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Modeling of high sodium intake effects on left ventricular hypertrophy

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ABSTRACT

Many clinical studies suggest that chronic high sodium intake contributes to the development of essential hypertension and left ventricular (LV) hypertrophy. In the present study, a system-level computer model has been developed to simulate the long-term effects of increased sodium intake on the LV mechanical functions and the body-fluid homeostasis. The new model couples a cardiovascular hemodynamics function model with an explicit account of the LV wall thickness variation and a long-term renal system model. The present model is validated with published results of clinical studies. The results suggest that, with increased sodium intake, the renal system function, the plasma hormone concentrations, and the blood pressure adapt to new levels of equilibrium. The LV work output and the relative wall thickness increase due to the increase of sodium intake. The results of the present model match well with the patient data.

1. Introduction

Left ventricular hypertrophy (LVH), manifested by an enlargement of myocardium tissue, is a predisposing factor for many cardiovascular diseases [1]. During the past decades, numerous studies have demonstrated a strong correlation between chronic hypertension and LVH [2–5]. A physiologic adaptation of the left ventricular structure to the chronic pressure loading is generally considered the main reason for hypertrophy [4,6]. Following the Laplace's law, this adaptation allows the wall stress and the pumping function to remain relatively unchanged by increase in the left ventricle (LV) tissue volume and LV wall thickness [7].

As a major contributor to the prevalence of essential hypertension [8,9], high sodium intake has been demonstrated to cause LVH by inducing chronically elevated blood pressure [10–12]. Meanwhile, some studies also suggest that high sodium intake can also contribute to LVH through a different route, independent of or in addition to the hypertensive effect [13–18]. In patients with essential hypertension and high sodium intake, an insufficiently down-regulated Angiotensin II concentration was found to correlate with cardiac hypertrophy [19]. Animal experiments also suggest that high sodium intake facilitates the activation of the local (cardiac) renin-angiotensin system (RAS) [20], increases the synthesis of cardiac aldosterone [21], and induces higher concentration of Angiotensin II in myocardium [22]. Based on these clinical findings, sodium restriction [23] and angiotensin-converting enzyme (ACE) inhibitor [24] have been used with positive effects on the regression of LVH and therefore successfully prescribed as treatments for LVH [6].

In the present study, a computer model has been developed to link high sodium intake to LVH based upon the existing clinical evidences. A long-term renal system model developed by Karaaslan et al. [25] is adapted and used to simulate the chronic effects of high sodium intake on body-fluid homeostasis. To account for the LV pressure loading, we used an open-source hemodynamics model of human cardiovascular system, i.e. CVSim [26]. A model for the response of the LV wall thickness to the pressure overload is developed. By combining and modifying the renal system model and the CVSim model, the new model is capable of simulating both the long-term effects of body-fluid homeostasis and the detailed structural properties of the human cardiac chambers. Since clinical studies are often restricted with test subjects and other medical issues, computer modeling will be particularly helpful for an enhanced understanding of the system-level response of the LV wall thickness to high sodium intake. The details of the model will be described in the following section.

2. Mathematical models

CVSim is based on a closed-loop circulation model for hemodynamic responses of cardiovascular system, the total blood volume is kept constant and the body-fluid homeostasis is not simulated. For the purpose of the present study, we couple a long-term renal system model to the existing CVSim model. The hybrid model then

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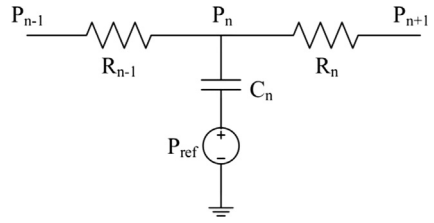

Fig. 1. Electrical analog of CVSim model.

has the capability of simulating both the short-term response of hemodynamics and the long-term fluid-electrolyte homeostasis.

2.1. Cardiovascular hemodynamics: CVSim

An open-source model, named CVSim, has been adapted and used for the hemodynamic simulation in the present study. Since 1984, CVSim has been developed and successfully utilized in teaching [26] and research [27–28]. This model is a closed-loop, lumped-parameter model based on electrical circuitry analogy. As shown in Fig. 1, each unit of the model consists of resistors and capacitors, representing the afferent/efferent resistance and reservoir functions of a modeled compartment in human body. Voltage and currents mimic blood pressure and blood flow rate, respectively.

According to Kirchhoff's current law, a first order ordinary differential equation can be written for a compartment:

$$\frac{P_{n-1}-P_n}{R_{n-1}}+\frac{P_{n+1}-P_n}{R_n}+\frac{d\left[C_n\left(P_{ref}-P_n\right)\right]}{dt}=0 \tag{1}$$

In the present study, the reference pressure in the interstitial space P_{ref} is assumed to be constant. Hence this equation becomes:

$$\frac{dP_n}{dt}=\frac{P_{n-1}-P_n}{R_{n-1}C_n}+\frac{P_{n+1}-P_n}{R_nC_n}+\frac{\left(P_{ref}-P_n\right)}{C_n}\frac{dC_n}{dt} \tag{2}$$

The capacitance is assumed to be constant in most of the compartments, except for the four cardiac chambers. Therefore, the equation is further simplified,

$$\frac{dP_n}{dt}=\frac{P_{n-1}-P_n}{R_{n-1}C_n}+\frac{P_{n+1}-P_n}{R_nC_n} \tag{3}$$

Therefore, by solving a system of first-order ordinary differential equations (ODE), the hemodynamics of the circulation system can be simulated. In the present study, a 21-comparment version of CVSim is adopted. The model includes the four cardiac chambers, pulmonary artery and vein, and other systemic arteries, veins, and micro-circulations, as shown in Fig. 2.

The pumping function of heart is simulated by varying the elastance of the four cardiac chambers, based on the following function:

$$\frac{E(t)}{E_{es}}=\begin{cases}\frac{E_d}{E_{es}}+\frac{E_{es}-E_d}{2E_{es}}\left[1-\cos\left(\pi\frac{t}{T_s}\right)\right], & 0\le t\le T_s\\ \frac{E_d}{E_{es}}+\frac{E_{es}-E_d}{2E_{es}}\left[1+\cos\left(2\pi\frac{t-T_s}{T_s}\right)\right], & T_s\le t\le\frac{3}{2}T_s\\ \frac{E_d}{E_{es}}, & t\ge\frac{3}{2}T_s\end{cases} \tag{4}$$

where $E(t)$ is the time-dependent elastance; E_d, E_{es} are diastolic and end-systolic elastance, respectively; T_s is the systolic time interval for each chamber. The modeled elastance is shown in Fig. 3. The time-varying capacitances of the cardiac chambers are then calculated as $C(t)=1/E(t)$. The validity of this model relationship has been verified by comparing the simulated curve with those found in clinical study, as can be found in [29]. The values of the resistance, capacitance, and initial volume of each compartment are assigned based on clinical studies. The system of ODE has been solved using fourth-order Runge-Kutta methods with a fixed time step of 0.001 s. A sample waveform of the left ventricular, aortic, and systemic venous pressures are shown in Fig. 4. The parameter assignments and details in model implementations can be found in [28].

2.2. Left ventricular wall thickness

To study the LV hypertrophy, the LV wall thickness is linked to LV pressure and volume by using the Laplace's law in the present study. The shape of LV is assumed to be a sphere and the stress acting on the mid-plane cross-section can be calculated as:

$$\sigma=\frac{P\pi R^2}{\pi\left[(R+h)^2-R^2\right]} \tag{5}$$

where σ is the wall stress, P the LV blood pressure, R the LV internal radius, and h LV wall thickness. By re-arranging the equation, the LV wall thickness can be written as a function of the LV pressure and radius:

$$\frac{h}{R}=\sqrt{1+\frac{P}{\sigma}}-1 \tag{6}$$

The parameter h/R, which can be referred as a relative wall thickness at the end-systolic state of LV, varies with the LV pressure. According to Grossman et al. [7], the LV wall stress does not change significantly in hypertrophic patients, as the LV tissues appear to adapt to the mechanical overloads and restore the wall stress. In the present study, the LV wall stress as a function of time is modeled using a similar function as the time-varying elastance. The equations are given as follows:

$$\frac{\sigma(t)}{\sigma_{ps}}=\begin{cases}\frac{\sigma_{ed}}{\sigma_{ps}}+\frac{\sigma_{ps}-\sigma_{ed}}{2\sigma_{ps}}\left[1-\cos\left(\pi\frac{t}{0.5T_s}\right)\right], & 0\le t\le\frac{1}{2}T_s\\ \frac{\sigma_{min}}{\sigma_{ps}}+\frac{\sigma_{ps}-\sigma_{min}}{2\sigma_{ps}}\left[1+\cos\left(2\pi\frac{t-0.5T_s}{0.5T_s}\right)\right], & \frac{1}{2}T_s\le t\le\frac{3}{2}T_s\\ \frac{\sigma_{ed}-\sigma_{min}}{\tau-1.5T_s}t\,, & t\ge\frac{3}{2}T_s\end{cases} \tag{7}$$

where σ_{ps}, σ_{ed}, σ_{min} are the peak-systolic wall stress, end-diastolic wall stress, and minimum wall stress during early diastole, respectively. τrepresents the time for a heartbeat and the inverse of the current heart rate. The time to reach the peak-systolic stress is reported shorter than the systolic time, as shown in Grossman et al. [7], and is assumed to be one half of the systolic time in the present study. As shown in Fig. 5, the time-dependent LV wall stress calculated by the equations matches reasonably well with *in vivo* results of Grossman et al. [7].

Fig. 6 shows the simulated behaviors of the LV pressure, wall stress, and thickness in a typical cardiac cycle. Data from Grossman et al. [7] are also included for comparison. Note that the LV wall stress and pressure have been normalized by the maximum LV pressure during systole, while the LV wall thickness by the maximum thickness. The simulated results agree reasonably well with the data. It can be seen that the LV wall stress reaches the peak value before the end of systole and then decreases, while the LV pressure remains at high level during systole. The LV wall thickness increases to its maximum when the LV pressure decreases sharply after the end of diastole. The capturing of these features in the simulations provides a validation of the present modeling of the LV wall thickness based on the clinical hemodynamic information.

2.3. Body-fluid homeostasis: a renal function model

Since 1970, several renal system models have been developed [30–32] and most of them are built following the pioneering effort described in Guyton et al. [33]. Guyton's model, which consists of 354 blocks, more than 400 equations, and 18 different functioning subsystems, is comprehensive and complicated. Karaaslan et al. [25] integrated parts of a simplified Guyton's model with two