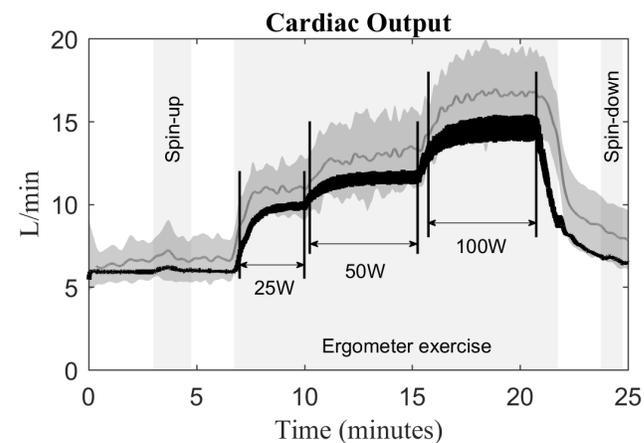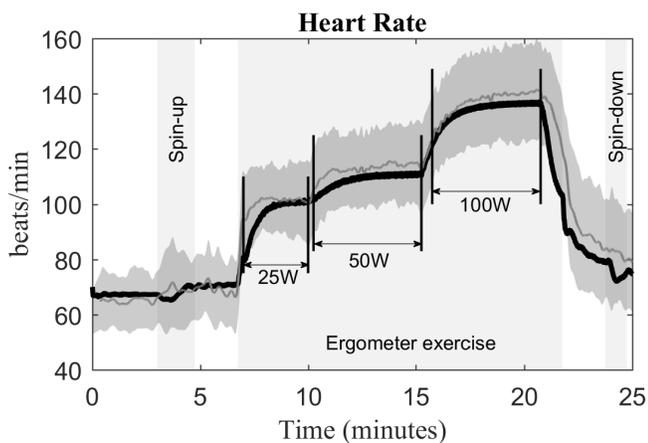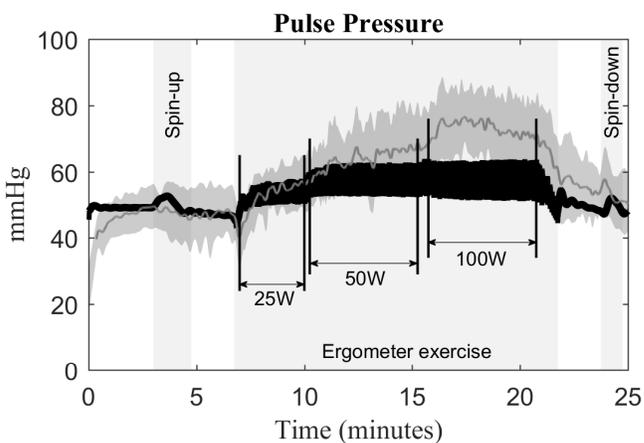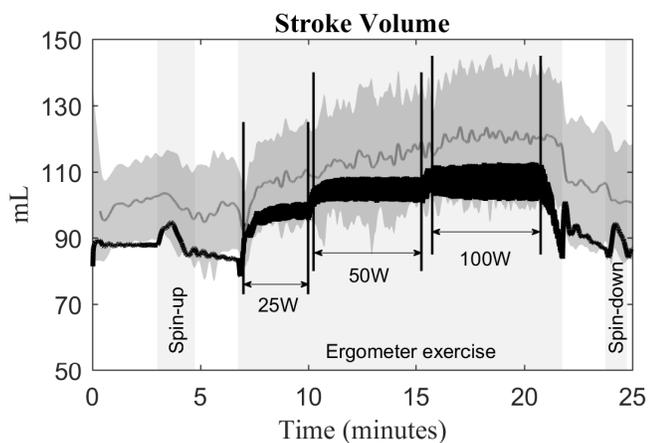871 ventricle; la, left atrium; lv, left ventricle;

Upper Body Circulation

4    Rub    3

SVC    5

Brachiocephalic Arteries    2

Right Heart    Pulmonary Circulation    Left Heart    1

Thoracic IVC    15

Thoracic Aorta    6

Abdominal Veins    14

Abdominal Aorta    7

Renal Circulation

9    Rrc    8

Splanchnic Circulation

11    Rsc    10

Leg Circulation

13    Rlc    12

**Mean Blood Pressure**

**Total Peripheral Resistance**

**Systolic BP**

**Diastolic BP**

**Stroke Volume**

**Pulse Pressure**

**Heart Rate**

**Cardiac Output**

—— Computational model prediction at 1.4G    —— Experimental data (mean ± SD) at 1.4G