Nonlinear Multiscale Circulation Model Reproducable Linear End-Systolic Pressure-Volume Relationship

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***Abstract*— As a well-known property of the heart, many studies has reported that the left ventricular end-systolic pressure-volume relationship (ESPVR) is linear. However, the reason of the linearity is poorly understood. This article presents a multiscale circulation model to be a tool for theoretical analyses on the mechanism of the linearity of ESPVR. The model is composed of three sub-models; a detailed closed-loop lumped-parameter model for cardiovascular system, geometric left ventricle model, a comprehensive ventricular myocyte model. Although the present model integrates nonlinear sub-models, the model can successfully reproduce highly linear ESPVR without any arbitrary modifications.**

I. INTRODUCTION

Cardiac contractility is an important index of the heart, since the heart is an organ to pump blood into the whole body by its contraction. A well-known property of the heart is the linearity of end-systolic pressure-volume relationship (ESPVR)[1], which is the relationship between ventricular pressure and volume at end-systole with varied cardiac afterload or preload. It has been reported that human, canine and gunea-pig ESPVR is linear in physiological conditions[1], [2], [3], [4]. The slope of the ESPVR is a well-established index of cardiac contractility and called E_{es}.

The linearity of the ESPVR was originally explained by using the time-varying elastance model[1], which assumed the left ventricle to have a linear elastance that depends only time. However, the left ventricle is not a linear elastic chamber, but the elastance is modulated by complicated interactions among phenomena on different spatial scales. Therefore, there is no explicit reason for the linearity, and the actual detailed mechanism of the linear ESPVR is not well understood.

The purpose of this study is to provide a tool for theoretically analysing the mechanisms of the liniarity of the ESPVR. To this end, we developed a multiscale mammalian circulation model that can reproduce linear ESPVR, by composing independently developed nonlinear sub-models; a multi-compartment cardiovascular model, a left ventricle model based on Laplace's law, and a comprehensive ventricular myocyte model.

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II. MODEL

A. Cardiovascular Model

The cardiovascular system is modeled as a closed-loop lumped-parameter circuit based on Heldt's human circulation model[5]. This model consists of the aortic capacitance and ten compartments that are composed of elastances and capacitances as shown in Fig. 1. The left ventricle is represented with the left ventricle model described below, instead of the time varying elastance in the Heldt's model. The change in the left ventricular volume V_{lv} is formulated as

$$\frac{dV_{\mathrm{lv}}}{dt} = q_{\mathrm{pv}} - q_{\mathrm{lo}}, \tag{1}$$

$$q_{\mathrm{pv}} = \begin{cases} (P_{\mathrm{pv}} - P_{\mathrm{lv}})/R_{\mathrm{pv}} & (P_{\mathrm{pv}} > P_{\mathrm{lv}}) \\ 0 & (\text{otherwise}) \end{cases}, \tag{2}$$

$$q_{\mathrm{lo}} = \begin{cases} (P_{\mathrm{lv}} - P_{\mathrm{a}})/R_{\mathrm{lo}} & (P_{\mathrm{lv}} > P_{\mathrm{a}}) \\ 0 & (\text{otherwise}) \end{cases}, \tag{3}$$

where q_{pv} and q_{lo} represent blood flow into and from the left ventricle, respectively, and P_{pv}, P_{lv} and P_{a} stands for the pulmonary venous, left ventricle, and aortic pressures, respectively, and R_{pv} and R_{lo} for the pulmonary venous and left ventricular output resistances, respectively. Table I shows the parameter values of resistances, compliances and unloaded volumes, which were scaled to 5.0 kg body weight.

B. Left Ventricle Model

The left ventricular volume V_{lv} is assumed to be an ellipsoid:

$$V_{\mathrm{lv}} = k_V R^3, \tag{4}$$

where R the left ventricular transverse radius. The relationship between the radius and mean half sarcomere length L of myocytes is expressed as

$$R = k_R(L - L_r), \tag{5}$$

where L_r is the residual half sarcomere length when the left ventricular volume is zero. The left ventricular pressure P_{lv} is formulated with Laplace's law for a spherical vessel:

$$P_{\mathrm{lv}} = \frac{hT}{R}, \tag{6}$$

where h and T are the left ventricular wall thickness and tension, respectively. Parameter values shown in Table II are determined by model fits.

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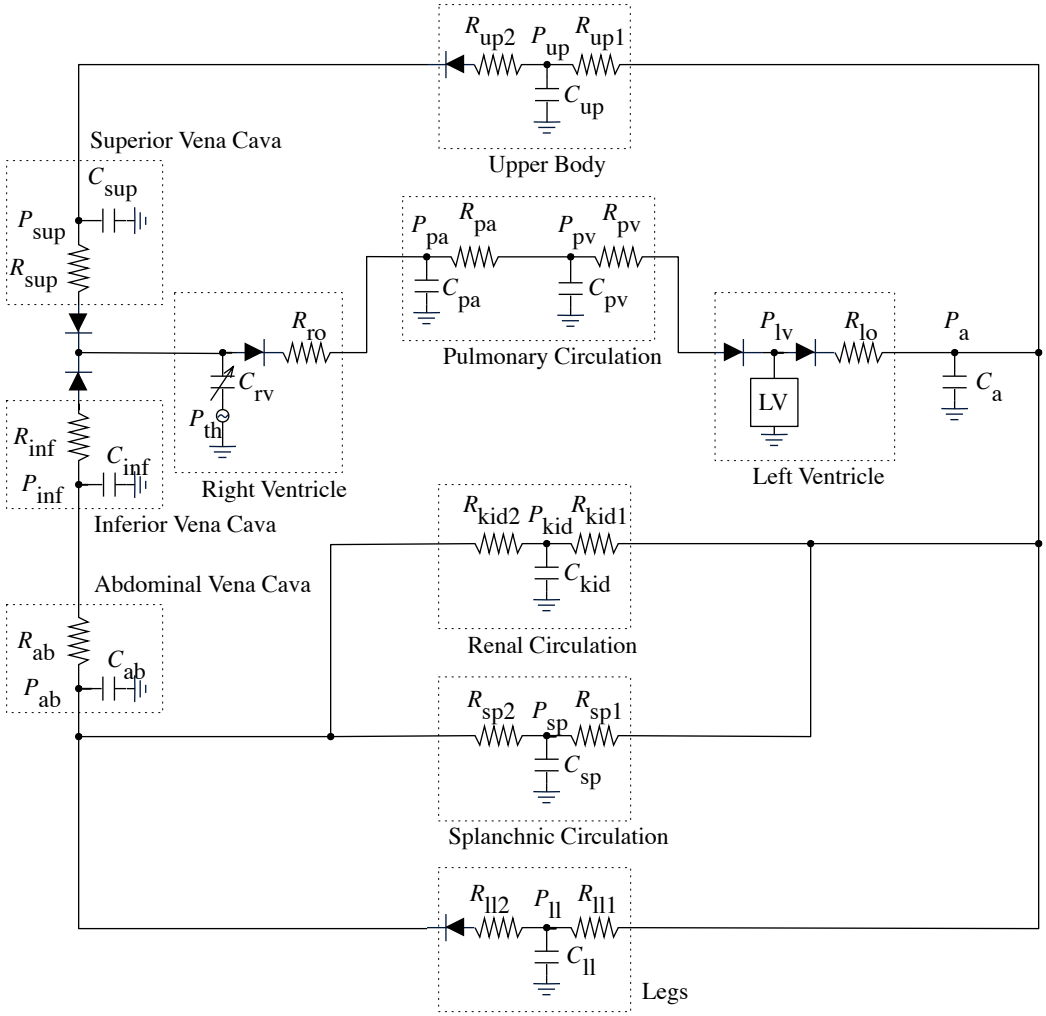

Fig. 1. Circuit Diagram of Cardiovascular Model

TABLE I
PARAMETER VALUES OF CARDIOVASCULAR MODEL

Compliances [ml/mmHg]															
C_{pa}	C_{pv}	C_a	C_{up}	C_{kid}	C_{sp}	C_{ll}	C_{ab}	C_{inf}	C_{sup}						
0.672	1.31	0.313	1.25	2.34	8.59	2.97	3.91	2.34	0.313						
Resistances [ms·mmHg/ml]															
R_{lo}	R_{up1}	R_{kid1}	R_{sp1}	R_{ll1}	R_{up2}	R_{kid2}	R_{sp2}	R_{ll2}	R_{sup}	R_{ab}	R_{inf}	R_{ro}	R_p	R_{pv}	
0.021	13.7	14.4	10.5	12.6	0.805	1.05	0.63	1.05	0.21	0.035	0.0525	0.0105	0.28	0.035	
Unloaded Volumes [ml]															
$V_{0,pa}$	$V_{0,pv}$	$V_{0,a}$	$V_{0,up}$	$V_{0,kid}$	$V_{0,sp}$	$V_{0,ll}$	$V_{0,ab}$	$V_{0,inf}$	$V_{0,sup}$	$V_{0,rv}$					
9.9	53.9	78.7	71.5	16.5	143	38.5	27.5	8.25	1.1	0.33					

TABLE II
PARAMETER VALUES OF LEFT VENTRICLE MODEL

h	12 mm
k_v	9.0 ml/cm^3
k_R	1.89 mm/μm
L_r	0.42 μm

C. Ventricular Myocyte Model

A guinea-pig ventricular myocyte model by Kuzumoto et al.[6] is employed to represent ventricular contraction. This model includes, in addition to membrane excitation and calcium dynamics, excitation-contraction coupling by importing a muscle contraction model by Negroni and Lascano[7]. For the left ventricular wall tension T, the cellular contractile tension F is used, which is expressed as

$$F = F_p + F_b, \tag{7}$$

where F_b and F_p are active and passive tension, respectively. The passive tension is formulated as a nonlinear elasticity:

$$F_p = K_p(L - L_0)^5, \tag{8}$$

where K_p (140 000 mN/mm^2/μm^5) and L_0 (0.97 μm) are an elastic coefficient and unloaded half sarcomere length, respectively. The active contractile tension is expressed as

$$F_b = A\,D_{\mathrm{cb}}\,(L - X), \tag{9}$$

$$dX/dt = B(L - X - h_c), \tag{10}$$

where A (1800 mN/mm^2/μm/μM), B (800 /s) and h_c (0.005 μm) are parameters. D_{cb} stands for attached cross-bridge concentration, and its derivative depends on the harf sarcomere length.

D. Simulation Method

To obtain ESPVR, the present model was simulated with varied afterload by multiplying parameters R_{up1}, R_{kid1} and R_{sp1} simultaneously by a scale factor, r (0.7–1.3). For triggering membrane excitation of the myocyte, stimulation current was injected in 430 ms periods. The system of model equations was solved using Euler method with 0.01 ms time steps. Simulation duration was 60 sec to obtain steady states. ESPVR was analyzed by the linear regression analysis on the end-systolic pressure-volume points, by using the R, a software environment for statistical computing.

III. RESULTS

Fig. 2 shows simulated pressure-volume loops for each afterload, or r, and calculated ESPVR. The simulated pressure-volume loops show a normal reaction against increased afterload, i.e. increases in end-systolic and end-diastolic pressure and volume. The determination coefficient (R^2) of linear regression analysis for ESPVR is 0.9998. This value justifies the high linearity of the obtained ESPVR.

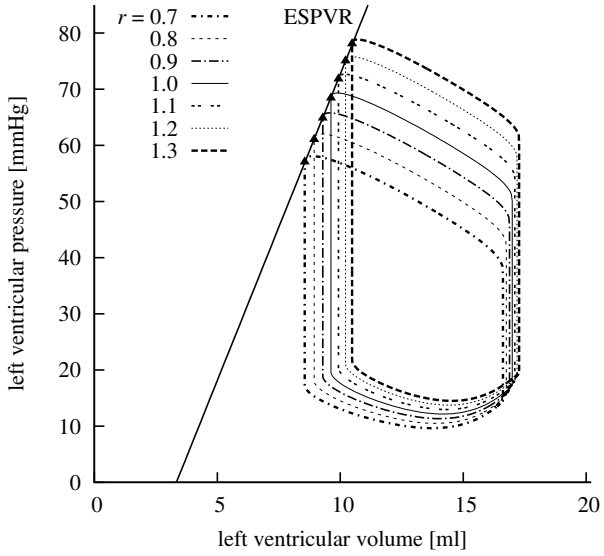

Fig. 2. Simulated Pressure-Volume Loops and ESPVR

IV. DISCUSSION

The present circulation model is composed of nonlinear sub-models, which were independently developed. Nevertheless, the model is able to reproduce linear ESPVR. Note that no arbitrary modification was applied to obtain the linearity. This fact indicates that the present model includes the physiologically inherent mechanism for the linearity of ESPVR. Furthermore, the present multiscale model couples whole body hemodynamics and myocardial cell physiology. Such multiscale model reproducable linear ESPVR has not been reported to the best of our knowledge.

The present model is a hybrid model, that is, parameters for cardiovascular system and left ventricle were based on human and canine reports while a guinea-pig model was used for the myocyte. Thus, this model does not represent any actual animal, and qualitatively agrees with general cardiovascular properties. However, human, canine and guinea-pig ESPVR's are linear. Therefore, the present model is usable to analyze the mechanism of the linearity of ESPVR theoretically. Detailed theoretical analyses using this model will lead better understanding of cardiac contractility.

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