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Assessing the cardiac function from micro-gravity to hyper-gravity conditions through a validated multiscale modelling approach / Tripoli, F., Ridolfi, L., Scarsoglio, S.. - In: THE JOURNAL OF PHYSIOLOGY. - ISSN 1469-7793. - (2025). [10.1113/JP287142]

Availability:

This version is available at: 11583/3003935 since: 2025-10-16T09:42:39Z

Publisher:

Wiley

Published

DOI:10.1113/JP287142

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First author profile

Francesco Tripoli is a Ph.D. student in Aerospace Engineering at Politecnico di Torino. He completed his MD in Biomedical Engineering at Politecnico di Torino in 2022. From October 2022 to October 2023, he received a post-graduate research scholarship at Politecnico di Torino. During this period, he applied numerical methods to investigate cerebral hemodynamics in atrial fibrillation. His current research focuses on both cardiovascular and cerebro-ocular functions under spaceflight conditions, exploiting mathematical multiscale modeling. His work aims to enhance the comprehension of cardiovascular and cerebral deconditioning during long-term human spaceflight and to support the identification of effective countermeasure strategies.

Key Points

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- Gravity changes from micro- to hyper-gravity induce several cardiovascular alterations, from fluid shift and blood volume reduction to orthostatic hypotension and venous pooling.
- Although the overall cardiovascular response is clear, details of the cardiac function in these extreme conditions are still incomplete and difficult to obtain.
- We propose a validated multiscale cardiovascular model to investigate the steady-state acute cardiac response to gravity changes (from 0g to 3g).
- After a thorough validation against the most common central hemodynamic parameters in literature, present results show: (i) a different behaviour between left and right heart hemodynamics; (ii) an improvement of cardiac efficiency and cardiac performance in micro-gravity; (iii) an energy supply/demand impairment in hyper-gravity.
- The computational approach is a useful and reliable tool in exploring the response of cardiac parameters which are difficult to investigate experimentally, aiming to shed light on the cardiac function under altered gravitational force.

Assessing the cardiac function from micro-gravity to hyper-gravity conditions through a validated multiscale modeling approach

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Abstract

Gravity changes with respect to the 1g terrestrial condition induce several cardiovascular alterations, from fluid shift and blood volume reduction to orthostatic hypotension and venous pooling. Micro-gravity and hyper-gravity exposure characterizes space missions and aeronautical flights, as well as terrestrial analogs such as centrifuges, bed rest studies, and parabolic flights. Despite a growing number of clinical measures is becoming available, cardiac function in these extreme conditions is still incomplete and difficult to be obtained. Thus, computational hemodynamics provides a powerful and reliable tool to understand the cardiac response.

We propose a 0D-1D multiscale cardiovascular model to investigate the steady-state acute cardiac response to gravity changes (from 0g to 3g). The model combines a 1D description of the coronary circulation and arterial tree, with a 0D parameterization of the peripheral microcirculation, the venous return, the cardiopulmonary and the cerebrovascular-ocular circulations. The

overall model is equipped with short-term regulation mechanisms, and accounts for gravity and posture changes.

After a thorough validation using measured data from literature involving the most common central hemodynamic parameters (i.e., *HR*, *MAP*, *SV* and *CO*), the model provides an in-depth description of the cardiac response from micro- (0g) to hyper-gravity (3g), highlighting: (i) a different behaviour between left and right heart hemodynamics; (ii) an improvement of cardiac efficiency and cardiac performance in micro-gravity; (iii) a worsening of cardiac efficiency and an energy supply/demand impairment both at heart and coronary levels in hyper-gravity. Therefore, the modeling approach proves to be an important tool in shedding light on space medicine.

Keywords: Space medicine, micro-gravity, hyper-gravity, cardiovascular modeling, cardiac hemodynamics

1. Introduction

One of the most challenging issues of human space exploration and aeronautical flights is the exposure of the human body to gravitational force changes. During spaceflights, astronauts experience a wide range of gravitational accelerations (*g*), from the weightlessness to the increased gravitational stress sustained during launch or re-entry/landing maneuvers. In addition, many terrestrial activities, from civil and military flights to skydiving or rollercoasters, expose the human body to varying levels of gravity force. Changes in gravitational acceleration induce a number of physiological adaptations affecting musculoskeletal, cardiovascular and neurovestibular systems (Buckey, 2006; Clément, 2011; Young & Sutton, 2021). The comprehension of these adaptations is crucial to ensure the health and safety

13 of astronauts during future space missions and to develop effective
14 countermeasures against deconditioning in the space environment (Traon *et al.*, 2007; Hargens & Richardson, 2009; Hargens *et al.*, 2013; Tanaka *et al.*,
15 2017).

17 The cardiovascular system is greatly affected by gravitational
18 acceleration, with deviations from terrestrial gravity eliciting a blood volume
19 redistribution due to the gravity-dependent hydrostatic component of the
20 blood pressure (Blomqvist & Stone, 1983). Despite the increasing number of
21 studies on the cardiovascular response to gravity changes (Blaber *et al.*, 2010;
22 Zhu *et al.*, 2015; Hughson *et al.*, 2018; Shen & Frishman, 2019; Norsk, 2020),
23 hemodynamic characterization is still incomplete and restricted to a limited
24 number of cardiac parameters. Although the acquisition of clinical measures
25 is difficult, it is thought that the micro-gravity-induced fluid shift from the
26 lower to the upper body is the main driver of cardiovascular deconditioning
27 (Hargens & Richardson, 2009; Norsk, 2020) – characterized by total blood
28 volume reduction, cardiac atrophy and reduced exercise capability (Arbeille
29 *et al.*, 2001; Grigoriev *et al.*, 2011; Zhu *et al.*, 2015) – and Spaceflight
30 Associated Neuro-Ocular Syndrome (SANS) – characterized by several
31 neuro-ocular anomalies triggered by elevated intracranial pressure (Berdahl *et al.*, 2012; Taibbi *et al.*, 2013; Zhang & Hargens, 2018). Conversely, hyper-
32 gravity elicits a fluid shift in the cranio-caudal direction, exerting significant
33 orthostatic stress on the cardiovascular system, which may result in reduced
34 venous return to the heart and impaired cerebral perfusion (Blomqvist &
35 Stone, 1983; Shender *et al.*, 2003). Despite being a hazardous condition, some
36 studies proposed that repetitive exposure to hyper-gravity may enhance
37

38 tolerance to orthostatic stress, leading to adaptive cardiovascular responses
39 (Newman *et al.*, 1998; Convertino, 1998; Newman & Callister, 2008; Lalande
40 & Buick, 2009), and that exposure to mild hyper-gravity may mitigate
41 deconditioning induced by spaceflight hostile environment (Burton, 1988;
42 Clément *et al.*, 2015). Hence, understanding the cardiovascular response to
43 micro- and hyper-gravity environments is critical for the implementation of
44 countermeasures to protect astronauts during long-term spaceflight.

45 Ground-based analogs – such as bed-rest studies (Traon *et al.*, 2007;
46 Saveko *et al.*, 2023), parabolic flights (Karmali & Shelhamer, 2008;
47 Shelhamer, 2016) and human centrifuges (Scott *et al.*, 2007; Goswami *et al.*,
48 2015) – represent the easiest way to study the effect of gravitational
49 acceleration changes in a controlled environment. However, these analogs
50 have some limitations: (i) in bed-rest studies, the gravitational force (which
51 typically acts on the longitudinal axis) is exerted on the antero-posterior axis,
52 thus not eliminating the body weight; (ii) in human centrifuges, a gravity
53 gradient along the longitudinal (head-feet) axis is produced due to the radius-
54 dependent centrifugal force achieved by steady rotation; (iii) in parabolic
55 flights, the real micro- and hyper-gravity environments are reproduced only
56 for a few seconds (Karmali & Shelhamer, 2008). Moreover, the challenge of
57 monitoring and recording detailed clinical data of the cardiovascular system –
58 which is a complex issue even in controlled environment conditions due to the
59 intrinsic limitations of the current acquisition methodologies – is amplified by
60 the several design constraints inherent to each analog.

61 Mathematical modelling may represent a feasible tool to investigate the
62 cardiovascular response to gravity alterations and clarify physiological aspects

63 that are still unclear. The computational approach and, in particular, the
64 multiscale modeling allow distinct elements of the cardiovascular system to
65 be described effectively, by combining submodels with different levels of
66 detail (from 0D to 3D models). Each compartment is able to reproduce the
67 main hemodynamic features of a specific vascular region and different
68 physiological mechanisms – such as short-term regulation mechanisms
69 mediated by the autonomic system – can be implemented. Due to these
70 properties, in recent years multiscale mathematical modeling has gained
71 success to investigate the hemodynamic response to different cardiovascular
72 diseases – e.g., cardiac arrhythmias and hemorrhages (Anselmino *et al.*, 2016;
73 Canuto *et al.*, 2018; Saglietto *et al.*, 2024) – and working conditions where the
74 gravitational acceleration plays a crucial role like head-up and head-down tilt
75 tests and human centrifuge (Heldt *et al.*, 2002; Diaz-Artiles *et al.*, 2019;
76 Whittle & Diaz-Artiles, 2021; Fois *et al.*, 2022a, 2024).

77 In this work, by exploiting a multiscale 0D-1D cardiovascular model, we
78 describe the cardiac function in standing posture across a broad spectrum of
79 gravity intensity: from micro-gravity (0g) to hyper-gravity (3g). In particular,
80 the steady-state acute response – which is mediated by short-term regulation
81 mechanisms and occurs within few minutes following the application of an
82 external stimulus – is investigated. The model includes a 0D-1D modelling of
83 the systemic and coronary circulation, a 0D model of the cerebrovascular
84 circulation, and has been recently validated and used to investigate the
85 cardiovascular and cerebro-ocular hemodynamics against different ground-
86 based and spaceflight applications (Gallo *et al.*, 2020; Fois *et al.*, 2022a,
87 2022b, 2024).

88 After an in-depth validation through existing literature involving the most
89 common central hemodynamic parameters, we study the cardiac response
90 from micro- (0g) to hyper-gravity (3g) by focusing on: left and right heart
91 hemodynamics (including central venous and pulmonary capillary wedge
92 pressures), left and right coronary circulation (left anterior descending artery
93 and right coronary artery), pulmonary artery pressure, and indexes of oxygen
94 consumption, cardiac work and efficiency.

95 **2. Methods**

96 *2.1. Mathematical modelling*

97 The mathematical framework employed in this work is based on a closed-
98 loop 0D-1D multiscale model of the entire cardiovascular system (Fois *et al.*,
99 2024). An overview of the model architecture is illustrated in figure 1. The
100 cardiovascular model comprises a 1D description of the arterial tree along with
101 the main coronary arteries and a 0D representation of the peripheral, venous,
102 cardiopulmonary, coronary and cerebro-ocular circulations. In this section, a
103 brief description of the model structure and the implemented physiological
104 features is given, whereas additional numerical details, including equations
105 and parameter settings, are reported in our previous work (Fois *et al.*, 2024)
106 and are available through the link attached in the Additional Information
107 section (please refer to the Supporting Information file).

108 The 1D arterial tree (left side of Fig. 1) consists of 48 main large arteries
109 (from the ascending aorta to upper and lower limbs arteries) and 15 coronary
110 arteries, for a total of 63 vessels. Each artery is modelled as a straight tapered
111 vessel with a circular cross-section. Blood is modelled as an incompressible
112 and Newtonian fluid with constant density $\rho = 1050 \text{ kg/m}^3$ and viscosity $\mu =$

113 $4 \cdot 10^{-3}$ Pa·s. These hypotheses permit the description of blood motion through
114 the 1D axisymmetric form of the Navier-Stokes equations, taking the lumen
115 area $A(x,t)$ and the blood flow rate $Q(x,t)$ as dependent variables (x is the axial
116 vessel coordinate, and t is the time). To close the 1D mathematical system and
117 to model the viscoelastic mechanical properties of the large artery walls, a
118 non-linear constitutive equation associating the arterial blood pressure $p(x,t)$
119 with $A(x,t)$ is introduced (Fois *et al.*, 2024). The model accounts for the gravity
120 force by explicitly including a properly orientated gravitational term in the
121 momentum balance equation. At each arterial bifurcation, the conservation of
122 mass and total pressure is imposed as boundary condition.

123 The inlet of the 1D ascending aorta is linked with the 0D aortic valve
124 model, and each of the twenty-four 1D terminal arteries is coupled by means
125 of a characteristic impedance Z_c with a three-element RLC Windkessel model
126 of the 0D arteriolar compartment. Each boundary value problem is treated by
127 applying the method of characteristics (Fois *et al.*, 2024). The 1D governing
128 equations are solved numerically using the Discontinuous Galerkin Finite
129 Elements method combined with a 2-step Runge-Kutta explicit time
130 integration scheme.

131 The 0D model of the peripheral and venous circulations is characterized
132 by several interconnected three-element RLC Windkessel models, with R , L
133 and C describing the hydraulic resistance, the blood inertia, and the
134 compliance of a specific 0D compartment, respectively. Specifically,
135 arteriolar compartments merge into five body regions: extracranial circulation,
136 arms, upper abdomen, lower abdomen and legs. Each of these regions
137 comprises a capillary, venular and venous district. Three additional districts,

138 describing the superior, inferior and abdominal segments of the vena cava,
139 connect the venous compartments with the right atrium, thus closing the
140 systemic circulation and completing the venous return to the heart. For each
141 compartment, the governing equations are written in terms of the flow rate
142 $Q(t)$, the blood volume $V(t)$, and the intraluminal pressure $p(t)$. For legs venous
143 and superior vena cava districts, two different non-linear pressure-volume
144 relationships are implemented to model the non-linear effects of distending
145 leg veins volume (Fois *et al.*, 2024) and venous collapse of neck veins (Lu *et*
146 *al.*, 2001; Holmlund *et al.*, 2018). Additionally, arms and legs venous
147 compartments are provided with a 0D model of venous valves. To insert
148 gravity contribution a pressure generator is added in the venous and vena cava
149 compartments according to Stevino's law.

150 The 0D model of the cardio-pulmonary circulation combines four 0D
151 models, each describing a specific cardiac chamber, with a 0D model of the
152 pulmonary circulation. To model the contraction of atria and ventricles a time-
153 varying elastance is employed, whereas to model cardiac valves non-ideal
154 diodes are used. Moreover, intrathoracic pressure (*ITP*), which depends on
155 both gravity and body position (Fois *et al.*, 2022a), acts as extravascular
156 pressure, affecting the behaviour of all compartments of the cardio-pulmonary
157 circulation.

158 The cerebro-ocular circulation is connected with the systemic arterial
159 circulation via the internal carotid and the vertebral arteries, whereas the
160 venous outflow is directly connected to the superior vena cava compartment.
161 The cerebral model (Fois *et al.*, 2024) describes the cerebral blood flow within
162 the large cerebral arteries, the circle of Willis and the distal cerebral

163 circulation. Furthermore, it models the cerebrospinal dynamics and estimates
 164 the intracranial pressure (*ICP*) by imposing the mass conservation and
 165 assuming a non-linear intracranial compliance. The 0D model of the eye (Fois
 166 *et al.*, 2024) includes six ocular compartments and is able to reproduce both
 167 intraocular pressure (*IOP*) and ocular globe volume.

168 The whole cardiovascular model is equipped with short-term autonomic
 169 control mechanisms, simulating the baroreflex and the cardio-pulmonary
 170 reflex (Fois *et al.*, 2024). For both reflexes, sympathetic and parasympathetic
 171 activities are governed by two sigmoid functions (which depend on the mean
 172 aortic-carotid sinus pressure for the baroreflex, and the central venous
 173 pressure for the cardiopulmonary reflex). The baroreflex model regulates both
 174 peripheral resistances and venous tone and exerts an inotropic and
 175 chronotropic effect on both ventricles, whereas the cardiopulmonary reflex
 176 accounts only for peripheral vascular adjustments. Additionally, the 0D
 177 cerebral model accounts for the cerebral autoregulation mechanism by
 178 changing the compliances and the hydraulic resistances of the distal cerebral
 179 circulation. The implementation of these regulation mechanisms allows the
 180 model to simulate the short-term response to both posture and gravity changes.

181 To obtain the steady-state cardiovascular response in a standing posture,
 182 we first simulated a head-up tilt test at 1g. In this first step, the time-
 183 dependence of the tilt angle α was computed as:

$$184 \quad \alpha(t) = \begin{cases} 0, & \text{if } t < t_{start}^I \\ \frac{\alpha_{tilt}}{2} \cdot \left[1 - \cos\left(\frac{t - t_{start}^I}{T_{tilt}} \cdot \pi\right) \right], & \text{if } t_{start}^I < t < t_{start}^I + T_{tilt} \\ \alpha_{tilt}, & \text{if } t > t_{start}^I + T_{tilt} \end{cases} \quad (1)$$

185 where α_{tilt} represents the angle reached after the tilt (90°), t_{start}^I indicates the
 186 tilting starting time, and T_{tilt} denotes the tilting period in which the posture
 187 change occurred (22.5 s), respectively. Subsequently, starting from the
 188 standing 1g steady-state condition, gravity transitions from 1g up to the
 189 desired level of gravity were imposed by the cosinusoidal function:

$$190 \quad \frac{g}{g_0}(t) = \begin{cases} 1, & \text{if } t < t_{start}^{II} \\ 1 + \frac{1}{2} \left[\left(\frac{g}{g_0} \right)_f - 1 \right] \cdot \left[1 - \cos \left(\frac{t - t_{start}^{II}}{T_g} \cdot \pi \right) \right], & \text{if } t_{start}^{II} < t < t_{start}^{II} + T_g \\ \left(\frac{g}{g_0} \right)_f, & \text{if } t > t_{start}^{II} + T_g \end{cases} \quad (2)$$

191 where $\left(\frac{g}{g_0} \right)_f$, t_{start}^{II} , and T_g indicate the final gravity level reached after the
 192 transition, the transition starting time, and the transition duration, respectively.
 193 To simulate both posture and gravity changes, t_{start} was selected in order to
 194 ensure that the initial transient resulting from model initialization was fully
 195 extinguished. Additionally, to prevent numerical instabilities, in particular at
 196 higher g values, all simulations were performed with a fixed gravity rate of
 197 ± 0.01 g/s. While this gravity rate may not reflect typical real-life applications,
 198 our study is focused on the short-term steady-state condition, which is
 199 independent of the gravity rate (Fois *et al.*, 2022a). A total of 31 simulations
 200 were conducted with g varying in the range [0g-3g].

201 *Cardiac and coronary hemodynamic parameters*

202 We here introduce the hemodynamic parameters used to describe the
 203 cardiac and coronary responses to gravity changes in the results section (see
 204 Section 4). To assess the cardiac function, we focus our attention on the main
 205 mechano-energetic and efficiency indexes of the left and right ventricles. In

particular, starting from each ventricle pressure-volume loop (*PV* loop) (see Fig. 3), it is possible to define the external work $EW_{lv/rv}$ [J] as the area of left/right *PV* loop, and the potential energy $PE_{lv/rv}$ [J] as the area of the triangles depicted in figures 3a and 3b (Westerhof *et al.*, 2019). An additional mechano-energetic parameter, which can be derived from $EW_{lv/rv}$ and $PE_{lv/rv}$, is the left/right ventricle pressure-volume area, $PVA_{lv/rv}$ [J], defined as:

$$PVA_{lv/rv} = EW_{lv/rv} + PE_{lv/rv}. \quad (3)$$

With regard to cardiac efficiency, left/right ventricular efficiency (*LVE* and *RVE*) and ejection fraction ($EF_{lv/rv}$) are considered:

$$LVE \text{ (or } RVE) = \frac{EW_{lv/rv}}{PVA_{lv/rv}}, \quad (4)$$

$$EF_{lv/rv} = \frac{SV_{lv/rv}}{EDV_{lv/rv}}, \quad (5)$$

where $SV_{lv/rv} = EDV_{lv/rv} - ESV_{lv/rv}$ is the stroke volume [ml], that is the blood volume ejected from the left/right ventricle during a single cardiac cycle, $EDV_{lv/rv}$ [ml] is the left/right ventricle end-diastolic volume (defined by the closure of the mitral/tricuspid valve), and $ESV_{lv/rv}$ [ml] is the the left/right ventricle end-sistolic volume (defined by the closure of the aortic/pulmonary valve).

In literature, the most common methods to assess the cardiac oxygen consumption indexes – which are mainly based on pressure and heart rate – are the rate-pressure product (*RPP* [mmHg/min]) and the tension-time index (*TTI* [mmHg·s]), both defined as (Westerhof *et al.*, 2019):

$$RPP = P_{aa,sys} \cdot HR, \quad (6)$$

$$TTI = P_{lv,mean} \cdot RR, \quad (7)$$

229 where $P_{aa,sys}$, $P_{lv,mean}$, HR and RR are the aortic systolic pressure, the mean left
 230 ventricle pressure, the heart rate and the cardiac cycle duration ($HR = 60/RR$),
 231 respectively. In this study, since we are interested in the cardiac work and
 232 oxygen consumption expressed per minute, these mechano-energetic and
 233 oxygen consumption indexes, apart from RPP , are multiplied by HR (i.e.,
 234 $EW_{lv/rv}/min$ [J/min], $PE_{lv/rv}/min$ [J/min], $PVA_{lv/rv}/min$ [J/min], and TTI/min
 235 [mmHg·s/min]).

236 To assess coronary perfusion at different levels of gravitational
 237 acceleration, two of the main branches of coronary circulation are
 238 investigated. Specifically, blood flows in the left anterior descending artery
 239 (LAD) – which is a branch of the left coronary artery and supplies blood to
 240 the anterior region of the left ventricle - and the right coronary artery (RCA)
 241 – which originates from the right aortic sinus and supplies blood to both the
 242 right ventricle and atrium – are evaluated. The analyzed hemodynamic
 243 parameters are the coronary stroke volume ($SV_{LAD/RCA}$ [ml]), the coronary
 244 blood flow ($CBF_{LAD/RCA}$ [ml/min]), and the coronary perfusion pressure
 245 ($CPP_{LAD/RCA}$ [mmHg]), which are respectively defined as follows:

$$\begin{aligned}
 246 \quad SV_{LAD/RCA} &= SV_{sys,LAD/RCA} + SV_{dia,LAD/RCA} = \\
 247 \quad &= \int_{RR_{sys}} Q_{LAD/RCA}(t) \cdot dt + \int_{RR_{dia}} Q_{LAD/RCA}(t) \cdot dt, \quad (8)
 \end{aligned}$$

248 where RR_{sys} , RR_{dia} are the systolic and diastolic intervals, and $Q_{LAD/RCA}$ is the
 249 flow rate within the LAD/RCA artery; and

$$250 \quad CBF_{LAD/RCA} = SV_{LAD/RCA} \cdot HR, \quad (9)$$

$$251 \quad CPP_{LAD/RCA} = P_{aa,dia} - EDP_{lv/rv}, \quad (10)$$

252 with $P_{aa,dia}$ being the diastolic aortic pressure.

253 3. Model validation

254 The existing literature provides very limited data on short-term cardiac
255 response to actual spaceflight conditions of micro- and hyper-gravity. In
256 particular, the hemodynamic parameters associated with the right heart, along
257 with metrics for oxygen consumption, and coronary and cerebro-ocular
258 circulations are poorly understood in both micro- and hyper-gravity
259 environments. To validate our model, we relied on experimental
260 measurements extracted from parabolic flight and centrifuge studies
261 (Fontolliet *et al.*, 2015; Ueda *et al.*, 2015; Habazettl *et al.*, 2016; Ogawa *et al.*,
262 2016; Diaz-Artiles *et al.*, 2018; Konishi *et al.*, 2019) (please, refer to the link
263 in the Additional Information section for raw data about the validation dataset
264 constructed from experimental measures extracted from the literature). In
265 order to enlarge the validation dataset, parabolic flight campaigns assessing
266 both standing (Lathers *et al.*, 1989; Mukai *et al.*, 1991; Caiani *et al.*, 2006,
267 2007; Liu *et al.*, 2012) and sitting postures (Norsk *et al.*, 1987, 2006; Pump *et al.*,
268 1999; Beckers *et al.*, 2003; Petersen *et al.*, 2011; Ogoh *et al.*, 2015;
269 Widjaja *et al.*, 2015; Klein *et al.*, 2019) were included. Parabolic flights
270 expose the cardiovascular system to a sequence of hyper-gravity and micro-
271 gravity phases, each lasting only a few seconds, during which accelerations of
272 1.8g and 0g are typically reached. Human centrifuge studies achieve higher g-
273 forces, thereby allowing us to extend the validation dataset to the gravity range
274 [0g-2.5g]. However, it should be noted that, as it happens in real space- and
275 aeronautical flight conditions, our model correctly reproduces a uniform
276 gravitational acceleration along the longitudinal axis, whereas centrifuge-
277 induced hyper-gravity entails a gravity acceleration gradient along the head-

278 feet axis (or z-axis). Moreover, in the considered experimental datasets the
279 radius of the centrifuge varied between 1.4 m and 7.2 m; this results in
280 different acceleration gradients along the body (in different centrifuges) for
281 the same reference value at a given point on the body itself. Finally, the
282 reference point along the z-axis for the acceleration measure was not uniform
283 across studies: some of them report it at heart level (Ueda *et al.*, 2015; Ogawa
284 *et al.*, 2016; Konishi *et al.*, 2019) and others at foot level (Habazettl *et al.*,
285 2016; Diaz-Artiles *et al.*, 2018). Due to the aforementioned differences, the
286 experimental data exploited to validate our model are inherently
287 heterogeneous.

288 The model was validated against the experimental behaviour of six
289 hemodynamic variables – which are the most commonly reported variables in
290 the literature – in the gravity range from 0g to 2.5g. The variables considered
291 are: heart rate (*HR* [bpm]), cardiac output (*CO* [l/min]), stroke volume (*SV*
292 [ml]) mean arterial pressure (*MAP* [mmHg]), systolic arterial pressure (*SAP*
293 [mmHg]), and diastolic arterial pressure (*DAP* [mmHg]). It is worth noting
294 that both in centrifuge and parabolic flight studies, all authors measured the
295 arterial blood pressure at the level of the finger. These measurements were
296 corrected either by maintaining the hand at the same level of the heart or
297 applying an appropriate pressure correction that accounts for the contribution
298 of the hydrostatic term. In addition, some of these authors computed *MAP*,
299 *SAP* and *DAP* after reconstructing the brachial artery pressure via a suitable
300 transfer function. Conversely, in our model, *MAP*, *SAP* and *DAP* are
301 computed at the level of the ascending aorta.

302 For each group of the dataset (centrifuges, parabolic flights at seated and
 303 standing posture), all hemodynamic variables were normalized with respect to
 304 the corresponding 1g values (the normogravity 1g condition is denoted as g_0).
 305 This normalization eliminates the heterogeneity in baseline mean values at 1g
 306 across individual studies, ensuring a direct focus on how each cardiac
 307 parameter changes with g . Following normalization, the experimental data of
 308 each variable collected from the literature were pooled. In particular, the data
 309 pooling was carried out across each investigated gravity level. For instance,
 310 considering that centrifuge studies provided HR measurements at $g/g_0 = [0,$
 311 $0.5, 1, 1.4, 1.5, 2, 2.5]$, the pooled mean (μ^p) and the pooled standard deviation
 312 (σ^p) were computed for each of these g values. It is important to note that the
 313 number of observations for each sample varies across the different studies.
 314 Therefore, values of μ^p and σ^p for each cardiac parameter X and gravity level
 315 j were computed as (Borenstein *et al.*, 2009):

$$316 \quad \mu_{Xj}^p = \frac{\sum_{i=1}^k n_i \mu_{Xi,j}}{\sum_{i=1}^k n_i}, \quad (11)$$

$$317 \quad \sigma_{Xj}^p = \sqrt{\frac{\sum_{i=1}^k \sigma_{Xi,j}^2 (n_i - 1) + \sum_{i=1}^k n_i (\mu_{Xi,j} - \mu_{Xj}^p)^2}{\sum_{i=1}^k n_i - 1}}, \quad (12)$$

318 where n_i , $\mu_{Xi,j}$, $\sigma_{Xi,j}$ denote the number of samples, the mean, and standard
 319 deviation for the X -th cardiac parameter, at gravity level j , in the literature
 320 study i , respectively. Additionally, it should be mentioned that due to
 321 differences in experimental protocols, methods, and purposes among the
 322 extracted literature studies, not all provided experimental measurements for
 323 every cardiac parameter at each gravity level investigated. This heterogeneity

324 resulted in a fragmented dataset, which did not allow for the computation of
 325 μ^p_{Xj} and σ^p_{Xj} for certain cardiac parameters at specific g values. In particular,
 326 experimental measurements for SV and CO are missing at $2.5g$, while data for
 327 SAP and DAP are not given at $0.5g$. After determining the values of μ^p_{Xj} and
 328 σ^p_{Xj} for each cardiac variable, a linear regression using the weighted least-
 329 squares fitting method was performed to verify the existence of a statistically
 330 significant trend with g . This approach enabled us to consider the impact of
 331 the different σ^p_{Xj} across the data by applying the weights $w_j = 1/(\sigma^p_{Xj})^2$ in the
 332 formula for the sum of squared errors (Neter *et al.*, 1996). Statistical
 333 significance of each trend was determined using a two-sided t -test for the slope
 334 coefficient, with a significance level of 0.05.

335 Figure 2 shows, for each parameter, the model outcomes and the
 336 regression lines (dashed curves) alongside the pooled means μ^p_{Xj} and the
 337 pooled standard deviation values σ^p_{Xj} (horizontal lines) of each dataset group
 338 collected from the literature.

339 Experimental data reveal an increasing trend in HR , MAP , SAP , and DAP ,
 340 while SV and CO exhibit a decreasing behaviour. In particular, the linear
 341 regression analysis confirms that the trends in HR , MAP , SAP , DAP , and SV
 342 are statistically significant (p -value < 0.05), whereas CO fails to pass the t -
 343 test, reporting a p -value of 0.13. In detail, as gravity increases from $0g$ to $2g$,
 344 centrifuges data (red lines) show a -37.8% decrease in μ^p_{SV} . Similarly,
 345 parabolic flight measures indicate reductions of -39.5% and -29.8% in the
 346 range $[0g-1.8g]$ in standing (blue lines) and sitting positions (yellow lines),
 347 respectively (Fig. 2a). This behaviour is attributed to the fact that an increase
 348 in g triggers a fluid shift from the upper to lower regions of the body, leading

349 to decreased venous return and reduced SV . To counteract this drop, short-
 350 term regulation mechanisms (arterial baroreflex and cardiopulmonary reflex)
 351 induce a rise in μ^p_{HR} (Fig. 2b): +57% from 0g to 2.5g, +33% and +12.8% from
 352 0g to 1.8g in parabolic flights with standing and seated posture, respectively.
 353 As a result, CO remains relatively stable within the investigated range of
 354 gravity, explaining the non-significant trend in CO (Fig. 2c).

355 Observing the pressure data, systemic MAP (Fig. 2d) appears to increase
 356 with increasing gravitational force – μ^p_{MAP} rises by 11.2%, 16.2% and 16.8%
 357 for centrifuges, parabolic flight in standing and seated posture, respectively –
 358 mostly due to increased μ^p_{DAP} (Fig. 2e). With regard to SAP , the experimental
 359 data show some discrepancies. Specifically, μ^p_{SAP} (Fig. 2f) does not exhibit a
 360 clear trend in relation to gravity in centrifuge measures (red lines). Conversely,
 361 during parabolic flights, an increase of +19% is observed from 0g to 1.8g in
 362 the sitting position (yellow lines), whereas in the standing posture (blue lines),
 363 the initial elevation occurring from 0g to 1g is followed by a slight decline in
 364 the hyper-gravity range.

365 Our cardiovascular model gives values which generally align with the
 366 experimental data, and all model outcomes (reported in Fig. 2 through solid
 367 black curves) fall within the range $\mu^p \pm \sigma^p$, indicating that the model is able to
 368 capture the cardiovascular response to gravity changes in both micro- and
 369 hyper-gravity conditions. In particular, SV (panel a) decreases by -46.1%
 370 within the range [0g-2g], in agreement with experimental data, and drops by -
 371 60.8% up to 3g, varying from 82.9 ml at 0g to 32.5 ml at 3g. Conversely, HR
 372 (panel b) initially exhibits a non-linear increase from 0g to 0.5g, followed by
 373 a linear behaviour beyond this value. Specifically, as gravitational

374 acceleration varies from 0g to 3g, the model detects an increment of 94%, with
375 *HR* growing from 66 bpm to 128 bpm. Moreover, a good correspondence
376 between the predicted values for both *SV* and *HR* and their respective
377 regression lines is observed. With regard to *CO* (panel c), the model predicts
378 a slight monotonic decrease from 5.45 l/min at 0g to 4.16 l/min at 3g (-23.7%).
379 Notably, although the weighted least-squares fitting analysis highlighted a
380 weakly non-significant trend for *CO*, the slope of the data-based regression
381 line is negative and closely aligns with the results provided by the model.

382 Due to the peripheral vascular adjustments governed by short-term
383 regulation mechanisms, *MAP* (panel d) mildly increases from 92 mmHg at 0g
384 to 96.2 mmHg at 1g (+4.6%). Beyond this value, *MAP* remains constant up to
385 2.2g, before gradually decreasing and returning to 92 mmHg at 3g. The model
386 correctly predicts the increase in diastolic pressure (panel e). In particular,
387 *DAP* grows monotonically from 0g to 2.5g, varying from 69 mmHg to 82
388 mmHg (+19%), while it remains quite constant from 2.5g to 3g. Concerning
389 *SAP* (panel f), the model predicts a non-monotonic behaviour with g. The
390 systolic pressure is constant at around 121 mmHg in the gravity range [0g-
391 0.5g]. Beyond this range, *SAP* exhibits a monotonic decrease, reaching a value
392 of 104 mmHg at 3g. This behaviour doesn't fully match with the fitting
393 analysis, where a positive slope was found for *SAP*. However, as above-
394 mentioned, the experimental data are quite contradictory, and a decline in *SAP*
395 is also observed during the hyper-gravity phase of parabolic flight in a
396 standing posture (blue symbols). We recall that this posture, among all the
397 experimental setups examined, is the most representative of that simulated by

our model, which reproduces a uniform gravitational acceleration along the head-feet axis during exposure to gravity transitions in standing posture.

4. Results

The previous section allowed us to validate and compare our cardiovascular model with existing experimental data of the main central hemodynamic variables. Here, by means of our mathematical model, we will explore the response of cardiac parameters which are difficult to investigate experimentally, aiming to shed light on the cardiac function under altered gravitational force. In particular, the short-term cardiac response to gravity changes will be first investigated by means of the main mechano-energetic cardiac parameters and oxygen consumption indexes. Secondly, the perfusion of the myocardial tissue will be examined by focusing on both the left and right coronary circulations. Finally, the gravity impact on mean and pulsatile values of the central venous pressure (CVP), the pulmonary artery pressure (P_{pa}), the pulmonary capillary wedge pressure ($PCWP$), and the central aortic pressure (P_{aa}) will be evaluated.

Figure 3 illustrates the acute hemodynamic response of the left and right ventricles from micro- ($0g$) to hyper-gravity ($3g$). In particular, the response is investigated in terms of the cardiac parameters introduced in the Section 2.2.

The right and left ventricles PV loops (Fig. 3a and 3b) exhibit significantly different responses to gravity changes. As g varies from $0g$ to $3g$, due to the reduced venous return at higher g values, both left and right end-diastolic volumes ($EDV_{lv/rv}$) decrease similarly between the two ventricles, with EDV_{lv} and EDV_{rv} varying from 133.0 ml to 67.7 ml and from 143.0 ml to

423 65.6 ml, respectively. A reduction in left and right end-systolic volumes
 424 ($ESV_{lv/rv}$) is also observed as g rises: ESV_{lv} decreases from 50.1 ml at 0g to
 425 35.2 ml at 3g, whereas ESV_{rv} diminishes from 60.7 ml to 33.8 ml.
 426 Additionally, due to the reduced ventricular filling both left and right
 427 ventricular end-diastolic pressures ($EDP_{lv/rv}$) decrease monotonically with
 428 increasing g . However, this similar behaviour between the ventricles does not
 429 apply to end-systolic pressures ($ESP_{lv/rv}$). In the systemic circulation, the
 430 baroreceptors and cardiopulmonary reflexes induce an increase in total
 431 peripheral resistance, maintaining an adequate ESP_{lv} even at higher g values,
 432 with ESP_{lv} slightly decreasing from 96.6 mmHg at 0g to 86.6 mmHg at 3g. On
 433 the contrary, in the right ventricle, ESP_{rv} decreases from 15.1 mmHg at 0g to
 434 2.23 mmHg at 3g (-85%). This entails a different behaviour of EW/min
 435 between the left and right ventricles (Fig. 3c and 3d). In particular, the
 436 decrease in EDV , elicited by the blood shift towards the lower extremities and
 437 the reduced venous return, affects the preload, reducing both the stroke
 438 volume and the EW via the Frank-Starling mechanism (Westerhof *et al.*,
 439 2019). However, while for the left ventricle, the PV loop shrinks primarily in
 440 a horizontal direction, thus limiting the reduction in EW/min , this does not
 441 occur for its right counterpart, where both a horizontal and vertical shortening
 442 of the PV loop is detected. Hence, the reduction in EW/min for the left
 443 ventricle is restricted to -15% up to 2.2g (from 76 J/min at 0g to 65 J/min at
 444 2.2g). Beyond this value, EW/min decreases with a higher rate and a drop of -
 445 27% is detected at 3g with respect to 0g. Conversely, the rate of decrease in
 446 EW/min is almost constant for the right ventricle, and a reduction of -47% is
 447 observed as gravity rises from 0g to 3g (from 11.8 J/min to 6.2 J/min).

448 Differences between the right heart and the left heart are also noticeable
449 in PE/min . In the left ventricle, the mechanical potential energy expressed per
450 minute (Fig. 3c) does not exhibit large variations. In particular, it displays a
451 non-monotonic trend, gradually increasing with gravitational acceleration and
452 reaching a maximum at around 2.3g (from 21.5 J/min at 0g to 27.6 J/min at
453 2.3g, +28.4%). Beyond this peak, PE/min declines slightly, but remains higher
454 compared to the value observed at 0g. In contrast, in the right ventricle,
455 PE/min decreases monotonically from 4.4 J/min at 0g to 2.4 J/min at 3g (-
456 45.5%), due to the abovementioned decline in ESP_{rv} .

457 Pressure-volume area PVA/min , which is given by the sum of PE/min and
458 EW/min (see shaded areas in panels 3a-b), follows a similar response to that
459 of EW/min in both ventricles. The strong dependence of PVA/min on EW/min
460 is primarily due to the minor variations in PE/min with respect to the changes
461 in EW/min as gravity rises. However, by observing the efficiency indexes LVE
462 and RVE (Fig. 3e and 3f) – which are defined as the ratio EW/PVA – two
463 different responses to gravity changes between left and right ventricles emerge
464 due to the different behaviour of PE/min . In the left heart chamber, LVE
465 decreases monotonically from 0.78 at 0g to 0.68 at 3g (-12.8%), whereas RVE
466 is almost constant, varying from 0.73 to 0.72 (-1.4% from 0g to 3g).

467 In figures 3e and 3f, another index of cardiac efficiency, EF , is reported.
468 EF expresses the emptying capability of the left/right ventricle during systole.
469 This capability worsens similarly for both ventricles as gravity rises. The
470 primary reason behind this decline is the reduction in SV (see Fig. 2a), which
471 is equal for right and left ventricles. In particular, as gravity rises from 0g to

472 3g, EF decreases from 62% to 48% in the left ventricle and from 58% to 48%
473 in the right one.

474 Finally, figure 3g illustrates the behaviours of the oxygen consumption
475 indexes RPP and TTI/min . Both indexes exhibit a non-linear increase with g .
476 TTI/min is characterized by a minimum in the proximity of 0.4g, followed by
477 a central section where TTI/min increases, reaching a maximum close to 2.7g.
478 However, as already observed in a previous study on the cardiovascular
479 response to parabolic flights (Fois *et al.*, 2022b), TTI/min remains slightly
480 affected by gravitational acceleration, with variations across the gravity range
481 limited to -0.6% (at 0.4g) and to +7.7% (at 2.7g) with respect to the 0g
482 condition. Conversely, RPP shows a +68.5% increase within the range [0g-
483 3g]. Hence, the behaviours of both TTI/min and, especially, RPP suggest an
484 increase in oxygen consumption and, therefore, in energy demand of the left
485 ventricle at higher g values. Moreover, being EW/min an index of the energy
486 supply, the comparison of EW/min and oxygen consumption indexes
487 highlights a mismatch between the left ventricle energy supply and energy
488 demand for increasing gravity levels.

489 In figure 4, the comparison between the short-term hemodynamic
490 response of the left and right coronary circulations is reported. Coronary
491 perfusion is evaluated at varying levels of gravitational acceleration in terms
492 of coronary $SV_{LAD/RCA}$, $CBF_{LAD/RCA}$ and $CPP_{LAD/RCA}$ (see Section 2.2).
493 Additionally, the LAD flow rate (Q_{LAD}) waveforms at four different levels of
494 g are reported.

495 Figure 4a displays SV_{LAD} , SV_{RCA} and their SV_{LAD}/SV_{RCA} ratio. SV varies
496 similarly with gravity in both LAD and RCA. Thus, the SV_{LAD}/SV_{RCA} ratio is

497 barely affected by gravity changes, varying from 1.54 at 0g to 1.42 at 3g (-
 498 7.8%). Specifically, at low g values, a slight increment in SV is observed,
 499 which reaches a maximum in the proximity of 0.5g. Beyond this value, SV
 500 sharply decreases, falling by -26.8% and -32.4% from 0g to 3g in the RCA
 501 and LAD, respectively. This drop is primarily due to the increase in HR with
 502 g . In fact, as HR increases, the duration of the cardiac cycle (RR) reduces,
 503 leading to altered diastolic and systolic lengths (RR_{dia} and RR_{sys}). It follows
 504 that – as blood flow within the coronary arteries occurs mainly during diastole
 505 due to the mechanical compression exerted by the cardiac muscle in the
 506 systolic phase – the coronary perfusion changes. In particular, diastolic length
 507 suffers a more significant contraction compared to systole (RR_{dia} is 59.8% of
 508 RR at 0g and 43.3% of RR at 3g), resulting in a decreased RR_{dia}/RR_{sys} ratio and
 509 a reduced SV . This response is well captured in figures 4b and 4c, where the
 510 fractions of SV during diastolic and systolic phases (SV_{dia} and SV_{sys}) in LAD
 511 and RCA are reported at different levels of g : while SV_{sys} is almost constant
 512 throughout the gravity range both in LAD and RCA, SV_{dia} mirrors the same
 513 behaviour of total SV . Hence, the SV_{dia}/SV_{sys} ratio decreases with g , varying
 514 from 3.7 at 0g to 1.7 at 3g in the LAD, and from 1.5 and 1.1 in the RCA.

515 Despite an overall decrease in SV is observed as g rises, CBF (Fig. 4d)
 516 grows with g in both coronary arteries due to the rise in HR . However, CBF
 517 exhibits a non-linear trend characterized by a downward concavity which
 518 reduces its increase at higher g values: in the LAD, an increase of +31.7% is
 519 detected at 3g with respect to 0g, whereas CBF rises by 42.5% in the RCA.
 520 Additionally, recalling that an increase in RPP of +68.5% is detected at 3g
 521 (recall panel 3d), the non-linear behaviour of CBF suggests an imbalance of

522 the energy supply/demand ratio even at coronary level during hyper-gravity
523 exposure.

524 *CPP* (in Fig. 4e) displays a similar behaviour to that of *CBF* in both
525 coronary arteries. We recall that, *CPP* is often used as a surrogate for *CBF*
526 (Koeppen & Stanton, 2023). According to its formulation, *CPP* is strictly
527 associated with aortic diastolic pressure. Therefore, the increment in *DAP* with
528 *g* is the main cause of *CPP* behaviour. Moreover, the CPP_{LAD}/CPP_{RCA} ratio is
529 constant throughout the gravity range and is equal to 0.93 (not shown in Fig.
530 4e), thus highlighting no impairment between right and left *CPP* as *g* varies.

531 Figure 4f highlights the impact of *g* on Q_{LAD} by showing the flow rate
532 waveforms at four different levels of *g* (0g, 1g, 2g and 3g). As *g* increases
533 from 0g to 3g, the waveform undergoes significant changes mainly during
534 diastole. In fact, besides a temporal shortening due to the rise in *HR*, an
535 amplitude stretch is observed, with the diastolic peak growing with rising *g*.
536 At lower *g* values, the diastolic maximum peak is followed by a slow
537 decreasing phase. This feature is completely lost at higher *g* due to the
538 contraction of the diastole duration. Consequently, the systole begins with
539 significantly higher Q_{LAD} values. This is the most significant change that can
540 be detected during the systolic phase. Additionally, figures 4g and 4h illustrate
541 how the length of the cardiac cycle affects the SV_{dia}/SV_{sys} ratio as *g* varies from
542 0g to 3g. The impact of *HR* on the imbalance of the RR_{dia}/RR_{sys} ratio is clearly
543 observed, with the ratio decreasing from 1.49 at 0g to 0.76 at 3g. Hence, at 3g
544 the systolic phase becomes predominant over diastole, resulting in the
545 aforementioned drop of the SV_{dia}/SV_{sys} ratio.

546 In figure 5, the mean values and amplitudes (computed as the difference
 547 between maximum and minimum values) of the central aortic pressure (P_{aa}),
 548 central venous pressure (CVP), pulmonary artery pressure (P_{pa}), and
 549 pulmonary capillary wedge pressure ($PCWP$) are displayed as function of the
 550 gravitational acceleration. These pressures provide crucial information
 551 regarding the overall hemodynamic status of the heart. In fact, P_{aa} and P_{pa}
 552 represent the pressure level at the left and right ventricular outlets, whereas
 553 CVP and $PCWP$ reflect the pressure within the right and left atria,
 554 respectively.

555 Figure 5a shows how mean and pulsatile values within the aortic root ($\overline{P_{aa}}$
 556 and ΔP_{aa} , respectively) vary with g . Specifically, $\overline{P_{aa}}$ initially increases with
 557 g , varying from 92 mmHg at 0g to 96.2 mmHg at 1g. This slight increase is
 558 due to the inotropic effect and the heightened peripheral vascular resistance
 559 triggered by short-term regulation mechanisms. $\overline{P_{aa}}$ is nearly constant up to
 560 2g, maintaining a value close to 96 mmHg, whereas at 3g a moderate decrease
 561 is detected, with $\overline{P_{aa}}$ reaching 92 mmHg. Due to the almost opposite
 562 behaviour of DAP and SAP , ΔP_{aa} decreases with rising g , reducing from 51.7
 563 mmHg at 0g to 23.0 mmHg at 3g (-55.5%). This decline in ΔP_{aa} reflects the
 564 drop in the left ventricle SV , confirming the close relationship between these
 565 two hemodynamic parameters (Hall & Hall, 2020).

566 CVP , mean pulmonary arterial pressure ($\overline{P_{pa}}$) and $PCWP$ (Fig. 5b, 5c and
 567 5d) are significantly affected by gravity acceleration and, contrary to $\overline{P_{aa}}$,
 568 exhibit a (non-linear) decreasing trend with increasing g . These pressures are
 569 characterized by much lower values than central aortic pressure and, therefore,
 570 are more susceptible to changes in intrathoracic pressure (ITP). Specifically,

571 at higher g values the diaphragm is pulled towards the abdominal cavity,
572 leading to a reduction in ITP (Videbaek & Norsk, 1997; Peterson *et al.*, 2002).
573 Hence, the mean values of CVP and $PCWP$ follow a similar decreasing
574 behaviour, reducing from 6.6 mmHg to -1 mmHg (-115% from 0g to 3g) and
575 from 8.1 mmHg to 0.5 mmHg (-94% from 0g to 3g), respectively. With
576 regards to pulsatile values of the pressure within the right and left atria, both
577 decrease with rising g , as a result of the progressively reduced venous return
578 and the subsequent decrease in atrial filling elicited by the increasing
579 gravitational force. Similarly, both the mean and pulsatile values of P_{pa} exhibit
580 a monotonic decline, diminishing from 15.4 mmHg to 5.5 mmHg (-64.3%
581 from 0g to 3g) and from 13.9 mmHg to 6.3 mmHg (-54.7% from 0g to 3g),
582 respectively. Notably, the trends observed for $\overline{P_{pa}}$, $\overline{CVP}$ and $\overline{PWCP}$ decrease
583 non-linearly with g . In particular, most of the drop occurs within the gravity
584 range [0g-2g], with minor variations in the upper region of the investigated
585 hyper-gravity range.
586

587 **Table 1.** Key findings of the cardiac function in micro- ([0g-1g]) and
588 hyper-gravity ([1g-3g]). Legend: $\approx$: not clear trend; $\approx\uparrow$ or $\approx\downarrow$: slight increase
589 or decrease; $\uparrow$ or $\downarrow$: increase or decrease; $\uparrow\uparrow$ or $\downarrow\downarrow$ great increase or decrease.

Hemodynamic parameters		[0g-1g]		[1g-3g]	
Left heart	mechano-energetic	PV loop	shifts and stretches horizontally	PV loop	shifts and shrinks horizontally
		EW/min	$\approx\uparrow$ (+6%)	EW/min	$\downarrow$ (-22.6%)
		PVA/min	$\approx$ (+0.8%)	PVA/min	$\downarrow$ (-15.7%)
	oxygen consumption	RPP	$\downarrow$ (-15.9%)	RPP	$\uparrow\uparrow$ (+41.8%)
		TTI/min	$\approx$ (-0.3%)	TTI/min	$\approx\uparrow$ (+6.8%)
	efficiency	EF	$\uparrow$ (+9.9%)	EF	$\downarrow$ (-15.3%)
		LVE	$\approx\uparrow$ (+5.3%)	LVE	$\approx\downarrow$ (-8.1%)
Right heart	mechano-energetic	PV loop	shifts and stretches vertically and horizontally	PV loop	shifts and shrinks vertically and horizontally
		EW/min	$\uparrow$ (+26.0%)	EW/min	$\downarrow\downarrow$ (-33.5%)
		PVA/min	$\uparrow$ (+25.5%)	PVA/min	$\downarrow\downarrow$ (-32.9%)
	efficiency	EF	$\approx\uparrow$ (+4.2%)	EF	$\downarrow$ (-12.3%)
		RVE	$\approx$ (+0.6%)	RVE	$\approx$ (-0.9%)
Coronary perfusion		SV	$\uparrow$	SV	$\downarrow$
		CBF	$\downarrow$	CBF	$\uparrow$
		CPP	$\downarrow$	CPP	$\uparrow$
		Amplitude and shape changes of Q_{LAD} signals as g increases from 0g to 3g			
Central pressures	Mean values	P_{aa}	$\approx$	P_{aa}	$\approx$
		P_{pa}	$\uparrow$	P_{pa}	$\downarrow$
		CVP	$\uparrow$	CVP	$\downarrow$
		PCWP	$\uparrow$	PCWP	$\downarrow$
	Amplitude	P_{aa}	$\uparrow$	P_{aa}	$\downarrow\downarrow$
		P_{pa}	$\uparrow$	P_{pa}	$\downarrow\downarrow$
		CVP	$\approx\uparrow$	CVP	$\downarrow\downarrow$
		PCWP	$\uparrow$	PCWP	$\downarrow\downarrow$

590 **5. Discussion**

591 The existing literature on cardiac function under altered gravity
592 conditions appears rather fragmented and characterized by several sources of
593 uncertainty. The limited number of studies, the challenges in acquiring clinical
594 measures in difficult conditions, and the significant inter- and intra-study
595 differences restrict the knowledge of the cardiovascular response to a small
596 set of hemodynamic parameters (Blaber *et al.*, 2010; Zhu *et al.*, 2015;
597 Hughson *et al.*, 2018; Shen & Frishman, 2019; Norsk, 2020; Goswami *et al.*,
598 2021). As a result, information is lacking regarding several key aspects of
599 cardiac behaviour, such as energy performance, oxygen consumption, right
600 heart function, and coronary perfusion at different levels of gravitational force.
601 In order to shed light on these gaps, in this work, we have exploited our
602 mathematical framework to provide novel insights into the left and right
603 cardiac hemodynamics within the gravity range [0g-3g].

604 Results indicate that transitions from micro- to hyper-gravity elicit
605 different responses between left and right heart hemodynamics. Within the
606 hypo-gravity range (i.e., [0g-1g]), the venous return is increased due to fluid
607 shift from the caudal to the cranial region. Consequently, in micro-gravity,
608 both the left and right ventricular chambers receive a larger quantity of blood,
609 with both end-systolic and end-diastolic volumes increasing as gravity
610 approaches 0g, resulting in an increased ventricular preload. However, as
611 depicted in figure 3, the left ventricular *PV* loop exhibits a horizontal shift,
612 whereas in the right ventricle, both horizontal and vertical shifts are detected,
613 as both end-systolic and end-diastolic pressures increase when entering the
614 hypo-gravity range. This different behaviour between left and right ventricles

615 was already observed by Gerber et al. (2018), who suggested that an increase
616 in *CVP* is responsible for this right ventricular *PV* loop upward shift.
617 Coherently with this observation, our cardiovascular model predicts an
618 increase in *CVP* (from 1.8 mmHg at 1g to 6.6 mmHg at 0g) during short-term
619 micro-gravity exposure in standing posture. However, actual spaceflight data
620 on *CVP* reveal some discrepancies. For instance, Buckey et al. (1996) reported
621 a decrease in *CVP* during micro-gravity with respect to supine and seated pre-
622 flight values, whereas Foldager et al. (1996) detected an increase in *CVP* both
623 in seated and standing postures. In addition to the rise in *CVP*, the upward
624 shift of the right ventricular *PV* loop could be explained by a reduced activity
625 of short-term regulation mechanisms for the cardiopulmonary circulation,
626 such as the baroreceptors and cardiopulmonary reflex. In systemic circulation,
627 these mechanisms regulate total peripheral resistance to maintain adequate
628 arterial pressure across a wide range of gravitational acceleration (see Fig 5a).
629 On the contrary, the total resistance of the pulmonary circulation is governed
630 by other factors, such as respiratory gasses, humoral and neural mechanisms
631 (Barnes & Liu, 1995). Our mathematical model does not implement these
632 mechanisms, resulting in a constant pulmonary vascular resistance throughout
633 the entire gravity range. Consequently, the micro-gravity-induced increase in
634 stroke volume and cardiac output leads to elevated right ventricle end-systolic
635 and diastolic pressures. As a result, the right ventricle *PV* loop is more affected
636 by gravity variations than its left counterpart. This is also evident from the
637 analysis of the mechano-energetic parameters. Specifically, as gravity varies
638 from 1g to 0g, *EW/min* increases by +6% in the left ventricle (from 71.6 J/min
639 at 1g to 76.1 J/min at 0g) and by +26% in the right ventricle (from 9.4 J/min

640 at 1g to 11.8 J/min at 0g), respectively. Moreover, PVA/min , which represents
641 the total mechanical energy produced by ventricular contraction, is almost
642 constant for the left ventricle (+0.8% from 1g to 0g), whereas an increase of
643 +25.5% is detected in PVA_{rv}/min . Additionally, together with a rise in the
644 mechano-energetic indexes, a reduction in oxygen consumption parameters
645 (i.e., RPP and TTI/min) and an increase in cardiac efficiency (i.e., $EF_{lv/rv}$, LVE
646 and RVE) are observed, suggesting that cardiac performance is enhanced
647 during short-term exposure to micro-gravity.

648 In the hyper-gravity range (i.e., [1g-3g]), a reduction in both PV loop
649 widths is observed (see Fig. 3a and Fig. 3b), affecting both SV and left/right
650 cardiac performance. Due to the above-mentioned different response between
651 left and right ventricles, the right PV loop also shrinks in the vertical direction.
652 However, contrary to micro-gravity, short-term exposure to hyper-gravity
653 elicits a significant decrease in both the left and right EW/min : EW_{lv}/min
654 decreases by -22.6% and EW_{rv}/min diminishes by -33.5% as g rises from 1g
655 to 3g. Since EW/min is a proxy of cardiac energy supply (Westerhof *et al.*,
656 2019; Koeppen & Stanton, 2023), its decrease indicates a loss of cardiac
657 performance, which no longer appears sufficient during hyper-gravity
658 exposure. In this context, our model outputs show that an increase in g is
659 associated with an increment in oxygen consumption indexes RPP and
660 TTI/min . In particular, RPP increases by +41.8% as gravitational force varies
661 from 1g to 3g. This indicates that the cardiac energy demand in hyper-gravity
662 is notably increased. Consequently, taking into account the simultaneous drop
663 in EW/min , our simulations suggest an imbalance between the energy demand
664 and supply within the hyper-gravity range. Impairment of cardiac performance

665 is further supported by the behaviour of the ventricular efficiency indexes:
666 LVE , EF_{lv} and EF_{rv} decrease monotonically with increasing g , while RVE is
667 nearly constant. Specifically, at 3g, both ejection fractions fall below 50%.
668 This value is critical, being EF values between 40% and 49% associated with
669 heart failure with mildly reduced ejection fraction (Savarese *et al.*, 2022).

670 The hyper-gravity scenario is further complicated by an impairment
671 between myocardial oxygen demand and coronary perfusion. Specifically, the
672 increase in HR , induced by the baroreflex, elicits an altered RR_{sys}/RR_{dia} ratio,
673 increasing the systolic phase over the diastolic duration. This results in a
674 $SV_{LAD/RCA}$ reduction, which is only partially mitigated by HR . In fact, both
675 CBF_{LAD} and CBF_{RCA} increase non-linearly, exhibiting a downward concavity
676 and reaching a maximum in the proximity of 2.8 g. Hence, at higher g values
677 the increase in CBF is slowed down, failing to compensate for the larger rise
678 in RPP , thus producing an energy mismatch even at the coronary level. Similar
679 findings have been observed in studies of coronary circulation during
680 arrhythmias at varying heart rates (Scarsoglio *et al.*, 2019; Gamilov *et al.*,
681 2020). Additionally, our numerical model allowed us to analyze the flow rate
682 waveform in the left ascending coronary artery, highlighting both amplitude
683 and shape distortions of Q_{LAD} signals as g increases from 0g to 3g.

684 One of the advantages of our mathematical framework is that it allows
685 for a direct investigation of mean and pulsatile values of the pressure signal in
686 regions of the cardiovascular system that are challenging to access using
687 current measurement methods. In this context, we evaluated the behaviour of
688 mean and pulsatile values of the pressure at the initial and final sites of the
689 systemic (P_{aa} and CVP) and cardiopulmonary (P_{pa} and $PCWP$) circulations,

690 respectively. The cardiovascular model highlights a different behaviour
 691 between the mean values of P_{aa} and the mean values of CVP , P_{pa} and $PCWP$.
 692 The latter (CVP , P_{pa} and $PCWP$) are more susceptible to changes in
 693 intrathoracic pressure with respect to aortic pressure, which, instead, remains
 694 stable across the entire range of gravitational acceleration. Additionally, the
 695 absence of a regulation mechanism similar to that of the baroreceptors
 696 contributes to the decline in P_{pa} mean values as g increases. Consequently, the
 697 driving pressures of the systemic ($P_{aa} - CVP$) and cardiopulmonary ($P_{pa} -$
 698 $PCWP$) circulations respond differently: at 3g with respect to 0g, the driving
 699 pressure varies by +13% in the systemic circulation and by -30% in the
 700 cardiopulmonary circulation. Conversely, the pulsatility of these pressures
 701 exhibits similar behaviour with g variation. Specifically, an increment in all
 702 the pulsilities is observed in the hypo-gravity range (from 1g to 0g: +28.0%
 703 for ΔP_{aa} , +28.8% for ΔP_{pa} , +8.7 for ΔCVP , and +26.8 for $\Delta PCWP$), whereas
 704 the exact opposite is detected in the hyper-gravity range (from 1g to 3g: -
 705 43.2% for ΔP_{aa} , -41.9% for ΔP_{pa} , -42.3 for ΔCVP , and -42.6 for $\Delta PCWP$).
 706 This behaviour is due to the strong association between the stroke volume and
 707 pressure pulsatility (Hall & Hall, 2020).

708 The present mathematical framework has some limiting aspects.
 709 Specifically, each model parameter has a degree of uncertainty, which is
 710 challenging to quantify due to the high inter-subject variability. These
 711 parameters are influenced by several factors, including the subject's sex,
 712 anthropometric features and age. In this context, future studies could
 713 investigate how some parameters affect the cardiac response to gravity
 714 changes, addressing important physiological and medical issues such as

715 arterial ageing, individual variability for subject-specific applications, and
716 gender differences. In addition, our model does not account for muscular
717 activation – which may play an important role in venous return to the heart,
718 especially during hyper-gravity exposure – and neglects the influence of tissue
719 weight. The implemented regulation mechanisms are limited to the
720 baroreceptors and the cardiopulmonary reflexes, thus neglecting other
721 mechanisms, such as metabolic regulation and reactivity to CO_2 and O_2
722 concentrations. Furthermore, in our model, the pulmonary vascular resistance
723 is assumed to be constant, whereas it is known to be non-linear and dependent
724 on active (respiratory gasses, humoral and neural mechanisms) and passive
725 factors (cardiac output, left atrial pressure, airway and interstitial pressure)
726 (Barnes & Liu, 1995). Finally, long-term regulation mechanisms related to
727 renal, hormonal activity and transcapillary blood flow are not described. The
728 reduction (even partial) of these limitations will be needed for future studies
729 aiming to investigate the long-term cardiovascular response.

730 **6. Conclusions**

731 The cardiovascular model described in this study provided valuable
732 insights into cardiac function under micro- and hyper-gravity conditions,
733 demonstrating to be a valid approach for investigating hemodynamic
734 parameters which are challenging to measure directly using current
735 acquisition methodologies. To the authors' knowledge, for the first time, the
736 cardiac response across the entire spectrum from micro- to hyper-gravity is
737 described in depth, and some crucial aspects emerge clearly. Firstly, the
738 different behaviour between the left and right hearts, with the latter being more
739 susceptible to gravity changes in terms of pressure and energy supply

740 (EW/min). Secondly, our findings indicated that, in the short-term, micro-
741 gravity exerted less stress on the heart due to enhanced venous return and
742 ventricular filling, leading to improved cardiac energy performance and
743 efficiency. Conversely, hyper-gravity imposed more stress on the
744 cardiovascular system, leading to an energy supply/demand imbalance at both
745 the cardiac and coronary levels. In particular, within the coronary circulation,
746 the increase in HR at higher g values was insufficient to compensate for the
747 reduction in coronary stroke volume, which occurred due to the reduced
748 RR_{dia}/RR_{sys} ratio. Finally, our study highlighted that gravity significantly
749 affected both mean and pulsatile values of central pressures, with increased
750 pulsatility in micro-gravity and reduced pulsatility in hyper-gravity.

751 The picture of cardiac behaviour under gravitational stress outlined in this
752 work opens the way to the study of the consequences that it has on other body
753 districts. In this regard, it is sufficient to mention that higher pulsatility at the
754 central level is typically associated with elevated variability in both cerebral
755 blood flow and intracranial pressure (Scarsoglio *et al.*, 2023). Since alterations
756 in CBF and ICP , along with variations in intraocular pressure, are implicated
757 in the onset of SANS, it follows that gravity-induced alteration of the cardiac
758 response plays a crucial role in one of the most serious pathologies that can
759 affect astronauts.

760 Our work demonstrates that mathematical modeling can usefully
761 complement the usual clinical and experimental approaches, helping to shed
762 light on currently unclear physiological and pathological mechanisms, with
763 the aim of identifying effective countermeasures to be adopted in space flights.

764 **Additional information**

765 *Data availability statement*

766 All model equations, parameter settings, code and generated raw
767 simulation data are available on Figshare, along with the experimental data
768 used for model validation (<https://doi.org/10.6084/m9.figshare.29064842>).

769 *Competing interests*

770 The authors declare that they have no competing interests that could have
771 appeared to influence the work reported in this paper.

772 *Author contributions*

773 F.T., L.R., and S.S. conceived and designed the research, analyzed and
774 interpreted the results, edited, and revised the manuscript. F.T. performed the
775 numerical simulations. F.T. drafted the manuscript and prepared the figures.
776 All authors reviewed and approved the final version of the manuscript.

777 *Funding*

778 This study was carried out within the I-2022-05387 "Optimizing
779 countermeasures against cardiovascular deconditioning and cerebral
780 hemodynamics changes in long-term human spaceflights" project, which was
781 selected via the Open Space Innovation Platform (<https://ideas.esa.int>) as a
782 Co-Sponsored Research Agreement and carried out under the Discovery
783 programme of, and funded by, the European Space Agency (contract number:
784 4000141523). This manuscript reflects only the authors' views and opinions
785 and the European Space Agency cannot be considered responsible for them.

786 **Figures**

787 **Figure 1.** Schematic representation of the closed-loop 0D-1D multiscale
788 model of the cardiovascular system. On the left, the 1D arterial tree is depicted
789 in red, with numbers, and yellow and green circles indicating the specific
790 arterial vessel, the outlets and the inlet of the 1D arterial tree, respectively. On
791 the right, a representation of the 0D peripheral circulation, which is organized
792 into five body regions (extracranial circulation, arms, upper abdomen, lower
793 abdomen, and legs), is shown. Vertical rectangles refer to arteriolar, capillary,
794 venular, venous and venae cavae compartments. The k -th generic 0D coronary
795 microvascular district is depicted in the left box, the boxes on the right
796 represent the cardio-pulmonary circulation, whereas the grey box at the
797 bottom shows the j -th generic 0D compartment Q_j is the flow rate, p_j is the
798 pressure, Δp_j^h is the hydrostatic gradient, and R_j , C_j and L_j are compartmental
799 resistance, compliance and inertance, respectively).

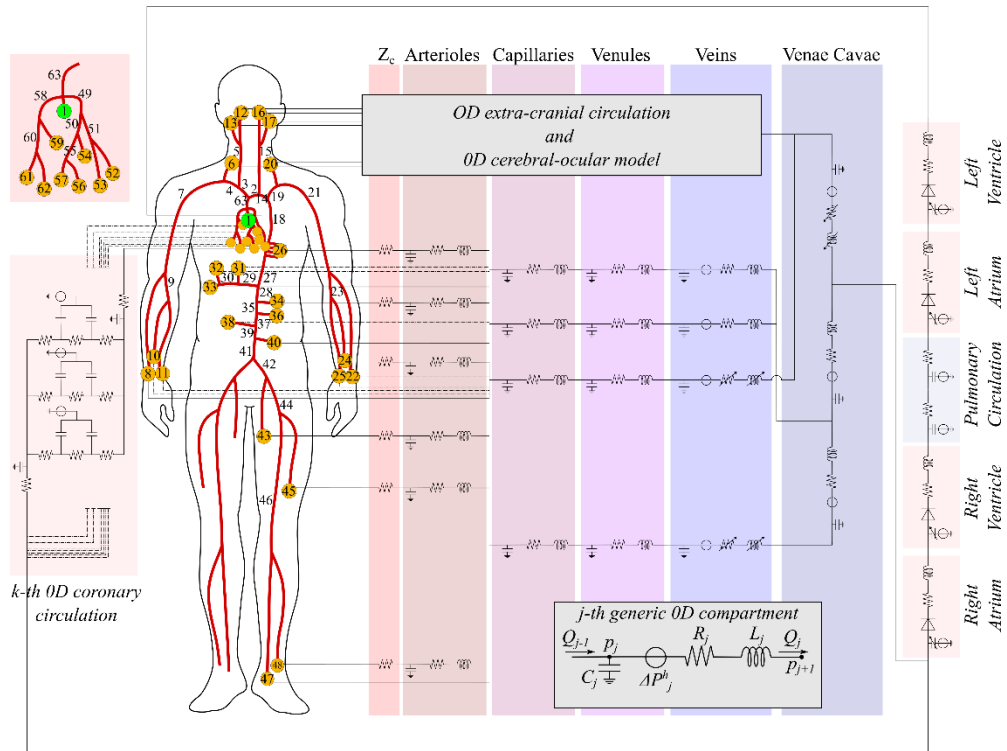
800 **Figure 2.** Pooled mean μ^p_{Xj} and standard deviation σ^p_{Xj} , for the X -th
801 cardiac parameter at gravity level j , are reported with vertical red (centrifuges
802 data), blue (parabolic flights data in standing posture), and yellow (parabolic
803 flights data in sitting posture) points and lines. The model outcomes are
804 depicted with black solid curves, whereas the dashed curves represent the
805 regression lines computed using the weighted least-squares fitting method.
806 Trends in SV (p -value < 0.001), HR (p -value < 0.001), MAP (p -value < 0.001),
807 SAP (p -value $= 0.0161$) and DAP (p -value < 0.001) are statistically significant,
808 whereas CO fails to pass the t -test with a p -value equal to 0.130.

809 **Figure 3.** Left and right columns report PV loops (panels a and b),
810 mechano-energetics (panels c and d), efficiency (panels e and f) and oxygen
811 consumption parameters (panel g) for left and right ventricles, respectively.

812 **Figure 4.** Coronary blood flow and coronary perfusion parameters: panel
813 a) shows the coronary stroke volume in the LAD (SV_{LAD}) and RCA (SV_{RCA})
814 along with the SV_{LAD}/SV_{RCA} ratio; panels b) and c) show the SV partition
815 between diastolic and systolic phases; panels d) and e) illustrate the coronary
816 blood flow (CBF) and the coronary perfusion pressure (CPP), respectively;
817 panels f), g) and h) show the impact of gravity changes on Q_{LAD} waveform.

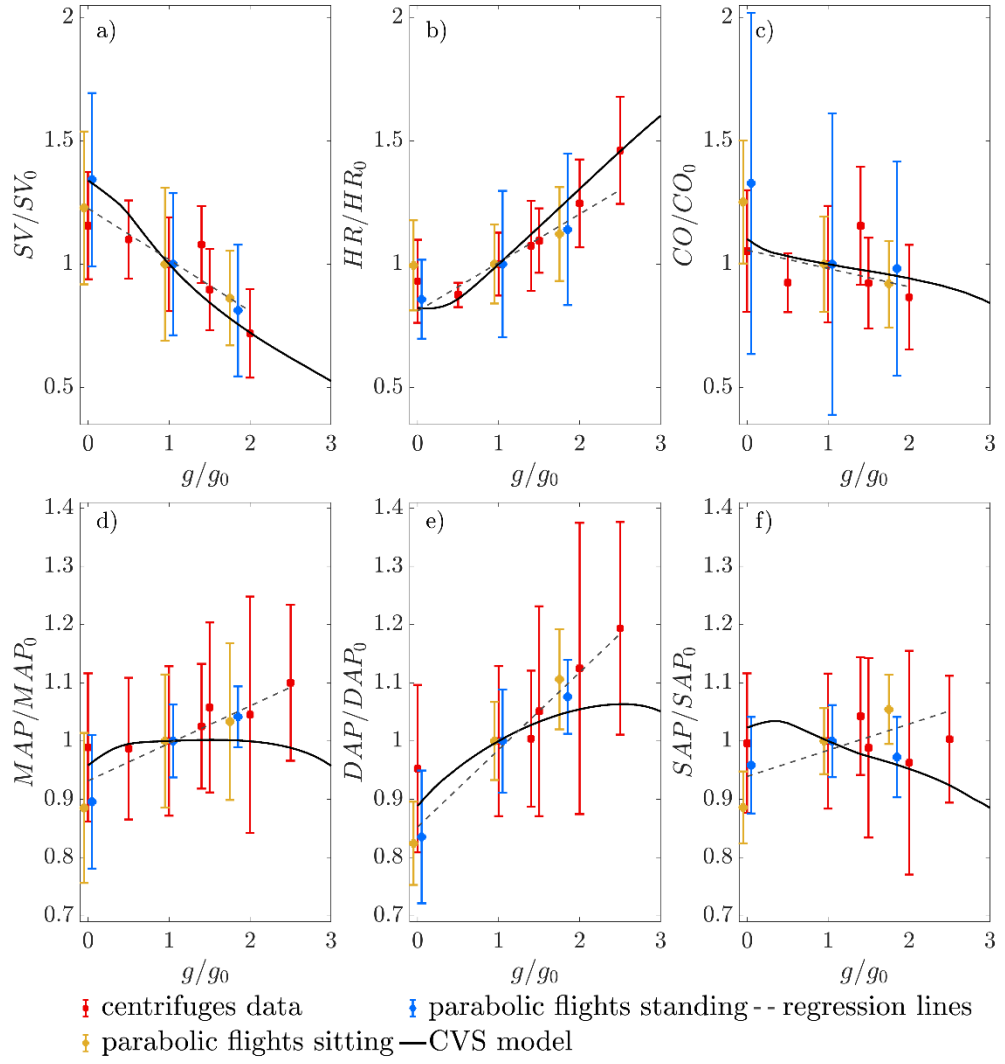
818 **Figure 5.** Mean values (solid lines) and amplitudes (shaded area) of: a)
819 ascending aortic pressure; b) central venous pressure; c) pulmonary artery
820 pressure; and d) pulmonary capillary wedge pressure.

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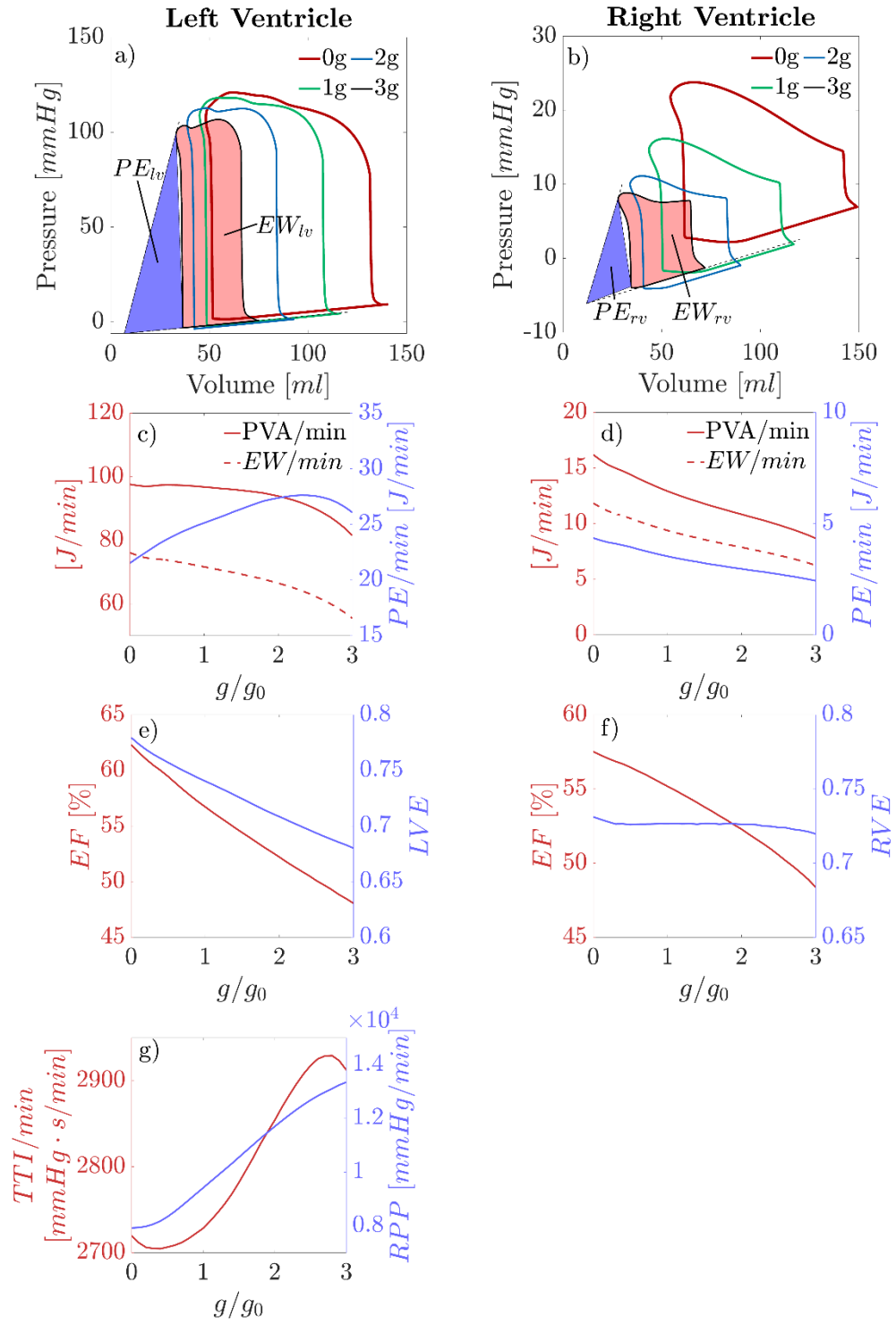
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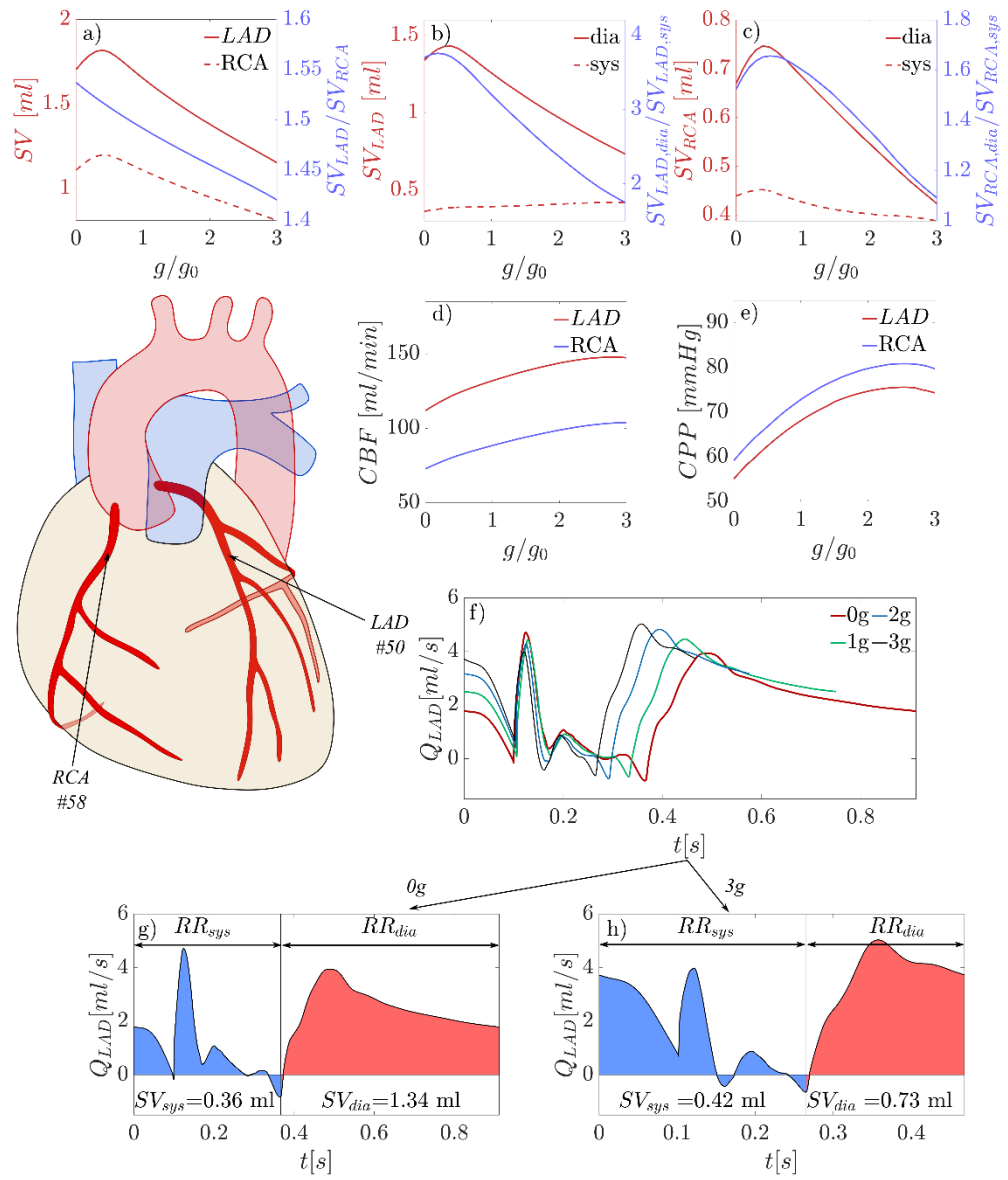
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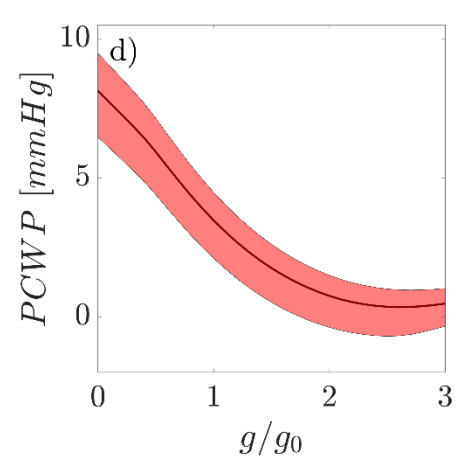
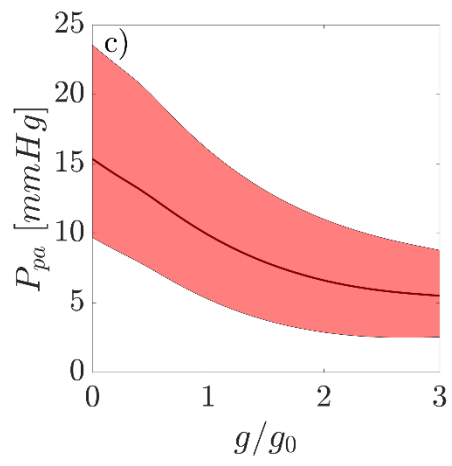
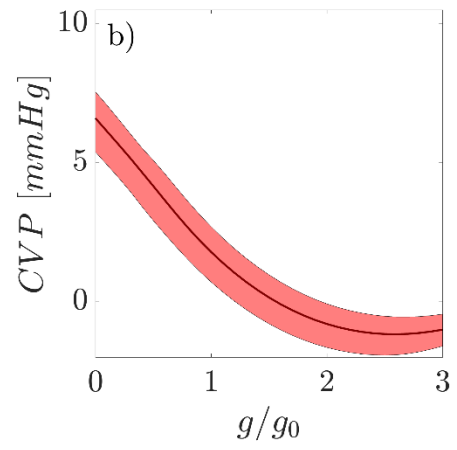
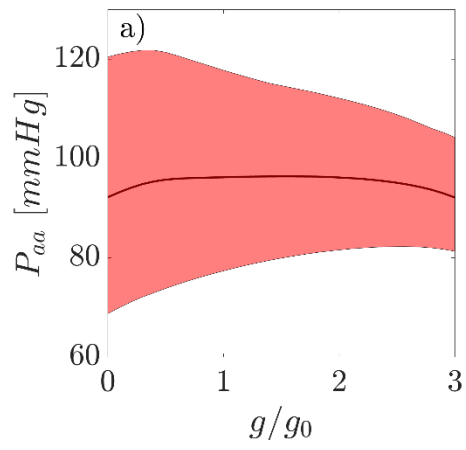


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