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A computer simulation of short-term adaptations of cardiovascular hemodynamics in microgravity

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ABSTRACT

Astronauts in the microgravity environment experience significant changes in their cardiovascular hemodynamics. In this study, a system-level numerical model has been utilized to simulate the short-term adaptations of hemodynamic parameters due to the gravitational removal in space. The effect of lower body negative pressure (LBNP) as a countermeasure has also been simulated. The numerical model was built upon a lumped-parameter Windkessel model by incorporating gravity-induced hydrostatic pressure and transcapillary fluid exchange modules. The short-term (in the time scale of seconds and minutes) adaptations of the cardiac functions, blood pressure, and fluid volumes have been analyzed and compared with physiological data. The simulation results suggest microgravity induces a decrease in aortic pressure, heart rate, lower body capillary pressure and volume, and an increase in stroke volume, upper body capillary pressure and volume. The activation of LBNP causes an immediate increase in lower body blood volume and a gradual decrease in upper body blood volume. As a result, the fluid shift due to microgravity could be reversed by the LBNP application. LBNP also counters the impacts of microgravity on the cardiac functions, including heart rate and stroke volume. The simulation results have been validated using available physiological data obtained from spaceflight and parabolic flight experiments.

1. Introduction

A transition from the Earth's gravity to the extraterrestrial microgravity environment causes direct and significant changes to human cardiovascular hemodynamics [4]. Due to the absence of the gravitational pull, a redistribution of body fluids occurs between the upper and lower body [17,29]. The fluid shift is linked with the changes of cardiovascular functions, for example, reductions in arterial pressure [13], variations in vascular volumes [36], and remodeling of carotid baroreflex system [11]. These adaptations may lead to discomfort and even diseases, such as orthostatic intolerance [9], impaired vision, and intracranial hypertension [26,39], during space missions and upon reentry to Earth. To counter the negative effects, a variety of methods have been proposed and applied in simulated and actual microgravity environment [1,16]. Lower Body Negative Pressure (LBNP) is one of the most extensively studied methodologies in space physiology research [10]. LBNP combined with treadmill exercise has been proven effective in providing protection against many health problems that are commonly associated with microgravity, such as orthostatic hypotension [16], muscle deconditioning [28], and renal system diseases [30].

Earth-based experiments, including parabolic flights [22,35], prolonged bed rest, or head-down tilt tests [3,21], have been performed to better understand the physiology and effective countermeasures. These tests, however, are typically expensive and need long-term involvements of human subjects. Computer models, built upon physiological data, can serve as a cost-effective alternative approach to investigate the dynamic responses of human physiological mechanisms and provide insights to unforeseen health problems related to microgravity in space. In recent years, computer simulations have been widely used in various studies of human physiology and bioengineering problems [7,14,25,37]. In particular, system-level cardiovascular simulations have provided significant insights into human hemodynamic responses to various external disturbance, such as orthostatic stress, hemorrhage, sodium overload, etc. [8,20,32,33,38,40,41]. To the authors' best knowledge, however, dynamic responses of the cardiovascular system due to the transition to microgravity and during the application of LBNP has not been extensively studied via system-level computer simulations. A lumped-parameter computer model that considers the removal of the hydrostatic pressure and the transmural fluid exchange would be helpful to reveal the short-term dynamics changes of the basic

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cardiovascular parameters with more quantitative details which are often difficult to obtain through experiments.

In this study, we utilized and modified a system-level mathematical model to simulate the short-term responses of the human cardiovascular hemodynamics to microgravity exposures and the effects of LBNP as a countermeasure. LBNP was simulated by a sudden reduction in external and interstitial pressures in the lower body. Through the simulation, we will demonstrate that the removal of hydrostatic pressure induces disturbances to intravascular pressure and transmural pressures in various cardiovascular compartments, leading to a new instantaneous equilibrium in the hemodynamic system. Adaptations of key cardiovascular parameters, including heart rate, stroke volume, arterial pressure, and fluid volumes will be analyzed in the time scale of seconds to minutes. Results will be validated against with available parabolic flight and space experiments.

2. Numerical model

2.1. The base hemodynamics model

The base numerical model of human cardiovascular hemodynamics is adapted from an open-source code, CVSim, which was developed for simulating human cardiovascular physiology [19] and available through PhysioNet.org [15]. As shown in Fig. 1, the lumped-parameter model is constructed based on electrical circuitry analogy, which consists of 21 Windkessel units in a closed-loop system. Each of the 2-element Windkessel unit consists of a resistor and a capacitor, representing the resistance to the input and out flow and the capacitance of the flow compartment as a blood reservoir (volume). The blood pressure serves as the dependent variable and is simulated by the voltage at each note of the electric circuit. The blood flow rate then can be calculated as the current passing each resistor. According to the Kirchhoff's law, a first-order ordinary differential equation (ODE) can be obtained for each compartment (2-element Windkessel unit) as follows:

$$\frac{dP_n}{dt} = \frac{P_{n-1} - P}{R_{n-1}C_n} + \frac{P_{n+1} - P}{R_n C_n} + \frac{(P_{ref} - P_n)}{C_n}\frac{dC_n}{dt}$$

where P is the blood pressure (subscripts n denotes the number index of the pressure node), P_{ref} is reference pressure in the interstitial space or thoracic chamber pressure, R is the resistance to blood flow, and C_n is the compliance of each compartment. Once the pressure is updated, the volume of each cardiovascular compartment is then calculated based on the pressure-volume relations related to the compliance values of each Windkessel unit. While a linear pressure-volume relation, i.e. constant compliance, is assumed for most of the arterial compartments, a non-linear compliance model has been implemented for the venous unit of the lower body compartments (legs) to consider the non-linear pressure-volume relations of a common iliac vein. Model parameters, including the effective resistance, compliance, zero-loading volumes, vascular lengths, and other physiological constants of each cardiovascular unit, were mostly obtained from existing clinical literature and were established to simulate the typical cardiovascular physiology of a general population. More details regarding the origins of parameters and the rationales of each parameter choice were discussed in Ref. [18].

The pressure waveforms driving the cyclic variations of cardiovascular parameters are generated by varying the elastances of four heart chambers. The elastances E(t) are defined as the reciprocals to the compliances and are modeled using the following cosine functions:

$$\frac{E(t)}{E_{es}} \begin{cases} \frac{E_d}{E_{es}} + \frac{E_{es}-E_d}{2E_{es}}\left[1 - \cos\left(\pi\frac{t}{T_s}\right)\right] & 0 \le t \le T_s \\ \frac{E_d}{E_{es}} + \frac{E_{es}-E_d}{2E_{es}}\left[1 + \cos\left(2\pi\frac{t-T_s}{T_s}\right)\right] & T_s \le t \le \frac{3}{2}T_s \\ \frac{E_d}{E_{es}} & t \ge \frac{3}{2}T_s \end{cases}$$

where T_s is the systolic time interval; E_d and E_{es} the diastolic and end-systolic elastance, respectively. The systolic time interval (P-R interval) and the heart rate (R-R interval) are controlled by a subroutine modeling the function of the cardiac pacemaker. In this subroutine, different timing parameters, including the P-R and R-R intervals, are assigned to atria and ventricles to modulate the heart rhythm typical of the general population. The model also incorporates arterial baroreflex and cardiopulmonary reflex as the short-term blood pressure regulation mechanisms resembling both sympathetic and parasympathetic nervous signals. The nervous reflex is simulated by using set-point control subroutines. Specifically, transmural pressures in the aortic arch and the carotid sinus pressure nodes are recorded using a moving average filter and then subtracted by a pre-defined set-point arterial pressure value. The error signal resulted from the difference is then convolved with impulse response functions and scaled by static gain values. Finally, the reflex subroutine provides an instantaneous update to the efferent effector variables, including the heart rate, cardiac contractility, arteriole resistance, and venous tone, which affects the ensuing cardiovascular adaptations. The iterative process minimizes the error signals arising from external perturbations. The detailed formulations of the nervous reflex modules and their parameter assignments can also be found in Ref. [18] and are not elaborated here.

In the present study, the original numerical code was adapted and partially modified in C programming language. The modification to the code includes two more pressure nodes and associated system parameters to simulate the gravity-induced fluid shifts. Overall, a system of 23 first-order ordinary differential equations were solved using the 4th order Runge-Kutta methods with adaptive time steps to obtain time-dependent pressure changes. Other variables such as flow, volume, and compliance were then updated with the new updated pressure values. The modifications to the code are discussed in the following paragraphs.

2.2. Transcapillary fluid exchange, gravity, and LBNP

Gravitational changes will cause disturbances in intravascular hydrostatic pressures, which affects the rate of transcapillary fluid exchange, particularly in the upper and lower extremities. In its original development, CVSim utilized a simple resistor-capacitor model in the three lower-body compartments (renal, splanchnic, and leg) to represent the blood flow filtration into a “virtual” interstitial space [18]. To account for the fluid shifts, we modified the upper-body and lower-body micro-circulation compartments (red boxes in Fig. 1) using the scheme proposed by Ref. [31]; as shown in Fig. 2. In this method, the capillary hydrostatic pressure (P_{cap}) and interstitial pressure (P_{int}) are strongly coupled to the system dynamics as state variables. The original single resistors of the micro-circulations are split into a pre-capillary resistor and a post-capillary resistor, which are assigned 90% and 10% of the original capillary resistance, respectively. The fluid exchange between the intravascular space and the interstitial space is determined by the Starling equation

$$q_f = K_f[(P_{cap} - P_{int}) - \sigma(O_{cap} - O_{int})]$$

where q_f is the filtration flow rate; K_f is the filtration coefficient calculated as the reciprocal of membrane resistance, i.e. $1/R_{int}$; P_{int} is the interstitial pressure.; The reflection coefficient σ, considering the leakage of plasma protein, is set to be a constant 0.9 for typical systemic capillaries [27]. O_{cap} and O_{int} are the oncotic pressures of the intravascular and interstitial fluids, respectively, which are calculated based on the van't Hoff Equation, $O = nRT/V$, where n is the colloid content in mol, V the total fluid volume, and T the absolute temperature. In the present modeling, P_{cap} and P_{int} are solved at each simulation time step and the oncotic pressures are updated based on the current intravascular and interstitial blood volume at the end of each computational loop. Additionally, pathways representing the lymphatic flows