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Functional Requirements of a Mathematical Model of the Heart

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***Abstract*— Functional descriptions of the heart, especially the left ventricle, are often based on the measured variables pressure and ventricular outflow, embodied as a time-varying elastance. The fundamental difficulty of describing the mechanical properties of the heart with a time-varying elastance function that is set *a priori* is described. As an alternative, a new functional model of the heart is presented, which characterizes the ventricle's contractile state with parameters, rather than variables. Each chamber is treated as a pressure generator that is time and volume dependent. The heart's complex dynamics develop from a single equation based on the formation and relaxation of crossbridge bonds. This equation permits the calculation of ventricular elastance via $E_v = \partial p_v / \partial V_v$. This heart model is defined independently from load properties, and ventricular elastance is dynamic and reflects changing numbers of crossbridge bonds. In this paper, the functionality of this new heart model is presented via computed work loops that demonstrate the Frank-Starling mechanism and the effects of preload, the effects of afterload, inotropic changes, and varied heart rate, as well as the interdependence of these effects. Results suggest the origin of the equivalent of Hill's force-velocity relation in the ventricle.**

I. Introduction

FUNCTIONAL description of the heart via models is important for study of the heart's pumping mechanism, for understanding of normal and disease conditions, and to serve as a building block in larger physiological systems. Models of the heart as a pump originally reflected prevailing physiological concepts of heart function. Accordingly, Starling's law became the basis of early models of this fluid pump, *e.g.*, the design of hydraulic pumps [1] representing the two sides of the heart in a closed-loop cardiovascular system model. Guyton [2] used a graphical technique to define an operating point for a variety of conditions. Early mathematical models expressed the Starling mechanism in equation form [3]. The strongly pulsatile nature of the heart beat was ignored in these models. Pulsatile phenomena were included by Warner [4] in his model of the closed circulatory system in which viscous, inertial and compliant properties play a role. The two ventricles were modeled by two time-varying compliances (inverse elastances) that changed their values stepwise. Subsequent work replaced this discontinuous description by continuous ones, *e.g.*[5].

Current mechanical descriptions of the heart as a pump typically depend on the time-varying elastance [6]. Ventricular elastance E_v is defined as the time varying ratio of instantaneous ventricular pressure p_v and volume V_v as $E_v(t) = p_v/(V_v - V_d)$. Ventricular elastance defined in this way measures both ventricular and arterial properties. Consequently, an elastance curve measured for an ejecting ventricle predicts isovolumic pressure curves very different from those measured [7].

Another approach is construction of the ventricle on the basis of individual myocardial fiber properties in conjunction with their geometric arrangement, *e.g.* [8]. The inherent complexity of the heart's geometry and muscle fiber arrangement leads to complex models. The nonlinear, time-varying, active properties of heart muscle lead to challenges in applying finite-element modeling techniques to the heart. This paper tests the ability of a simple functional model of the heart as a pump to demonstrate fundamental cardiovascular dynamics.

II. Methods

Ventricular pressure p_v is described as a function of time t and ventricular volume V_v according to [10]:

$$p_v(t, V_v) = a(V_v - b)^2 + (c\,V_v - d)f(t) \qquad (1)$$

Generated pressure results from the sum of passive (diastolic) and active (systolic) components, shown on the left and right sides of the plus sign in eq. 1, respectively. Considering the passive term first, measurement of diastolic isovolumic pressure on isolated dog hearts for different volumes shows that a and b are constants for a given ventricle [9]. b corresponds to the diastolic volume at zero pressure. a is a measure of diastolic (passive) ventricular elastance. The second, systolic term was similarly determined from measured peak isovolumic pressure at different volumes, where c and d are directly related to volume dependent and volume independent components of developed pressure, respectively. The function $f(t)$ describes the time course of active force generation, a product of contraction and relaxation exponentials related to myofilament crossbridge bond formation and detachment, respectively:

$$f(t) = \frac{(1 - e^{-(\frac{t}{\tau_c})^\alpha})e^{-(\frac{t-t_b}{\tau_r})^\alpha}}{(1 - e^{-(\frac{t_p}{\tau_c})^\alpha})e^{-(\frac{t_p-t_b}{\tau_r})^\alpha}}, \quad t_b < t < 1 \qquad (2)$$

τ_c and τ_r are time constants characterizing the contraction (pressure increase) and relaxation (pressure decrease) processes, respectively, while α is a measure of the overall rate of onset of these processes. The combination of diastolic and systolic terms yields an analytical function describing ventricular pressure as a function of both time and ventricular

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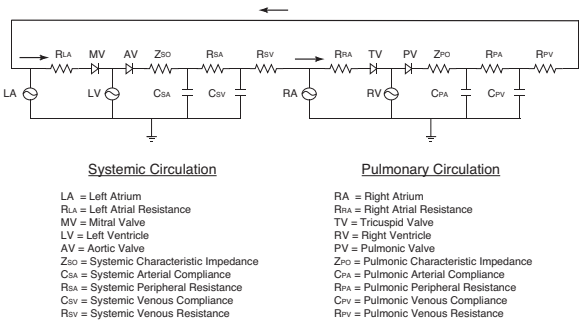

Fig. 1. Human circulatory system model.

volume. t_b is a time constant derived from t_p, τ_c, τ_r and α:

$$t_b = t_p \left\{ 1 - \left(\frac{\tau_r}{\tau_c} \right)^{\frac{\alpha}{\alpha-1}} \left[\frac{e^{-(\frac{t_p}{\tau_c})^\alpha}}{1 - e^{-(\frac{t_p}{\tau_c})^\alpha}} \right]^{\frac{1}{\alpha-1}} \right\} \quad (3)$$

All model constants are determined from experimental data [9], [7]. For ten dogs, average error between experimental data points and analytical curves was <=1% [10].

This pressure model was adapted to describe each of the four human heart chambers, as part of the complete circulatory system model depicted in fig. 1. Model constants in eq. 1 are listed in Table I for each heart chamber. A pressure-voltage analogy was employed, with flow depicted by current and volume by charge. The circulation model elements, from left to right in fig. 1, begin with the left atrium (LA), described by eq. 1. This pressure source ejects into the left ventricle (LV) via the mitral valve (MV), depicted as a diode, with finite flow resistance R_{LA}. The left ventricle is also described by eq. 1. Ejected blood then flows through the aortic valve (AV) into the systemic arterial tree, consisting of systemic characteristic impedance of the aorta (Z_{SO}), systemic arterial compliance (C_{SA}) and systemic peripheral resistance (R_{SA}). The systemic venous compliance and venous flow resistance are next described by C_{SV} and R_{SV}, respectively. The pulmonary circulation is described similarly. The right atrium (RA) and right ventricle (RV) are each described as time- and volume-dependent pressure sources (eq. 1). The right atrium fills the right ventricle via the tricuspid valve (TV) with flow resistance R_{RA}. Blood is ejected via the pulmonic valve (PV) into the pulmonary arterial circulation, another 3-element modified windkessel, composed of Z_{PO}, C_{PA} and R_{PA}, and finally through the pulmonary venous vessels, described by C_{PV} and R_{PV}.

Circulatory system parameter values, chosen guided by literature data, e.g. [11], are listed in Table II. Values were chosen to yield computed volumes, flows and pressures consistent with typical human values. Network theory techniques were used to write pressure and flow expressions at each circuit node (fig. 1), and flow equations were numerically integrated, yielding volumes. Each circuit node requires three equations to solve for the three unknowns pressure, volume and flow. Final computed nodal volumes at the end of one beat are used as the initial volumes for subsequent beats,

TABLE I

CONSTANTS FOR DESCRIPTION OF EACH HEART CHAMBER (EQ. 1).

Constant	L Atr.	L Vent.	R Atr.	R Vent.
a [$\mathrm{mmHg/ml^2}$]	0.005	0.0007	0.005	0.0007
b [ml]	5	20	5	10
c [$\mathrm{mmHg/ml}$]	1	3.5	1	1.5
d [mmHg]	15	80	15	50
τ_c [s]	0.06	0.264	0.06	0.264
t_p [s]	0.1	0.371	0.1	0.371
τ_r [s]	0.08	0.299	0.08	0.299
α	2.88	2.88	2.88	2.88

TABLE II

MODEL CIRCULATION ELEMENTS AND THEIR CONTROL VALUES.

Model Element	Symbol	Control Value
Systemic Circulation		
Left atrial resistance	R_{LA}	0.007 mmHg-s/ml
Systemic characteristic impedance	Z_{SO}	0.1 mmHg-s/ml
Systemic arterial compliance	C_{SA}	1 ml/mmHg
Systemic peripheral resistance	R_{SA}	1.5 mmHg-s/ml
Systemic venous compliance	C_{SV}	190 ml/mmHg
Systemic venous resistance	R_{SV}	0.1 mmHg-s/ml
Pulmonary Circulation		
Right atrial resistance	R_{RA}	0.001 mmHg-s/ml
Pulmonic characteristic impedance	Z_{PO}	0.08 mmHg-s/ml
Pulmonic arterial compliance	C_{PA}	4 ml/mmHg
Pulmonic peripheral resistance	R_{PA}	0.08 mmHg-s/ml
Pulmonic venous compliance	C_{PV}	90 ml/mmHg
Pulmonic venous resistance	R_{PV}	0.1 mmHg-s/ml

computing until left and right side ventricular stroke volumes equilibrate in steady-state. Ventricular elastance, E_v, defined as $\partial p_v / \partial V_v$, may be computed as

$$E_v(t, V_v) = 2a(V_v - b) + cf(t) \quad (4)$$

III. RESULTS

The isolated left ventricle model (eq. 1) was filled with a constant pressure source and coupled to a three-element systemic arterial load (Z_{SO}, C_{SA}, and R_{SA} in fig. 1). The ventricle produces pressure-volume work loops as shown in fig. 2. As end-diastolic volume is increased by changing filling pressure, stroke volume SV increases as expected, since the model has the force-length relation built in ($cVv-d$ of eq. 1). Work loops shift to the right via two interdependent effects: increased preload leads to an increase in stroke volume (Frank-Starling), and the end-systolic volume shifts to the right since the increased stroke volume leads to an increase in cardiac output and arterial pressure, thereby increasing afterload. This increased afterload partially offsets the increased stroke volume due to increased end-diastolic volume. The increased afterload reduces the constituent heart muscles' velocity of shortening and therefore the heart's ejection velocity. Hence, the ventricle model itself has muscle's force-velocity relation [12] built in without separate assumptions of a hyperbolic curve.

Afterload was changed by varying arterial peripheral resistance R_{SA} for the isolated ventricle filled from a pressure source, producing work loops as shown in fig. 3. Increased afterload reduces stroke volume since the increased arterial

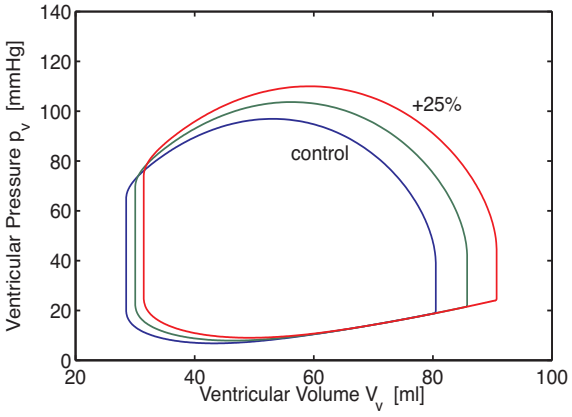

Fig. 2. Pressure-volume work loops computed for the isolated left ventricle model filled by a constant pressure source. Preload was increased by 12.5 and 25% by increasing filling pressure.

pressure reduces the velocity of muscle shortening and, consequently, the velocity of blood ejection. The reduced stroke volume at the same end-diastolic volume reduces the ejection fraction.

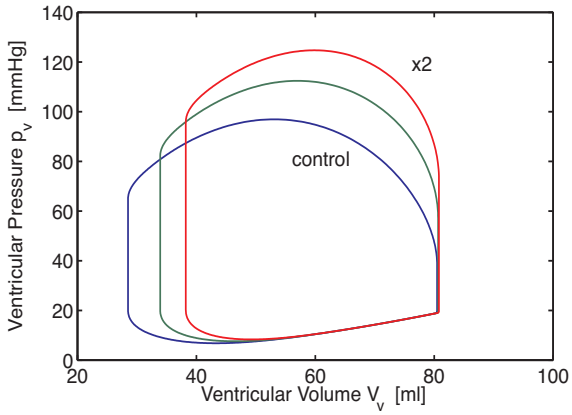

Fig. 3. Work loops computed for the isolated left ventricle model filled with a constant pressure source. Afterload was increased by increasing peripheral resistance R_{SA} by a factor of 1.5 and 2.

The interdependence of preload and afterload is evident in the complete cardiovascular system model (fig. 1). Afterload was changed by altering peripheral resistance in both the systemic and pulmonary circulations. As for the natural system, the Starling mechanism partially compensates for the reduction in stroke volume (fig. 4). Starling's law is also evident in the complete CV system model by changing the total blood volume $\pm 10\%$ as seen in fig. 5.

Inotropic changes may be studied by changing the c coefficient of eq. 1. Each of the four heart chambers were subjected to 33% increased and decreased contractility, depicted in the work loops of fig. 6. For positive inotropic changes, increased pressure generation is due to increased numbers of bonds within the cardiac muscle. This serves to shift the muscle to a new force-velocity curve, so that a given muscle force yields higher velocity of muscle shortening. Subsequently, the heart

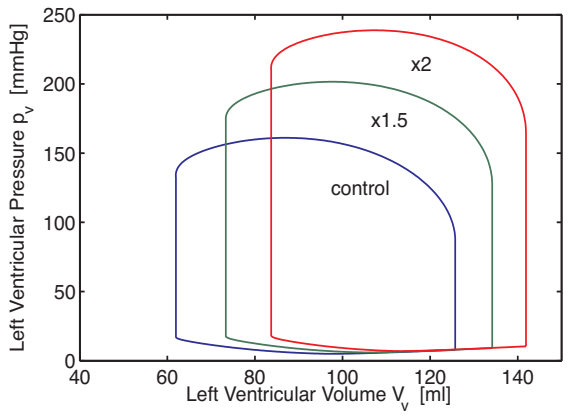

Fig. 4. Work loops computed for the full cardiovascular system. Afterload was increased on both the left and right circulations by increasing both arterial and pulmonary peripheral resistance by a factor of 1.5 and 2.

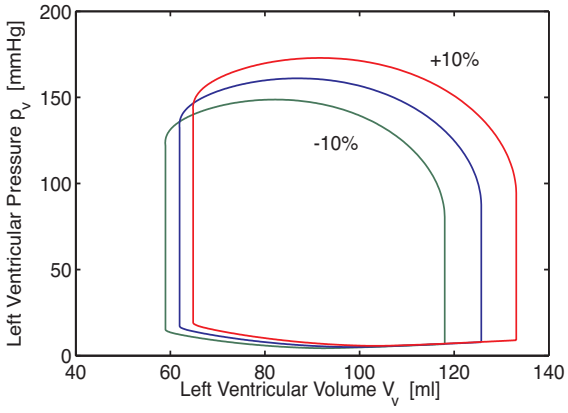

Fig. 5. Work loops computed for the full cardiovascular system. Total blood volume was increased and decreased 10% from the control 5 liters.

chamber's ejection velocity increases, thereby increasing stroke volume. Increased contractility ejects more volume, so a small decrease in EDV leads to a somewhat smaller SV via Starling's law, thereby slightly lowering the increase in stroke volume.

Heart rate can be varied in the model by simple time scaling of the activation function $f(t)$ (not shown). Ventricular elastance was also computed via eq. 3 for all of the above situations (not shown). Computed elastance was found to be strongly sensitive to the heart's contractile state, but insensitive to preload or afterload.

IV. Discussion

Using a time-varying elastance defined as the ratio of instantaneous pressure and volume is problematic since elastance is predetermined. In the ventricle, or its constituent heart muscle, the contraction process is dynamic. For example, the force-length relation is believed to arise from additional crossbridge bonds formed at longer muscle lengths [13]. Similarly, increased calcium ion concentration shifts muscle's force-velocity relation to a different curve. Both processes should affect muscle or ventricle elastance.

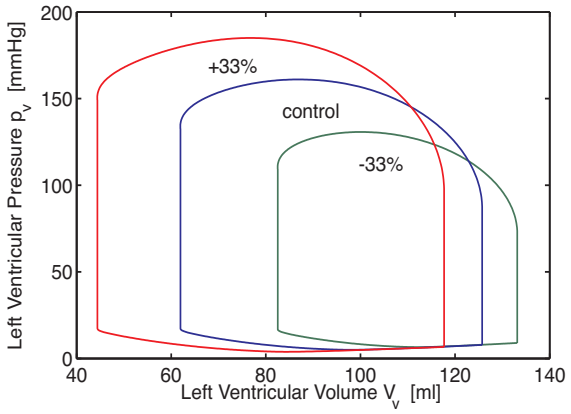

Fig. 6. Work loops computed for the full c.v. system (fig. 1). Varied contractile state via inotropic measures was implemented by increasing and decreasing the model parameter c for all four heart chambers by 33%.

Description of the heart as an isovolumic pressure source seems destined to limit this model to isovolumic behavior. The added feature of continuous volume dependence greatly expands this analytical description to include all of the main features of ventricular pumping.

Equation 1 includes Otto Frank's pressure-volume relation directly, since the model was derived from isovolumic pressure curves at different end-diastolic volumes. Starling's law arises from the same force-length relation. For the isolated ventricle, we observe moderation of increased stroke volume with increased filling due to the increase in afterload produced by the more strongly ejecting ventricle.

Heart models must show inverse sensitivity to afterload, and since this is more a vascular than heart property, most models do. However, the interdependence of increased afterload yielding smaller stroke volume must be moderated by the resulting increase in end diastolic volume via Starling's law. Using eq. 1 to describe each of the heart's chambers as part of a lumped model of the closed cardiovascular system demonstrates the model's ability to show Starling's law accompanying increased afterload, and for changes in total blood volume.

The underlying cause of increased afterload leading to decreased stroke volume is the inverse force-velocity relation of the constituent heart muscle. During higher afterload conditions, whether due to changes in the peripheral resistance of the blood vessels or increased contractility of the heart, the resulting increased pressure requires heart muscle to operate at a lower velocity of shortening. This lower velocity reduces ejection velocity, and hence amount of blood ejected. The proposed model has the force-velocity relation built in without assuming a hyperbolic force-velocity curve.

A functional heart model must allow for changes in heart rate. Heart rate variability is included in the proposed model by scaling the contraction activation function $f(t)$, whose exponential functions describe bond attachment and detachment. The approach presented in this paper includes all of the main features of ventricular pumping with a single equation and set of model constants. At the same time, it is as dynamic as the natural system and does not require adjustment of an adopted elastance curve or force-velocity curve for different loading conditions.

Time-varying elastance models of the heart are unable to isolate ventricular properties from circulatory properties [7]. The generalized pressure description (eq. 1) was shown to well describe the isolated canine left ventricle independent of vascular effects. This paper demonstrates the generalized pressure model's ability to functionally describe each chamber of the human heart. This model embodies a wide range of phenomena using a small number of equations and assumptions. With additional experimental data, it may be developed into a research model for predicting new physiological mechanisms, and to stimulate new questions and experiments, for example, the ejection effect [14]. The latter is the experimental observation of initially lower and then higher than expected pressure during blood ejection [9]. The ejection effect is likely directly related to crossbridge bond formation and should directly affect muscle and heart elastance. Insight gained may lead to better understanding of altered heart function and, ultimately, facilitate clinical diagnosis of cardiovascular disease.

REFERENCES

[1] Starr, I. and Rawson, A.J.: Role of "static blood pressure" in abnormal increments of venous pressure, especially in heart failure. I. Theoretical studies on an improved circulation schema whose pumps obey Starling's law of the heart. Am. J. Med. Sci. 199:27–35, 1940.

[2] Guyton, A.C.: Determination of cardiac output by equating venous return curves with cardiac response curves. Physiol. Rev., 35:123–129, 1955.

[3] Grodins, F.S.: Integrative cardiovascular physiology: a mathematical synthesis of cardiac and blood vessel hemodynamics. Quart. Rev. Biol. 34:93–116, 1959.

[4] Warner, H.R. The use of an analog computer for analysis of control mechanisms in the circulation. Proc. IRE 47:1913–1916, 1959.

[5] Defares, J.G., Hara, H.H., Osborn, J.J. and McLeod, J.: Theoretical analysis and computer simulation of the circulation with special reference to the Starling properties of the ventricle. In: Circulatory Analog Computers, A. Noordergraaf, G.N. Jager and N. Westerhof, eds., North-Holland Publ., Amsterdam, p. 91–122, 1963.

[6] Sagawa, K., Suga, H. and Nakayama, K. (1978) Instantaneous pressure-volume ratio of the ventricle versus instantaneous force-length relation of papillary muscle. In: *Cardiovascular System Dynamics*, J. Baan, A. Noordergraaf and J. Raines, eds., MIT Press, Cambridge, p.99.

[7] Palladino, J.L., Drzewiecki, G.M. and Noordergraaf, A.: Modeling Strategies and Cardiovascular Dynamics, Chapter 8 in: The Biomedical Handbook (3ed.), Volume 1 Biomedical Engineering Fundamentals, J.D. Bronzino, ed., CRC Press, Boca Raton, FL, pp. 8:1-27, 2006.

[8] Guccione, J.M., Costa, K.D. and McCulloch, A.D.: Finite element stress analysis of left ventricular mechanics in the beating dog heart. J. Biomech. 28:1167–77, 1995.

[9] Mulier, J.P.: Ventricular pressure as a function of volume and flow. PhD dissertation, Univ. of Leuven, Belgium, 1994.

[10] Palladino, J.L., Mulier, J.P. and Noordergraaf, A.: Closed-loop systemic circulation model using the Frank mechanism. In: *Mathematical Models in Physiology*, Surv. Math. Indust. 7:177-186, 1997.

[11] Westerhof, N., Elzinga, G. and Sipkema, P. (1971) Artificial arterial system for pumping hearts. J. Appl. Physiol. 31:776.

[12] Hill, A. V.: The heat of shortening and dynamic constants of muscle. Proc. Roy. Soc. London (B) 126:136, 1939.

[13] Gordon, A., Huxley, A. and Julian, F.: The variation in isometric tension with sarcomere length in vertebrate muscle fibers. J. Physiol. 184:170–192, 1966.

[14] Danielsen, M., Palladino, J.L. and Noordergraaf, A.: The left ventricular ejection effect. In: *Mathematical Modelling in Medicine*, M. Danielsen, J.T. Ottesen, eds., IOS Press, Amsterdam, pp.13–28, 2000.