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Computational Simulation To Understand Vision Changes During Prolonged Weightlessness

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Abstract— **A mathematical model of whole body and cerebral hemodynamics is a useful tool for investigating visual impairment and intracranial pressure (VIIP), a recently described condition associated with space flight. VIIP involves loss of visual acuity, anatomical changes to the eye, and, usually, elevated cerebrospinal fluid pressure. Loss of visual acuity is a significant threat to astronaut health and performance. It is therefore important to understand the pathogenesis of VIIP. Some of the experimental measurements that could lead to better understanding of the pathophysiology are impossible or infeasible on orbit. A computational implementation of a mathematical model of hypothetical pathophysiological processes is therefore valuable. Such a model is developed, and is used to investigate how changes in vascular compliance or pressure can influence intraocular or intracranial pressure.**

I. Introduction

Visual impairment and intracranial pressure (VIIP) is a recently described condition associated with space flight which has affected approximately 20% of American astronauts on missions to the International Space Station lasting six months or longer.[1] VIIP involves loss of visual acuity and anatomical changes to eye structures. VIIP also usually involves elevated cerebrospinal fluid (CSF) pressure. Loss of visual acuity is a significant threat to astronaut health and performance. It is therefore important to understand the pathogenesis of VIIP. Some of the experimental measurements that could lead to better understanding of the pathophysiology are impossible or infeasible on orbit, and a computational model of the system may be valuable.

A shift of body fluid toward the head is a well-known consequence of microgravity. Jugular venous distension and increased swelling of tissue of the face and neck, seen in many astronauts on orbit, are signs of such changes. Experimental evidence suggests that about 2 liters of fluid may shift from lower to upper body[2] (out of a total of 40 liters of total body water, and 14 liters of extracellular fluid, in a typical 70 kg earth-bound subject[3]). Such a shift has multiple possible causes. On earth, gravity creates a hydrostatic pressure gradient which lowers venous pressure at the base of the skull, relative to pressure at the right atrial-caval junction in a standing or sitting subject, by 10 to 15 mmHg. The absence of such a hydrostatic pressure gradient will lead to a direct increase in cerebral (and extracranial) venous pressure, and therefore to an increase in cerebral blood volume (ΔV) which, to first order, equals $C*\Delta P_{hyd}$, where C and ΔP_{hyd} are the aggregate vessel compliance and the hydrostatic pressure change. The increased cerebral blood volume will tend to raise intracranial pressure (ICP) due to the rigidity of the cranium. The hydrostatically-driven increase in cerebral venous pressure will cause higher capillary pressure, and therefore more capillary filtration. This will cause an increase in interstitial fluid in the cranium, which will tend to increase ICP. The outflow resistance of cerebral veins is quite sensitive to the transmural pressure gradient (venous pressure minus ICP). Superimposed on these effects are the autoregulatory capabilities of the cerebral circulation, and the slow dehydration which occurs with weightlessness[4,5]. A further important effect may be changes in capillary permeability during microgravity[6,7].

What is different about the 20% of long duration space flyers who develop VIIP and the 80% who do not? Knowing the answer might lead to strategies for countermeasures. It has been observed that astronauts who developed VIIP had higher levels of homocysteine and related 1-carbon compounds whose metabolism depends on folate and vitamin B_{12}, both pre- and post-flight, than did those who did not develop VIIP. This observation has led to the hypothesis that polymorphisms in enzymes of the 1-carbon transfer pathway interact with microgravity to cause VIIP[8]. It has further been suggested that vascular permeability differences might be the mechanism by which polymorphisms could affect susceptibility to VIIP.[9] An alternative hypothesis is that there are differences in other pre-existing vascular properties, such as compliance, resistance, or other factors. A computational model can allow us to test the plausibility of these different hypotheses, since with simulations we can determine how large a difference in permeability, or compliance, or resistance, and of what vessels, could account for the observed spectrum of differences in the response of the visual system to microgravity.

The aim of this research project is to create a computational implementation of a mathematical model of cerebral hemodynamics, intracranial pressure, and intraocular pressure that includes the presence and absence of gravity and/or tilt. By combining the best aspects of various existing models, and making adjustments in key areas, it is possible to create and implement a model that generates realistic responses to short-term perturbations, such as head-up tilt for a minute or two, and long-term perturbations, such as microgravity for several months.

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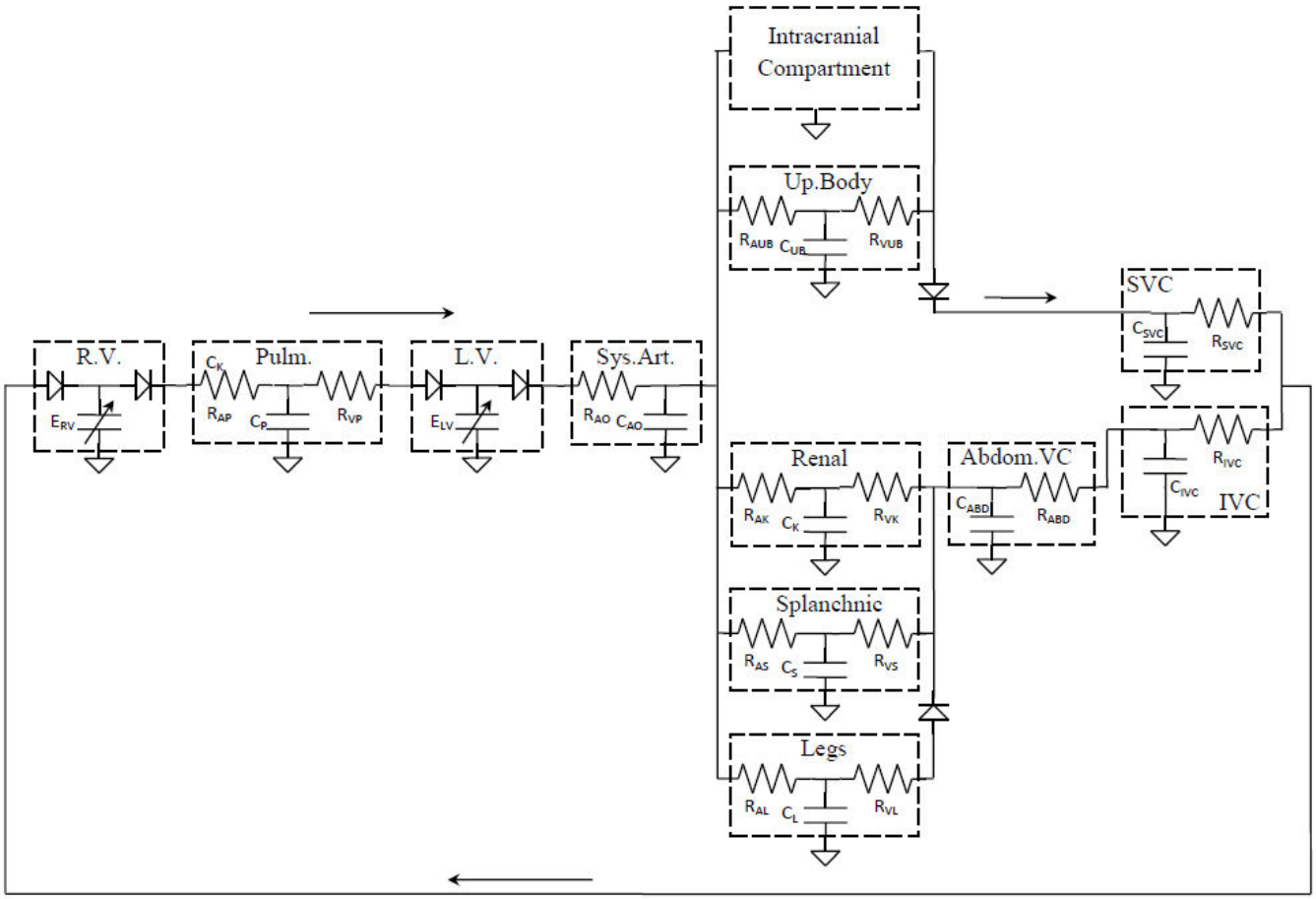

Figure 1. Cardiovascular system model.

II. Description of the Model

A. Cardiovascular System

Changes in pressure in the cranium are the subject in which we are most interested. However, it is necessary to develop a model of the entire cardiovascular system in order to give realistic inputs of input and output pressure and flow during changes in gravity. For this reason we start with a model based on that of Heldt et al.[10] This model includes the right and left ventricles, pulmonary circulation, and four major branches for the systemic circulation, which are at different heights, and therefore are affected differently by gravity. The systemic branches are the upper body, renal, splanchnic, and legs. Outflow from the three lower body branches combines and passes through the abdominal vena cava and inferior vena cava (which are at different heights). The upper body circulation includes intracranial and extracranial pathways. The outflow from both upper body pathways combines and returns through the superior vena cava. The superior and inferior vena cava, heart, and lungs are all located in the thoracic compartment, and as a result they share a common extramural pressure, the intrathoracic pressure, which varies cyclically in the present model, due to breathing.

The left and right ventricles are modeled as time varying elastances with one-way valves on the inflow and outflow sides of each ventricle. The circulation is modeled with resistances, capacitances, and one way valves, which are known to exist in the jugular veins and in the veins returning blood from the legs. The model does not include a description of pulse wave propagation in the arteries. The arterial and venous resistances are linear. The veins of the abdominal, legs, and splanchnic compartments have nonlinear pressure-volume relationships. Their pressure-volume relationships are described by a smooth function whose parameters are chosen to give a specified compliance C at low transmural pressures and to have a specified maximum total volume V_{max}:

$$V = V_0 + \frac{2(V_{max} - V_0)}{\pi} \cdot \tan^{-1}\left(\frac{\pi C \cdot P_{trans}}{2(V_{max} - V_0)}\right)$$

where V_0 is the unstressed volume. The other vessels have linear pressure-volume relationships. An electrical analog of the model is shown in Fig. 1. The unstressed volumes of compartments and the gravity- and height-dependent external pressures are not shown in Fig. 1.

B. Reflex Control

Baroreflex reflex control of the cardiovascular system is also implemented. The baroreceptor reflexes regulate the contractility of the heart (specifically, the peak systolic values of the elastances E_{LV} and E_{RV}), the heart rate (by influencing the rate of change of a phase variable which drives the heart beats), and the resistance and unstressed volume of the upper

body, renal, splanchnic, and legs compartments (R_{AUB}, R_{AK}, R_{AS}, R_{AL}, and V_{0UB}, V_{0K}, V_{0S}, V_{0L}).

C. Gravity

The effect of gravity is introduced by having different external pressures at different parts of the circulation. A negative external pressure results in a greater transmural pressure, and therefore a larger blood volume. Vessels that are farther below the heart have more negative external pressure. The external pressure is related to gravity and height as follows:

$$P_{ext} = \rho g h$$

where ρ=blood density, g=gravity (which is zero while in orbit), and h=vessel height (negative for vessels below the heart).

D. Intracranial Circulation

In place of Heldt's "upper body" pathway, this model uses two parallel pathways, as does the model of Olufsen et al.[11] One pathway is intracranial and one is extracranial. Olufsen's model of the intracranial circulation is modified by introducing a more realistic model which combines aspects of the models of Ursino[12] and of Lakin et al.[7]. Therefore this model of the cranium includes four volume compartments: the arterial and venous blood compartments, the tissue compartment, and the cerebrospinal fluid compartment. They each have their own (nonlinear) compliance but are also subject to the constraint that the total intracranial volume is constant. The model also includes CSF production from the cerebral capillaries and reabsorption into cerebral veins. Capillary filtration across the blood-brain barrier is modeled using Starling's equation[7]. Cerebral autoregulation is also modeled[13].

III. Model Implementation

The model is implemented using Matlab. It is described by a system of coupled nonlinear ordinary differential equations. Volumes are chosen as the main state variables. Pressures or flows could have been chosen as the main state variables. A section of the circuit diagram of the model is redrawn and expanded below as a representative example.

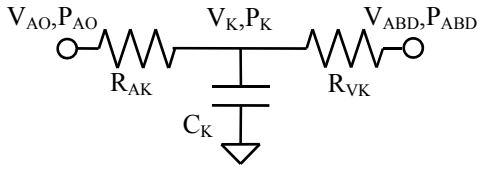

Figure 2. Renal vascular compartment.

In Fig. 2, V's are volumes and P's are pressures. For example, $P_K=(V_K-V_{0K})/C_K$, where V_{0K} is the unstressed volume of the kidney vessels. Then the differential equation for $V_K(t)$ is

$$\frac{dV_K}{dt} = Q_{in} - Q_{out} = \frac{(P_{AO} - P_K)}{R_{AK}} - \frac{(P_K - P_{ABD})}{R_{VK}}$$

where each pressure is a function of the corresponding volume.

The model also includes state variables for the level of reflex activation and the values of parameters (such as resistances and unstressed volumes) that are controlled by the reflexes. In order to use the built-in differential equation solvers in Matlab (or other software packages), one must be able to write a first order differential equation for each state variable, using only the other state variables, constants, and external forcing functions whose behavior is known in advance. An example of an external forcing function is gravity, which "turns on" and "turns off" at pre-specified times. These requirements mean that we cannot use "the duration of the previous heart beat" as a variable in the model (as Heldt et al. did[10]), because "the duration of the previous beat" cannot be expressed as a differential equation. Instead, we use a low-pass filtered version of the "target heart rate" variable which drives the rate of change of pacemaker phase. By choosing the filter cutoff frequency appropriately, this low-pass filtered signal has a delay approximately equal to one beat, and so its value reflects the heart rate one beat previously.

The presence of valves in the system may be handled by using "if" statements in the differential equations: if the pressure across the valve is negative, the flow is zero, otherwise the flow is as one would expect, given the resistance in series with the diode. The initial implementation of this approach resulted in large, rapid (>200 Hz) fluctuations in left ventricular outflow in late ejection, when the ventricular and aortic pressures are almost equal. The valve was "chattering". This was cured by eliminating the "if" statements and, instead, describing each valve a time-varying resistance whose resistance quickly (with a time constant of about 0.5 ms) rises when reverse-biased. This had the disadvantage of making the system stiffer, but it cured the chattering problem.

Matlab's "ode45" solver produced useful results. This is a general purpose fourth- and fifth-order solver with adaptive step size control. The stiff system solver "ode15s", which also has adaptive step size, sometimes failed because even at the minimum step size it had unacceptably large errors.

IV. Conclusion

A computational implementation of a mathematical model of cerebral hemodynamics and intracranial pressure, that includes the presence and absence of gravity and/or tilt, has been described. By combining the different aspects of various existing models, and making adjustments in key areas, it is possible to create and implement a model that generates realistic responses to short-term perturbations, such as head-up tilt, and long-term perturbations, such as prolonged microgravity.

The model described above is useful for investigating different ideas that could account for the spectrum of different responses of ICP and intraocular pressure to long duration spaceflight. Simulation can reveal which model

parameters and modules are most important for particular responses of interest, such as slowly developing, long lasting changes in ICP and intraocular pressure. This will allow some hypotheses about the sources of susceptibility to be ruled in and others to be ruled out.

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REFERENCES

[1] T. H. Mader, C. R. Gibson, A. F. Pass, L. A. Kramer, and A. G. Lee, Optic disc edema globe flattening, choroidal folds, and hyperopic shifts observed in astronauts after long-duration space flight. *Opthamology* vol. 118, pp. 2058-2069, 2009.

[2] T. P. Moore and W. E. Thornton, Space shuttle inflight and postflight fluid shifts measured by leg volume changes. *Aviat. Space Envir. Med.* vol. 58, pp. A91-A96, 1987.

[3] A. C. Guyton and J. E. Hall, *Textbook of Medical Physiology*, 11th ed. Phildelphia: Elsevier, 2006, p. 295.

[4] J. V. Meck, W. W. Waters, M. G. Ziegler, H. F. deBlock, P. J. Mills, D. Robertson, and P. L. Huang, Mechanisms of postspaceflight orthostatic hypotension. *Am. J. Physiol. Heart. Circ. Physiol.* vol. 286, pp. H1486-H1495, 2004.

[5] W. W. Waters, M. G. Ziegler, and J. V. Meck, Postspaceflight orthostatic hypotension occurs mostly in women and is predicted by low vascular resistance. *J. Appl. Physiol.* vol. 92, pp. 586-594, 2002.

[6] S. E. Parazynski, A. R. Hargens, B. Tucker, M. Aratow, J. Styf, and A. Crenshaw, Transcapillary fluid shifts in tissues of the head and neck during and after simulated microgravity. *J. Appl. Physiol.* vol. 71, pp. 2469-2475, 1991.

[7] W. D. Lakin, S. A. Stevens, and P. L. Penar, Modeling intracranial pressures in microgravity: the influence of the blood brain barrier. *Aviat. Space Envir. Med.* vol. 78, pp. 932-936, 2007.

[8] S. R. Zwart, C. R. Gibson, T. H. Mader, K. Ericson, R. Ploutz-Snyder, M. Heer, and S. M. Smith, Vision changes after spaceflight are related to alterations in folate- and vitamin B-12-dependent one-carbon metabolism. *J. Nutrition* vol. 142, pp. 427-431, 2012.

[9] J. D. Symons, U. B. Zaid , C. N. Athanassious, A. E. Mullick , S. R. Lentz, and J. C. Rutledge, Influence of folate on arterial permeability and stiffness in the absence or presence of hyperhomocysteinemia. *Arterioscler. Thromb. Vasc. Biol.* vol. 26, pp. 814-818, 2006.

[10] T. Heldt, E. B. Shim, R. D. Kamm, and R. G. Mark, Computational modeling of cardiovascular response to orthostatic stress. *J. Appl. Physiol.* vol. 92, pp. 1239-1254, 2002.

[11] M. S. Olufsen, J. T. Ottesen, H. T. Tran, L. M. Ellwein, L. A. Lipsitz, and V. Novak, Blood pressure and blood flow variation postural change from sitting to standing: model development and validation. *J. Appl. Physiol.* vol. 99, pp. 1523-1537, 2005.

[12] M. Ursino, A mathematical study of human intracranial hydrodynamics, part I. *Ann. Biomed. Eng.* vol. 16, pp. 379-401, 1988.

[13] M. Ursino and P. Di Giammarco, A mathematical model of the relationship between cerebral blood volume and intracranial pressure waves: the generation of plateau waves. *Ann. Biomed. Eng.* vol. 19, pp. 15-42, 1991.