우주비행 직후 인체 심혈관계의 혈류역학적 변화에 대한 수치적 연구

Computational analysis of the hemodynamic changes in human cardiovascular system after space flight

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Orthostatic stress in human cardiovascular system following spaceflight remains a critical problem in the current life-science space program. The study presented in this paper is part of an ongoing effort to use mathematical models to investigate the effects of gravitational stresses on the cardiovascular system of normals and microgravity adapted individuals. We employ a twelve compartment lumped parameter representation of the hemodynamic system coupled to set-point models of the arterial baroreflex and the cardiopulmonary reflex to investigate the transient response of heart rate to orthostatic stress. We simulate current hypotheses concerning the mechanisms underlying post-spaceflight orthostatic intolerance over a range of physiologically reasonable values and compare the simulations to astronaut stand-test data pre- and post-flight.

1. Introduction

Orthostatic intolerance (OI) following spaceflight has been recognized as being a problem since the early days of manned space missions. It has been extensively investigated in flight and in ground-based microgravity simulations such as bedrest studies. Even though a number of countermeasures (fluid loading, lower body negative pressure, pressurized suits, and mineralocorticoids) have been proposed and evaluated over the past 30 years, post- spaceflight OI still remains a safety concern for current missions and a potential limiting factor for future long term exploration of space. To date, the lack of a single unifying theory of the pathophysiology of OI testifies to the difficulty of the problem at hand. Hypotheses regarding the mechanisms underlying OI include increased venous compliance of the legs [1], cardiac atrophy [2], central hypovolemia [3], reduced gain of the arterial baroreflex [4], and reduced vasoconstrictor response [5] yet a basis for discriminating between competing hypotheses is lacking. Computational models of the cardiovascular system can help in that they represent in a quantitative manner the current state of physiologic understanding and can be designed at a

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level of detail appropriate to the problem under consideration. They are powerful adjuncts to experiments and permit investigators to quantitatively examine whether experimental observations are consistent with a particular hypothesis. We have developed a computational model capable of simulating the short term (within 2 min) response of the cardiovascular system to orthostatic challenge such as head-up tilt (HUT) or lower body negative pressure (LBNP) to investigate the possibility of discriminating between competing hypotheses.

2. Hemodynamic and control model

We have modified a previously reported closed loop lumped parameter representation to allow for simulation of gravitational stress and regional blood pooling in the systemic circulation [6, 7]. Briefly, the hemodynamic system is represented by twelve compartments each of which consists of an inflow resistance, a capacitance, and an outflow resistance (see Fig. 1).

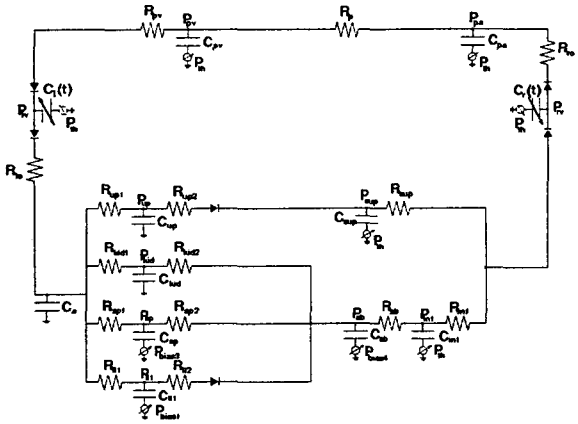


Figure 1. Hemodynamic model

The systemic portion of the model consists of four parallel circulatory branches (representing the upper body, kidneys, splanchnic, and leg circulations) feeding into central venous compartments representing the abdominal (AVC), inferior (IVC), and superior vena cavae (SVC). The pumping action of the heart is modeled by time-varying ventricular compliances. Centrally, diodes mimic cardiac valves and ensure unidirectional blood flow through the heart. Peripherally, they represent venous valves in the extremities. Bias pressures across the dependent compartments are used to simulate changes in posture by changing regional transmural pressures (see below). The compliances of the legs, splanchnic, and abdominal venous compartments account for the nonlinearity of the venous pressure-volume relations at high levels of transmural pressure. Sequestration of blood plasma into the interstitial fluid compartment is modeled by reducing total blood volume (TBV) as a function of time and orthostatic stress.

The reflex model consists of setpoint representations of the arterial baroreflex and cardiopulmonary reflex [6]. A maximum of five effector mechanisms (heart rate, venous tone, peripheral arteriolar resistance, and left and right ventricular contractility) respond to a given perturbation in blood pressure (see Fig. 2).

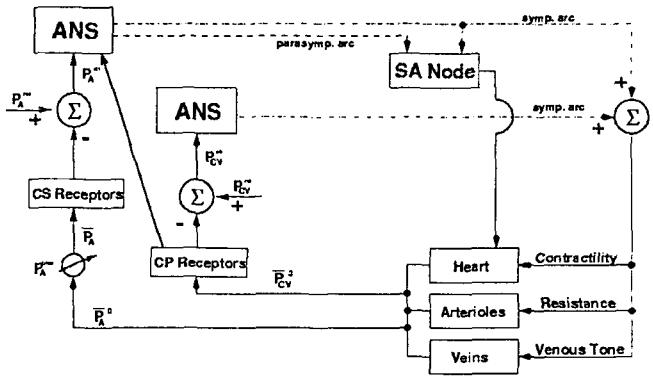


Figure 2. Reflex model

Briefly, predefined setpoint pressures are subtracted from locally sensed time averaged pressures to yield an error signal. To mimic the effect of receptor saturation at large deviations from the setpoints, the error signal is mapped onto an inverse tangent. This signal is then convolved with impulse response functions to yield the effector variable for the next time step. Two impulse response functions are implemented to allow for differentiation of the fast acting parasympathetic arc from the slower acting sympathetic arc. To account for a reduced hydrostatic pressure component at the carotid sinus, a bias pressure modifies the sensed arterial pressure during tilt. Furthermore, the static gain value of heart rate is modulated by changes in central venous pressure [7].

3. Tilt/stand simulation

To simulate the rapid redistribution of blood volume during the initial phase of a change in posture, we change the bias pressures at the dependent venous compartments according to:

$$P_{bias-i} = P_{max-i} \cdot \sin(\alpha(t)) \qquad (1)$$

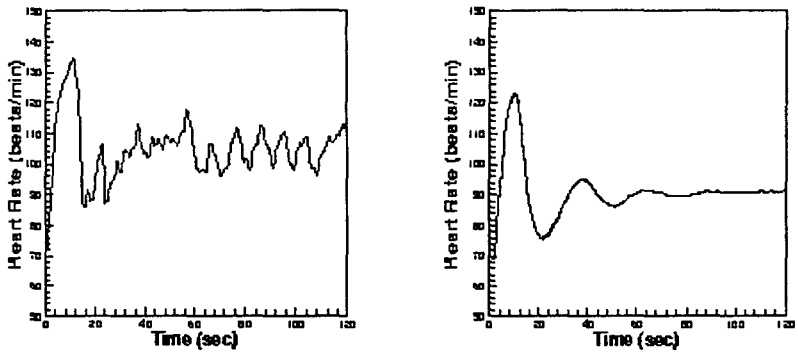
where $\alpha(t)$ represents ramp in time from zero to the maximal angle of tilt. P_{max-i} denotes the maximal bias pressure across the respective compartment when upright posture is assumed. The slower reduction in blood plasma is modeled by appropriately modifying overall blood volume according to:

$$V_{total} = 5300 + 400 \cdot 0.9^{t/60s} \qquad (2)$$

Here t is the time after onset of tilt measured in seconds.

4. Astronaut stand tests

Stand tests have been used by NASA investigators pre-and post-spaceflight to assess the integrated cardiovascular response to gravitational stress [8]. We attempted to simulate the pre-flight recording by a 2 sec tilt to 90° with maximal bias pressures of 60 mmHg at the leg compartment, 7 mmHg at the splanchnic compartment, and 5 mmHg at the abdominal venous compartment, respectively. Comparison of the pre- flight recording and the simulation are shown in figure 3. The timing, general shape, and magnitude of the heart rate increase are well matched between simulation and data.



(a) (b)

Figure 3. (a) Astronaut stand test before flight and (b) simulation of rapid tilt

The current model, however, is not capable of reproducing the fine structure of the heart rate response such as the low frequency oscillations (about 0.1 sec) mechanisms responsible for the marked difference between the pre-flight and post-flight heart rate response by simulating a series of hypotheses and comparing the simulation outputs to the actual post-flight recordings. 6. Simulation of hypotheses Several mechanisms have been hypothesized as being responsible for or at least contributory to post-flight orthostatic intolerance. They include cardiac atrophy [2], reduced plasma volume [3], reduced heart rate gain [4], reduced vasoconstrictor response [5], and increased venous leg compliance [1]. We simulated each of these changes over a range of physiologically reasonable values. Figure 4 depicts the individual simulation results. Figure 4a shows the heart rate response during various levels of hypovolemia which was simulated by reducing total blood volume (solid line: TBV=5300 ml (baseline); dotted line: TBV=5100 ml; dashed line: TBV=4900 ml). Venous leg compliance was increased to generate the tracings shown in figure 4b (solid line: baseline; dotted line: 10% increase in venous leg compliance; dashed line: 20% increase in venous leg compliance). We reduced the static gain value of the

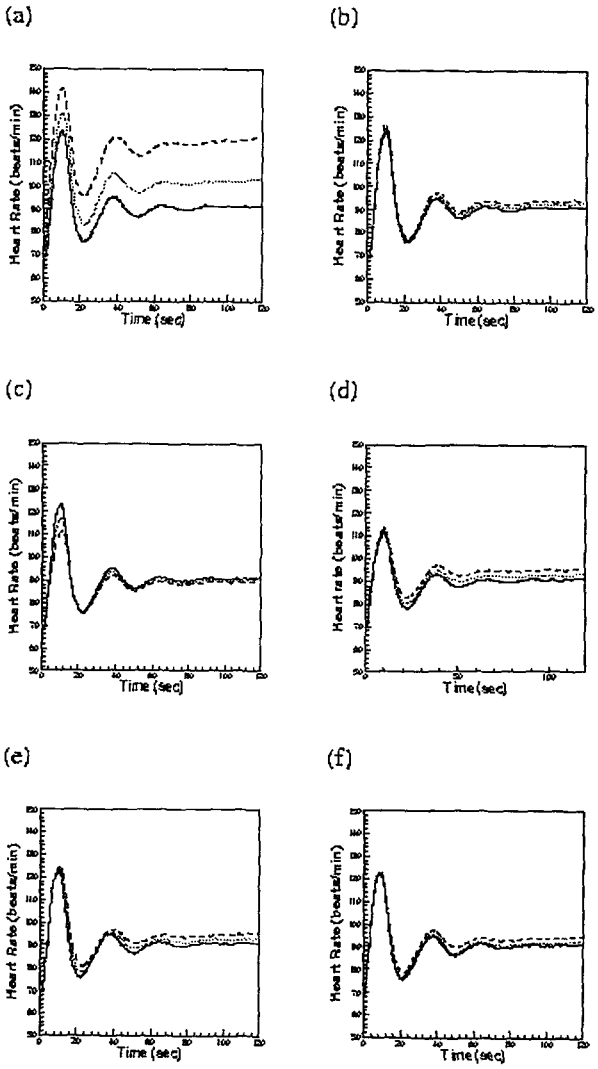


Figure 4. Heart rate response to rapid tilts after various interventions. See text for detail

parasympathetic reflex arc to heart rate to generate the heart rate response shown in figure 4c (solid line: baseline; dotted line: 10% reduction in parasympathetic heart rate gain; dashed: 20% reduction in parasympathetic heart rate gain). Cardiac atrophy was simulated in figure 4d by reducing the zero pressure filling volume of both ventricles, decreasing their end-diastolic compliance, and increasing their end- systolic compliance all by the same percentage (solid line: baseline; dotted line: 10% change in cardiac parameters; dashed line: 20% change in cardiac parameters). To show the differential effect of vasoconstriction on arteries and veins, we simulated a reduction in vasoconstrictor response to standing by decreasing the static gain of the venous tone reflex limb only and by reducing the static gain of the resistance feedback only.

In both figures, the dotted lines represent the heart rate response after a 10% reduction and the dashed lines after a 20% reduction of the respective static gain values. As can be seen from the simulations in figure 4, none of the hypotheses simulated individually can account for the morphology of the postspaceflight heart rate response seen in figure 3b. Figure 5 shows the effects of hypovolemia (solid line: TBV=5000 ml), hypovolemia plus reduced resistance feedback (dotted lines: 30% reduction in resistance gain), and hypovolemia plus reduced resistance.

5. Conclusion

We have presented a closed loop representation of the cardiovascular system capable of simulating the short term transient response to orthostatic stress in normals and microgravity adapted individuals. Our simulations capture the major transient features such as timing, magnitude, and shape of the stand test recordings and elucidate the contributions of various parameters on the dynamics of the heart rate response. We have given examples of how the model could be used to differentiate between competing hypotheses regarding the mechanisms of post- spaceflight orthostatic intolerance and have documented the model's use in aiding countermeasure research. Although volume depletion is a major contributor to the altered heart rate dynamics postflight, our simulations indicate that the additional factors of diminished arteriolar and venoconstriction must be invoked to obtain a good match between experimental data and simulations.

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