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Steady-State Analysis of Gravitational Effects on Hemodynamics

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ABSTRACT

Human tolerance to hypergravity is of increasing importance given the rising number of spaceflight participants. In this paper, we present a mathematical model of the human circulatory system that can predict an individual's tolerance to hypergravity. We adopt a steady-state approach, where simplicity enables us to predict an individual's tolerance to high gravitational acceleration (G-tolerance) with lower computational cost. Moreover, while our parameter set can be personalized to individual parameters, the model only requires cardiac output, three anthropometric measurements, vital signs, and sex to make a satisfactory prediction. Key features of the model include compartmentalization of the upper and lower circulation to allow for gravitational acceleration in the vertical direction to be varied, a model of venous collapse of the systemic veins, and feedback control to simulate regulation of heart rate and reserve volume. We also provide a case study of parameter calibration to predict G-tolerance for a single subject based on physiologic measurements before and during centrifuge-induced hypergravity. Simulation results were consistent with physiological expectations and subject report of G-related symptoms. These findings suggest that our model of the circulatory system has the potential to predict G-tolerance and serve as a clinical decision support tool to risk stratify subjects prior to spaceflight.

Introduction

Cardiovascular response to hypergravity has been a subject of study by aerospace professionals and scientists for over a century^{1,2,3,4,5}. Hypergravity can be induced by significant accelerations; G represents multiples of Earth's gravitational force induced by high acceleration states and applied to the body in variable directions (20) to (29). In a hypergravity environment, the increase in vertical acceleration ($+G_z$) reduces vascular flow to the brain, resulting in relative cerebral hypoxia⁶. Initial symptoms can include visual dimming or peripheral field loss and light-headedness but can rapidly progress to altered consciousness. G-induced loss of consciousness (G-LOC) occurs if sustained forces exceed innate and artificial countermeasures to maintain cerebral perfusion. Operationally, G-LOC is of concern during aerial combat maneuvers, civilian aerobatics, and potentially spacecraft launch and re-entry, particularly for spaceflight profiles (such as for suborbital winged vehicles) which have a significant $+G_z$ component⁷.

Although incompletely understood, G-tolerance has been found to modulated by factors including height of the body's vertical column⁸ (or heart-brain vertical distance⁶), age^{8,9}, and weight⁸ or body mass index¹⁰ (which correlate with blood volume^{11,12}). While some individuals can tolerate approximately $+15 G_x$ (acceleration in the horizontal vector), $+G_z$ tolerance can be as low as $+3 G_z$ without countermeasures⁶. To mitigate $+G_z$ intolerance, trained subjects often employ anti-G straining maneuvers (AGSM). However, with the emergence of commercial spaceflight, a diverse population with limited exposure to intensive aerospace training or experience is expected to encounter these gravitational conditions. The development of reliable and accessible mathematical models to predict the physiological alterations posed by hypergravity, particularly for those less experienced in managing its consequences, can assist aerospace professionals to identify higher-risk individuals that may need additional training or countermeasures.

Mathematical models can have varied levels of detail, but increasing realism incurs additional complexity and computational cost. The level of detail required depends on the question being asked of a model. Deterministic models of the human circulation typically follow the analog circuit model put forth by Guyton¹³.

Many models are ordinary differential equation (ODE) or partial-differential equation (PDE) based. These models typically simulate the heart using an pulsatile integral model and the flow throughout the systemic vasculature using an inflow/outflow

model for each subsystem.^{14,15,16} The inflow/outflow to a particular organ can be minimalistically modeled¹⁴ following Guyton's theoretical framework. Arteries and veins can also be modeled more precisely using deformable cyclinder models and flow through them using a valve model at each artery or vein junction.¹⁵ These models are able to simulate reasonably accurate waveforms¹⁵ for blood pressure and flow in the cardiopulmonary and systemic circulation. They are then run to a steady-state to measure various hemodynamic properties (e.g. flow rates, pressures, volumes, etc.).

From a clinical standpoint, most ODE and PDE-based models are too computationally expensive and complex to be practical, in some cases taking days to produce results or requiring specialized knowledge for implementation¹⁷. In contrast, a personalized diagnostic tool to risk-stratify commercial spaceflight participants would ideally be near-instantaneous for real-time clinical use. A review by Morris et al.¹⁷ highlights the challenges of model development, application, and personalization. Difficulties include obtaining data with sufficiently high temporal resolution to make use of the structure of these models and the difficulty of obtaining clinical measurements to parameterize these models in general.

To address these issues, we designed a mathematical model of the human circulation with variable G_z that is computationally inexpensive, conveniently parameterizable, and readily interpretable. We demonstrate that our model is sufficient for simulating accurate physiology. This is possible despite the fundamentally nonlinear effects of acceleration on blood flow and shows promise for granular tasks such as predicting an individual's unmitigated G-tolerance. To our knowledge, this is the first steady-state model with feedback control of heart rate that includes partial venous collapse and gravitational acceleration. Further novelty of this work comes from the calibration of model parameters to real subject centrifuge data.

Physiology

Circulation is divided into systemic circulation and pulmonary circulation. Homeostasis of blood flow in these circuits is achieved by changes in the vascular, cardiac, and renal systems¹³. For the purposes of the mathematical model, we will disregard the function of kidneys as the acceleration profile of launch and landing generally occurs within seconds to minutes. The kidneys regulate blood volume and secrete hormones that control blood pressure on a timescale of hours to days¹³; thus the ability for renal inputs to affect real-time acceleration response is minimal. In the cardiac system, flow is modified by changing cardiac output, which is the product of the heart rate and contractility. In the vascular system, flow is modified by the resistance in arteries and veins. At any given time, roughly 84% of the entire blood volume in humans is in the systemic circulation, with 16% in the heart or pulmonary circulation. Importantly, 64% of systemic circulation is located within the veins.¹³ Therefore, the venous system functions as a reservoir that can increase the supply of blood to the arteries by contraction of venous muscular walls to maintain homeostasis. This will be referred as the venous reserve volume, or simply reserve volume.

Multiple mechanisms control blood volume and blood flow within the body; in particular, flow can increase to as high as tenfold the resting level.^{18,19} Regulatory mechanisms include nervous system signaling and hormonal expression, which can alter physiological parameters. Nervous system signaling can drive contraction of venous reservoirs to provide more blood return to the heart and constriction of arterioles in some tissues to increase the arterial pressure in large arteries. The heart automatically responds to increased inflow of venous blood (preload) with increased outflow of arterial blood, but it also receives nervous system regulation through altered contractility to modify output and deliver the required blood flow.²⁰ Cardiac output thus results in total blood flow, which can be represented by the sum of all local tissue flows.

Modeling Considerations

Ideally, a useful clinical model should require the fewest possible number of biological parameters that are commonly available or easily obtained. Our model requires the heart-brain distance and heart-seat measurements, as well as total height and body weight, which are used to calculate estimated blood volume^{11,12}. Arterial and venous compliances are taken from the literature, but can be customized to an individual patient or patient cohort if desired. We incorporate age by proxy of compliance, as average vascular compliance decreases with age. Parameters and corresponding clinical measurements are discussed in more detail in the **Supplementary Materials ("Input Parameters")**.

Typically, $+G_x$ is well-tolerated within the limited acceleration parameters experienced during spaceflight and aerobic flight; in most cases, symptoms are limited to various discomforts. In contrast, $+G_z$ in excess of physiologic compensation can result in loss of visual fields, altered mentation, or loss of consciousness, with the potential to negatively impact the flight experience or even risk the health and safety of the participant. The purpose of our model is to determine the G-tolerance of a relaxed subject who is not performing AGSM in order to identify "worst-case" scenario G-tolerance (in other words, the lowest $+G_z$ acceleration that might result in G-LOC) and thus identify individuals who may need additional training or intervention to prevent undesirable G-related symptoms. Of note, combining $+G_x$ and $+G_z$ acceleration exposures results in variable physiological outcomes, and in some cases may slightly reduce G-tolerance⁶ (e.g., through $+G_x$ -induced bradycardia that decreases overall cardiovascular compensatory response to reduced cerebral blood flow²¹). Isolated $+G_z$ physiological response is more predictable than combined vector exposures. Commonality of isolated $+G_z$ response and etiologies of variable

combined vector acceleration response are further explored in other literature^{6,7,22}. Here, we choose to selectively model isolated $+G_z$.

Although maximum G-tolerance depends on the onset rate of $+G_z$ and improves with a "warm-up" period, experience, and/or frequent exposure⁶, maximum sustained G-tolerance should be roughly constant for each individual based on their physiology.⁶ The question of predicting the response to hypergravity, irrespective of a specific time, can be seen at the steady state of the system. Given the need for a simple, low-parameter model, we choose to directly model the cardiovascular system at steady state.

Model

The following subsections describe a steady-state flow model with seven compartments. This model incorporates the effects of vertical acceleration (G_z) on hemodynamics. A unique feature of this model is the inclusion of partial collapse of the systemic veins. We additionally describe a method for feedback control in the circulation to allow the model to appropriately respond to changes in its parameters (e.g. changes in gravity, loss of blood volume, etc).

Blood Flow Model

We divide the circulation into systemic, pulmonary, and heart components, and further subdivide each component into compartments. The systemic component is comprised of four compartments: systemic arteries above the heart, systemic veins above the heart, systemic arteries below the heart, and systemic veins below the heart. The pulmonary circulation is subdivided into arterial and venous compartments. The heart is modeled as one compartment.

Each compartment has a compliance and resistance, and is identified by a unique index. We assume the following relation between the compliance of a compartment: C_i , the pressure difference between the interior and exterior of the vessel P_i , and the volume V_i :

$$V_i = V_i^0 + C_i P_i = V_i^0 + C_i (P_i^{\text{interior}} - P_i^{\text{exterior}}) \quad (1)$$

In practice, the contractions of cardiac chambers result in the compliance values periodically oscillating between a minimum and maximum value during the phases of systole, and diastole respectively. In our steady-state model, compliance values are constant. The dead volume, V_i^0 is equal to the residual chamber volume at zero pressure. We will interchangeably refer to dead volume as reserve volume, since a reduction in V^0 may compensate for a loss in total volume. The total volume, V_{total} is the sum of the volumes in all compartments:

$$V_{\text{total}} = \sum_i V_i, \quad (2)$$

and similarly, the total reserve volume, V_{total}^0 is the sum of each of the reserve volumes:

$$V_{\text{total}}^0 = \sum_i V_i^0. \quad (3)$$

Subtracting equation (3) from (2) and substituting (1) yields:

$$V_{\text{total}} - V_{\text{total}}^0 = \sum_i C_i P_i. \quad (4)$$

In a resistance vessel, the flow is proportional to the pressure difference from one end of the vessel to the other. Thus any flow through a resistance vessel between chamber i and j , Q_{ij} is given by Ohm's Law/Poiseuille's Equation:

$$Q_{ij} = \frac{P_i - P_j}{R_{ij}}. \quad (5)$$

We model the systemic arteries (sa), systemic veins (sv), pulmonary arteries (pa) and pulmonary veins (pv) as compliance vessels, and tissues and organs as resistance vessels. Figure 1 illustrates the relation between these elements.

As this model describes a steady state of the cardiovascular system, the pressures, flows and volumes are time-independent. Cardiac output is defined as the volume of blood delivered to the systemic circulation per unit time. For the purposes of this model, we consider it simply to be the volume of blood being delivered to the systemic circulatory system. In this context, it makes sense to refer to cardiac output as the systemic flow Q_s .

$$Q_{\text{sa,sv}} = F V_{\text{stroke}} \quad (6)$$

where $Q_{sa,sv} = Q_s$ is the flow between the systemic arteries and systemic veins, F is the heart rate in beats per unit time and V_{stroke} is the stroke volume or the volume of blood ejected by the left ventricle per heart beat.

Letting t be time, and recalling our steady-state assumption of time-independence for all chambers i :

$$\frac{dV_i}{dt} = \sum_{j=1}^n Q_{ji} - \sum_{k=1}^m Q_{ik} = 0 \quad (7)$$

Here, we assume that the total flow entering a vessel is equal to the flow exiting a vessel and drop the subscript on Q_{ij} for any i and j and simply refer to Q as flow in general.

External pressure in systemic circulation is defined to be zero unless it is in the thoracic region, in which case it is subject to variable external pressure, P_{thorax} (cf equations (19) and (20)). As shown in equation (1), the thoracic region comprises the heart, and a portion of the systemic circulation. For the systemic circulation elsewhere, we define the external pressure to be zero (when not influenced by thoracic pressure). Indeed, in steady-state within a pressure-controlled chamber (e.g. the atmosphere or a spacecraft), the external pressure does not vary with respect to the pressure within the vessels. Furthermore as this is a steady-state model, time-dependent maneuvers such as AGSM, which affect external pressure through muscle contraction are not explicitly considered.

For the pulmonary circulation and both sides of the heart, the external pressure is the intrathoracic pressure, denoted P_{thorax} , which varies during the cycle of breathing and is lower during inspiration and higher during expiration. On average, the value of P_{thorax} is negative and is to be thought of as the pressure in the tissue surrounding the lungs. The lungs are elastic and tend to collapse. Therefore, a pressure difference between the air in the lungs and the air in the surrounding tissue is needed to keep them open. Negative intrathoracic pressure is generated by contraction of the diaphragm and is a parameter in our model.

The heart rate F is the same for both the left and right sides of the heart in persons with a single pacemaker. The output of either side of the heart is its stroke volume times the heart rate. In a steady-state, the right and left cardiac outputs are necessarily equal. Therefore the stroke volumes of the left and right heart are equal and are approximated by equation (1) for the volume in a ventricle at the end of diastole. The stroke volume equations (8) and (9) make the approximation that the end systolic volume is negligible. This assumption is reasonable in our case as we do not consider the heart failure subtype and are primarily interested in the systemic behavior.

$$V_{stroke} = C_{LVD}(P_{RA} - P_{thorax}) \quad (8)$$

$$= C_{RVD}(P_{pv} - P_{thorax}) \quad (9)$$

where C_{LVD} and C_{RVD} are the left and right ventricular diastolic compliances respectively. Combining equations (6) with (8) and (9), respectively, yields the following:

$$Q = FC_{LVD}(P_{RA} - P_{thorax}) \quad (10)$$

$$= FC_{RVD}(P_{pv} - P_{thorax}) \quad (11)$$

Additionally, by equation (5) and the steady state assumption, we have pulmonary flow given by:

$$Q = \frac{P_{pa} - P_{pv}}{R_p} \quad (12)$$

Incorporation of Gravity

To incorporate the effects of gravity in the vertical direction, $\pm G_z$, we compartmentalize the systemic circulation into upper and lower components, each with their own pressures, flows, and resistance values. **Figure 1** illustrates the spatial compartmentalization of this model. Then, by equation (5),

$$Q_s^u = \frac{P_{sa}^u - P_{sv}^u}{R_s^u} \quad (13)$$

$$Q_s^l = \frac{P_{sa}^l - P_{sv}^l}{R_s^l} \quad (14)$$

In the systemic circulation, there are multiple tissues and organs connected in parallel; their flows add to give the total systemic flow:

$$Q_{sa,sv} = \sum_j Q_{sj} \quad (15)$$

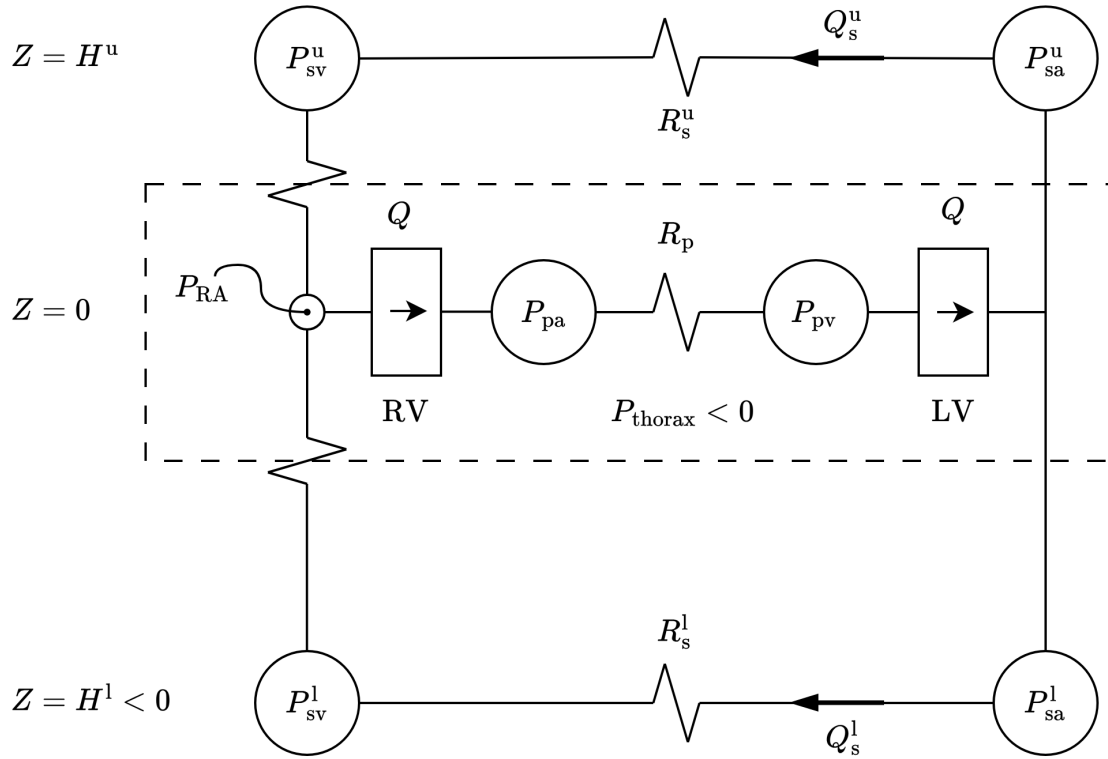


Figure 1. Schematic of the model, illustrating the relation of systemic thoracic and pulmonary compartments and the spatial relation between their components (H = height, u = upper, l = lower, p = pulmonary, s = systemic, pv = pulmonary veins, sv = systemic veins, sa = systemic arteries, pa = pulmonary arteries, RA = right atrium, RV = right ventricle, LV = left ventricle).

Note that by equation (15),

$$Q = Q_s^u + Q_s^l \quad (16)$$

Then, we are able consider the blood between the upper and lower compartment of the systemic circulation as a fluid-filled column to obtain the following relationship:

$$P_{sa}^l - P_{sa}^u = \rho g (H^u - H^l) \quad (17)$$

where, ρ is the density of blood, g is the gravitational acceleration, and H^u and H^l denote upper and lower heights respectively such that

$$H^u > 0 > H^l. \quad (18)$$

Venous Return

Venous return to the heart is modulated by thoracic pressure. Thoracic pressure is deliberately modified by pilots using AGSM. A common respiratory component of AGSM consists of a cyclic combination of forced exhalation against a closed glottis (L-1 maneuver) followed by <1 second of shallow rapid expiration and inspiration while maintaining tension in the lower extremity abdominal musculature^{6,23}. Additionally, pilots of high-performance aircraft may use positive-pressure breathing systems, which increase air pressure entering the lungs and thus raise intrathoracic pressure (Case III)^{24,25}. Although use of AGSM may provide the benefit of sustained cerebral arterial pressure and consciousness, sustained intrathoracic pressure also causes decreased venous return to the right atrium. This is countered with cyclic brief interruptions (expiration/inhalation) that permit venous return to the heart (as well as respiratory exchange) while incurring only a transient drop in cerebral blood pressure²³.

Our model incorporates various modalities of venous collapse determined by the right atrial pressure (and therefore indirectly by the intrathoracic pressure). These include partial collapse of the upper and lower systemic veins, partial collapse of the upper systemic veins only, and no venous collapse. These cases are mathematically more fully described below in equations (19) to (29). This approach enables us to study what happens at different intrathoracic pressures (for example, altered pressure

from AGSM or positive pressure breathing). We can assume some less-experienced individuals will improperly execute AGSM with negative physiological results. Indeed, forgetting (or waiting too long) to interrupt the forced exhalation against the glottis is also an issue for some fighter pilots-in-training²³.

The following aspect of our model enables us to study what happens if an individual holds intrathoracic pressure for longer than 7-10s (as in an excessively prolonged respiratory exchange cycle in AGSM)²³. The heart chambers are lumped into one chamber which we choose to be the right atrium. Depending on right atrial pressure, P_{RA} , we get the following equations

$$P_{sv}^u = \max\{0, P_{RA} - \rho g H^u\} \quad (19)$$

$$P_{sv}^l = \max\{0, P_{RA}\} - \rho g H^l \quad (20)$$

which give rise to three cases.

Case I:

$$P_{thorax} < P_{RA} < 0 \quad (21)$$

$$P_{sv}^u = 0 \quad (22)$$

$$P_{sv}^l = \rho g(-H^l) \quad (23)$$

Case II:

$$0 < P_{RA} < \rho g H^u \quad (24)$$

$$P_{sv}^u = 0 \quad (25)$$

$$P_{sv}^l = P_{RA} + \rho g(-H^l) \quad (26)$$

Case III:

$$\rho g(H^u) < P_{RA} \quad (27)$$

$$P_{sv}^u = P_{RA} - \rho g H^u \quad (28)$$

$$P_{sv}^l = P_{RA} + \rho g(-H^l). \quad (29)$$

We now have a linear system of equations that describes the flow through the circulatory system, as well as the relation between flow, pressure, volume and compliance for each part of that system. Regarding nomenclature, the unitless G is the number of multiples of Earth's gravity. In equations 19-29, g indicates the acceleration force (potentially microgravity or hypergravity) rather than Earth's gravitational acceleration constant.

Idealized Controller

To model cardiovascular responses to a changing environment, a control element must be incorporated into the model. We model homeostatic control of the baroreceptor-feedback loop using an instantaneous idealized controller.

Consider the heart rate F and total reserve volume V_{total}^0 to be unknown variables rather than parameters. Cardiac output Q can be proportionally adjusted during dynamic changes to the circulation. Since total volume is still fixed, the reduction of total reserve volume serves to increase the volume of distributed blood between the chambers, thereby increasing flow. We assume that the autonomic nervous system is able to make adjustments to heart rate and total reserve volume to maintain specific target values of the upper systemic arterial pressure P_{sa}^u and also the pressure difference that stretches the wall of the right atrium, ΔP_{RA} . For each individual, we define the target values for $(P_{sa}^u)^*$ and $(\Delta P_{RA})^*$ as follows:

$$P_{sa}^u = (P_{sa}^u)^* \quad (30)$$

$$P_{RA} - P_{thorax} = (\Delta P_{RA})^* \quad (31)$$

These four variables define the instantaneous idealized controller, whereby the heart rate F and reserve volume V_{total}^0 vary instantaneously to maintain $(P_{sa}^u)^*$ and $(\Delta P_{RA})^*$ at their set values. An idealized controller obviates the need for more detailed modeling (i.e. PDE or pulsatile) of how the changes in heart rate or reserve volume occur, and presumes simply that they do occur. As a result, this model avoids a great deal of additional complexity.

We assume that the controlling variables F and V_{total}^0 can vary within physiological limits, as we need them to, in order to maintain the controlled variables $((P_{sa}^u)^*$ and $(\Delta P_{RA})^*$) at their set points. The physiological limits between which F and V_{total}^0 can vary define an area of validity for the model. For the model to be valid, V_{total}^0 must be nonnegative as a working system always has some venous reserve volume. We will derive analytical solutions for F and V_{total}^0 for each case separately, using the following procedure:

1. Identify the state of partial venous collapse (I, II, or III) as defined previously in the section **Venous Return**.
2. Use the upper and lower systemic venous pressures (19, 20) and the control equations (30, 31) to solve for the lower systemic arterial pressure.
3. Solve for the upper and lower systemic flows with the appropriate systemic pressure values to obtain an expression for the cardiac output Q .
4. Use Q from the previous step to obtain F as a function of parameters.
5. Solve for pulmonary pressures knowing Q and rewrite total reserve volume V_{total}^0 and heart rate F as a function of parameters.

Using this algorithm, we derive control equations for the model. These equations and their derivation is described in the **Supplementary Materials** ("Controller Solutions").

Computing G-tolerance

Each individual has an estimated maximum heart rate and total reserve volume. We consider an individual to be in G-LOC when the model's controller is no longer able to compensate for changes in gravity by adjusting the heart rate F or reserve volume V_{total}^0 . We can estimate total reserve volume from the total blood volume (which we can estimate from height and weight)²⁶. An individual's estimated maximal heart rate can be derived using a simple formula (or more exact formula that accounts for athletes) that is based on age²⁷. Height, weight, and heart rate are easily measurable parameters that do not require specialists or expensive equipment.

Recall from the previous section that the controller manipulates heart rate and total reserve volume to maintain set values for the upper systemic pressure and thoracic pressure differential. Consider that an individual's total reserve volume varies within the interval $[0, V_{\text{total}}^0]$, and heart rate within the interval $[F_{\text{min}}, F_{\text{max}}]$. We observe that the control equations in all three cases are strictly monotonic functions of g . Therefore, in each equation there is only one value of g for which the controller hits its limiting value.

Numerical simulations showed reserve volume to be the limiting factor on individual G-tolerance for all of our patients. Note that for certain patient populations (i.e. patients on beta-blocker medications), the limiting factor could theoretically be heart rate. Setting the limiting control parameter to its min / max (in this case $V_{\text{total}}^0 = 0$) and solving for g yields a unique value, which is equivalent to the maximal G-tolerance obtainable with this control mechanism.

Contingent on the control variable $V_{\text{total}}^0 \geq 0$ and $F \leq F_{\text{max}}$, we can write down an analytical expression of the G-tolerance : In case I, if $V_{\text{total}}^0 = 0$ is the limiting variable, the G-tolerance is :

$$g = \frac{R_s^l \left(V_{\text{total}} - C_p \frac{C_{\text{RVD}}}{C_{\text{LVD}}} (\Delta P_{\text{RA}})^* - (T_p G_s + C_{\text{sa}}) (P_{\text{sa}}^u)^* - C_s^l \rho g (-H^l) \right)}{\rho H^u (T_p + C_{\text{sa}}^l + R_s^l)} \quad (32)$$

In case I, if F is the limiting variable, the G-tolerance is :

$$g = \frac{R_s^l (F_{\text{max}} C_{\text{RVD}} (\Delta P_{\text{RA}})^* - G_s (P_{\text{sa}}^u)^*)}{\rho H^u} \quad (33)$$

Explicit expressions for G-tolerance can be written down in cases II and III following the same procedure. Note that within our modeling framework this equation should not be used to directly compute G-tolerance from an individual's estimated heart rate or reserve volume, as we do not necessarily know in advance which case we are in (I, II, III) or which control parameter is the limiting variable for G-adaptation.

Having a closed-form solution for G-tolerance is of particular relevance, given the difficulty in obtaining large quantities of patient data for this particular prediction task. If future small-to-medium datasets validate our approach, these equations can be used to develop a decision-support calculator to enable physicians to quickly reason about which factors impact an individual's G-tolerance in a clinical setting.

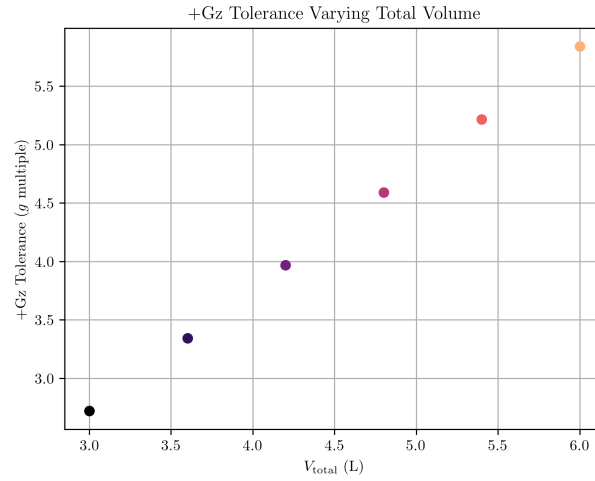


Figure 2. G-tolerance as a function of total volume

Results and Discussion

G-tolerance and blood volume

Figure 2 shows the effect of a decrease in blood volume on G-tolerance. G-tolerance decreases with total volume loss, and increases with total volume gain. This is consistent with physiological expectations, as changes in volume affect blood pressure and the ability to compensate for changes in G.

Many factors can affect blood volume, including temperature stress (typically +5% but ranging +0-30% with heat acclimation, -3% with cold acclimation), physical exercise (+10% increase), hyperhydration (+5%) or hypohydration (up to -15% total body water), altitude (up to -29% for initial acclimatization), microgravity (-10 to -15%)^{28–30}, pregnancy (+50%)³¹, and dialysis (around 5-10% loss)³². Clinically, G-tolerance has been observed to decrease by 25% with long-duration microgravity exposures³³ and up to 40% with heat stress³⁴, both of which affect blood volume. Operationally, fluid loading (increasing blood volume) has been used as a countermeasure for reduced G-tolerance in deconditioned astronauts returning from the International Space Station³⁵.

Reserve volume is proportional to total volume. **Figure 3** shows the effect of reserve volume on G-tolerance. Although the model permits either reserve volume or heart rate to be the limiting factor, for the patient whose individual parameters form the basis of the simulations, we found G-tolerance to be limited by available reserve volume rather than heart rate. This is consistent with studies showing that usage of beta-blockers, a class of medications that limit maximum heart rate, did not impair layperson tolerance of +G_z centrifuge profiles⁹. Even so, there may exist some populations for whom heart rate rather than reserve volume is the limiting factor on G-tolerance. For example, military student pilots with a smaller initial heart rate increase in response to a high-G exposure test were noted to be nearly 10-fold more likely to fail than those with a larger heart rate increase¹⁰.

G-tolerance and intrathoracic pressure

Figures 3 and **5** decompose the controller response into its components of reserve volume and heart rate, illustrating the effect of each, and the effect of increased intrathoracic pressure on controller compensation. **Figure 3** shows the controller's response to increased intrathoracic pressure. Controller-mediated vasoconstriction enables the reserve volume to overcome increases in +G_z and intrathoracic pressure until there is no reserve volume available. The point where there is no reserve volume available is an effective limit of G-tolerance.

Figure 5 shows that heart rate needed to maintain homeostasis increases proportionally to G-tolerance. Heart rate compensation ceases well before its physiological maximum (we set $F_{\max} = 180$), and the simulation ends limited by reserve volume, as the reserve volume decreases to zero before the heart can achieve a reasonable physiological maximum (we set $F_{\max} = 180$) in this simulation).

Figure 4 shows that G-tolerance decreases with sustained high intrathoracic pressure. While we might expect a high intrathoracic pressure to increase G-tolerance, at a steady state it has the opposite effect. In the short term, high intrathoracic pressure can keep blood from flowing downwards. However, at a steady state, intrathoracic pressure prevents the blood from returning to the heart, significantly reducing cardiac preload and thus decreasing cardiac output³⁶.

Countermeasures to high-G exposure such as AGSM²³ and use of positive-pressure breathing²⁴ or anti-G suits with direct

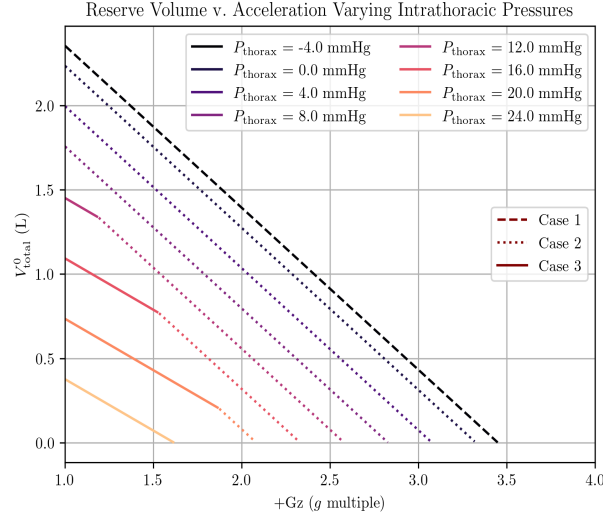


Figure 3. G-tolerance as a function of reserve volume compensation

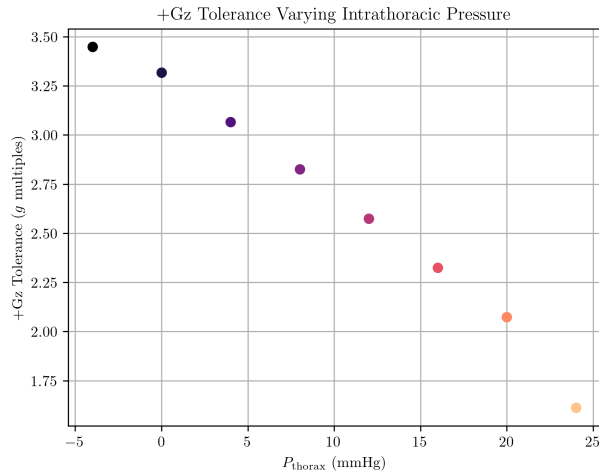


Figure 4. Simulation of G-tolerance varying G_z and intrathoracic pressure

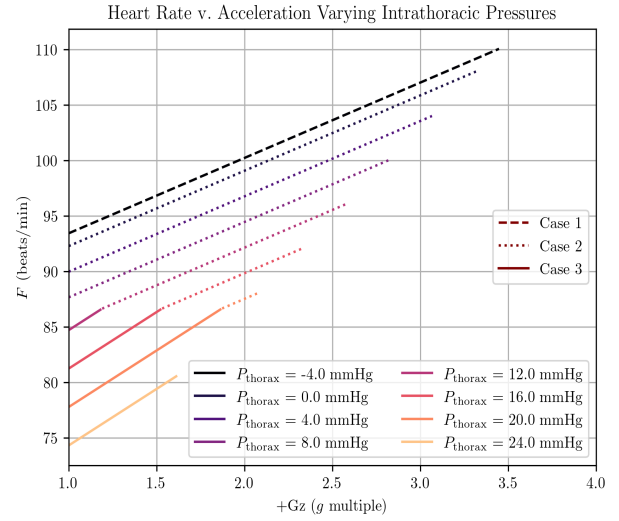


Figure 5. G-tolerance: ontrroller compensation over different thoracic pressures

abdominal pressure³⁷ involve increases in intrathoracic pressure; unfortunately, this intrathoracic pressure elevation has adverse side effects, as demonstrated by the model, particularly in decreasing cardiac preload through impeding venous return. The AGSM respiratory maneuver is periodically interrupted by a brief respiratory exchange; this brief period also allows venous return to the heart particularly if forceful isokinetic contraction of extremity musculature is adequate⁶. However, incorrect AGSM technique in which the breath is held or not cycled frequently enough, or in which extremity muscular contraction is inadequate in promoting rapid venous cardiac return during the brief respiratory exchange, *decreases* G-tolerance²³ because high intra-thoracic pressure prevents return of blood to the heart³⁶. This is consistent with the findings of the model simulations (Figure 4 and Figure 5).

G-tolerance and height

Figure 6 illustrates the model's response over a hypothetical range of heart-brain (H^u) and heart-to-seat (H^l) distances, varied 50 % from the subject's baseline. G-tolerance depends on both H^u and H^l (cf Figure 6 and Figure 7). Decreasing the heart-to-seat and heart-brain heights increases G-tolerance. This is consistent with physiological expectations, as a taller person will have a longer distensible fluid column that is more prone to the effects of hypergravity.

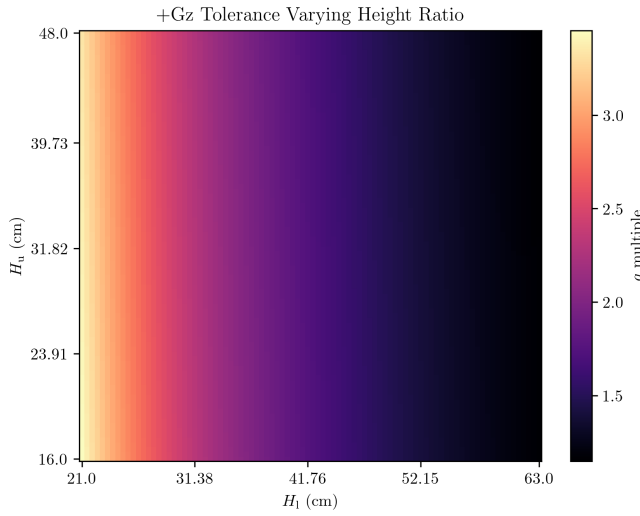


Figure 6. G-tolerance varying both head-to-heart and heart-to-seat 50% from subject's values

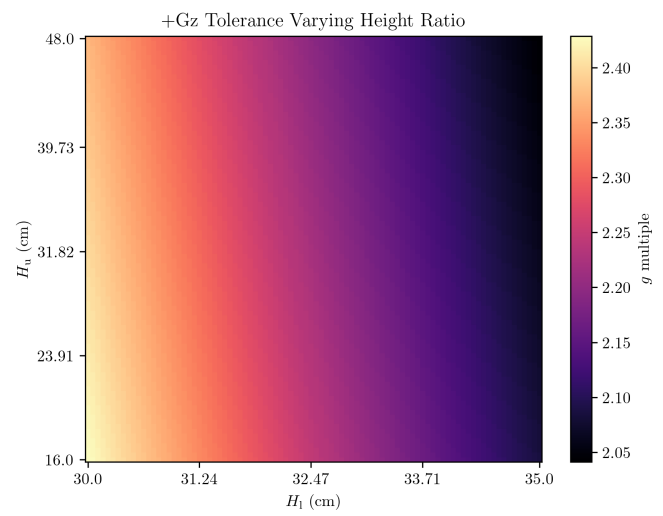


Figure 7. G-tolerance varying upper height 50% from subject's value and lower height by 5% from subject's value.

In a centrifuge study of 1434 subjects, height was inversely correlated to relaxed (no-strain) G-tolerance⁸. Furthermore, there was a 0.9G difference in tolerance between the shortest and tallest persons in the study (160 to 195 cm). We observe a similar G-tolerance differential over the same span of heights in our model (with other variables held constant) in **Figure 6**.

Figure 7 illustrates the relative influence of upper and lower compartment heights, and demonstrates that variations in the size of the lower compartment have a greater influence over G-tolerance than variations in the upper compartment.

G-tolerance and compliance

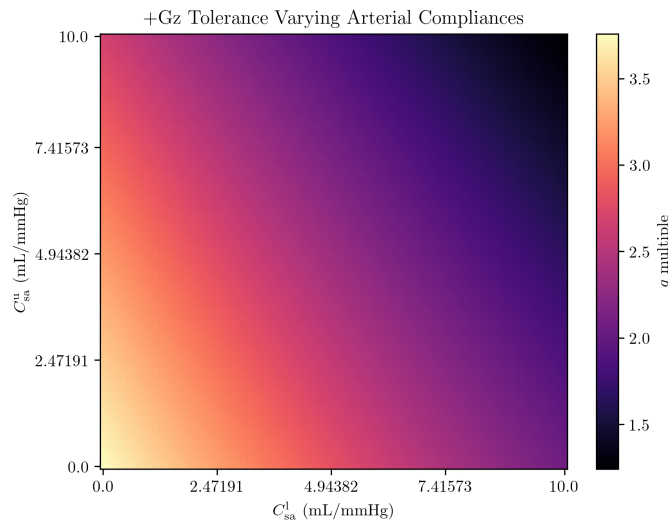


Figure 8. Effect of perturbations to systemic arterial compliance on predicted G-tolerance

Figure 8 illustrates the effect of systemic arterial compliance on G-tolerance. Decreases in both upper and lower systemic arterial compliance both increase G-tolerance. This is consistent with studies illustrating increased G-tolerance in older subjects^{9,38,39}, likely because of the association of age with decreased vascular compliance⁴⁰ which allows maintenance of blood pressure despite application of the acceleration gradient.

Model simulations show that the model behaves according to physiological expectations and that the controller compensates for changes in the steady state to keep upper systemic pressure and thoracic pressure at their set points.

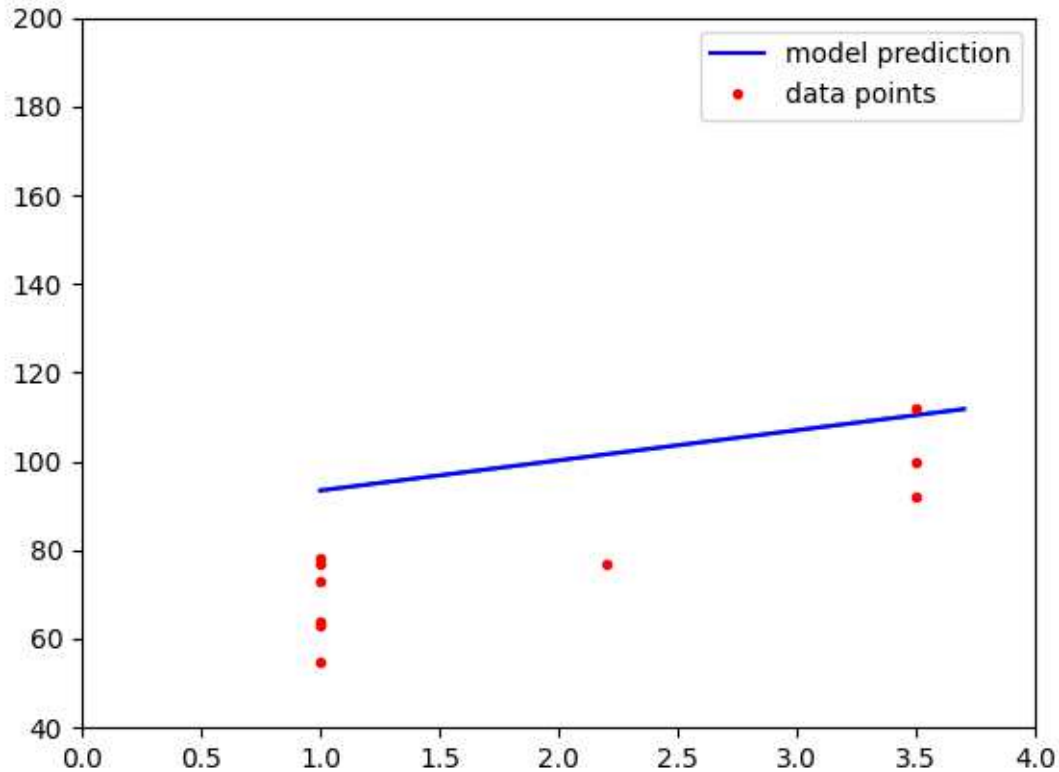


Figure 9. Simulated vs real heart rate in one subject

Predicted Individual G-tolerance

Figure 9 compares model predictions of heart rate at various $+G_z$ against existing centrifuge data for an individual experiencing increasing step-wise $+G_z$ (maximum of +1, +2.2, and +3.5 G_z)⁴¹. In earlier centrifuge runs, the subject likely had not reached complete steady-state cardiovascular response as the stepwise centrifuge profile had a total duration of 15s with the maximum peak $+G_z$ sustained for 5s⁴¹. This is less than the time (15-20s) expected to maximum heart rate³⁷ or cardiovascular steady state^{42,43}. However, cardiovascular adaption to $+G_z$ have been found to persist despite brief breaks between exposures⁴⁴. Because multiple centrifuge trials were performed sequentially with short rest periods between, the individual's physiologic adaptions to high $+G_z$ may have continued to increase with subsequent trials. Thus, the intersection of model prediction with the highest heart rate (recorded at +3.5 G_z) likely reflects that the subject had finally received sufficient $+G_z$ exposure to effectively achieve physiological "steady state" (e.g. compensatory heart rate elevations or vascular constriction). Additional sources of error might stem from the use of parameters from the literature that may have come from a population less representative of subject physiology.

Conclusion

With the drive to achieve high-volume commercial spaceflight, we anticipate potentially hundreds or even thousands of spaceflight participants of varied anthropometry and health statuses flying per year. These commercial spaceflight participants will likely experience $+G_z$, particularly in winged space vehicles. AGSM is essential to prevent G-LOC in during these flight profiles. Given the limited training time anticipated, the ability to predict individual G-tolerance and anticipated minimum heart rates would be very useful to commercial space flight operators and regulators. Such a tool could identify individuals who may need additional AGSM training and countermeasures such as aggressive hydration, emphasis on appropriate nutrition, minimizing fatigue, avoidance of high temperatures, or external support tools such as mechanical counterpressure garments. Furthermore, this enables operators to estimate safety margins by comparing an individual's predicted G-tolerance versus the

maximum expected vehicle acceleration.

When developing mathematical models in biology, physiological realism must be balanced against the complexity and cost of developing and using such models in practice. Our approach has been to develop the simplest possible model that can adequately answer the question: what is the G-tolerance a particular individual? In this paper, we propose a mathematical model of the human circulation under hypergravity and demonstrate its capability to predict individual G-tolerance and heart rate response to elevated $+G_z$. The model adequately predicts heart rate and G-tolerance for an individual case with parameters derived from population averages in the literature and four non-invasive clinical measurements, but can be further customized to an individual if desired. Furthermore, due to the mathematical modeling choices we made, model prediction of G-tolerance takes less than a fraction of a second on a laptop computer. This facilitates the process of parameter estimation and sensitivity analysis in a context in which clinical data is sparse.

Although multiple mathematical models for population-level G-tolerance predictions exist^{30,42,45–49}, this model provides the ability to directly predict a value for individual G-tolerance with readily accessible parameters, near-instantaneous compute time, and easily measurable model parameters. Additionally, this model simulates deformations in upper thoracic vasculature induced by changes in intrathoracic pressure. The three modalities of intrathoracic pressure we consider enable the validation of clinical findings pertaining to the effects of excessive extension of the Valsalva maneuver or the effects of positive-pressure breathing equipment.

A significant limitation of this model is its direct formulation as a steady-state model. A consequence of the steady-state formulation is the inability to predict time to G-LOC, or G-LOC in contexts where steady-state is not achieved, such as rapid G-onset. Furthermore, model predictions were only compared to centrifuge data for a single individual, and validation using additional subject data is necessary to assess model accuracy on a larger cohort.

This effort underlines the importance of developing standardized, accessible datasets of well-characterized laypersons in hypergravity settings that can be used for validation of this and other mathematical models for operational and clinical use. Future work should involve validation of this model within a large group of individuals with varied anthropometry, age, and health statuses, as well as incorporating the effects of extremity muscular strain, the effect of non-linearities in compliance, and/or temporal aspects of G-tolerance. Future efforts directed at clinical use should consider computer runtime, accessible parametrization, and ease of attaining measurements for model input.

Data Availability

Parameters and solutions to the model are available in the supplementary materials. The data to reproduce the centrifuge runs for the patient is available in the code at: https://github.com/alexoblomov/steady_state_cardiac_model. The cardiac ultrasound data is not available. The data for generating the figures in this paper and the code for generating them are available on Github at: https://github.com/alexoblomov/steady_state_cardiac_model.

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