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Left Ventricular Model Parameters and Cardiac Rate Variability

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***Abstract*— A recent functional model of the left ventricle characterizes the ventricle's contractile state with parameters, rather than variables. The ventricle 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 within underlying heart muscle. 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. The model parameters were extracted from measured pressure and volume data from isolated canine hearts. The purpose of this paper is to present in some detail how to describe a particular canine left ventricle from measured data. The model is also extended to include heart rate variability, which arises naturally from the model structure. Computed results compare favorably with measurements both in this study and from the literature.**

I. Introduction

THE heart is a dynamic pump that embodies, at a minimum, a direct relation between filling and output, an indirect relation between load and output, and large variation in output with activity, for example exercise. Creating models of the heart that are equally dynamic is challenging. A recent study presented a new functional description of the heart, proposing a single analytical function built from parameters extracted from animal experiments [1]. This compact model was found capable of describing the heart's response to changes in preload, afterload, and contractile state.

Although the model has been presented in some detail, the method of parameter extraction from a particular heart has not. This paper aims to correct that shortcoming. Also shown is the model's ability to handle heart rate (chronotropic) variability, yielding isovolumic pressure curves consistent with those from the literature.

II. Methods

Ten hearts from dogs weighing between 20–25 kg were isolated and blood perfused. Anesthesia with pentobarbital (25 mg/kg) was administered intravenously and a thoracotomy was performed. The aorta and right atrium were cannulated and connected to an extracorporeal circulation, delivering 37° C oxygenated blood to the beating heart. Coronary perfusion pressure was maintained at 100 mmHg and the heart was isolated. A ventricular cannula was placed to drain the blood and to keep the aortic valve closed. The atria were cut away to expose the mitral and tricuspid valves, and the valves and chordae were then removed. A latex balloon was inserted through the mitral annulus into the left ventricle and sutured in place. The ventricular drain was left in place to prevent blood collection between the balloon and endocardial wall. The sinus venosus was opened for drainage and the heart was suspended in a temperature controlled chamber (37° C). Venous blood was collected and filtered in a cardiotomy reservoir, pumped via constant flow roller pump to a heat exchanger and membrane oxygenator (Medtronic Minimax 1381) for oxygenation and carbon dioxide removal, and then to the aorta. Pacing electrodes sutured to the anterior and posterior ventricular walls paced the heart at a rate below 120 bpm under computer control.

Intraventricular volume was varied in steps with a computer-controlled servo pump, with maximum end-diastolic pressure of 25 mmHg. Ventricular volume was detected by the servo pump position, and ventricular pressure was measured by a catheter-tip pressure transducer (Gaeltec 12CT/4F). Diastolic and systolic isovolumic pressures were recorded as functions of time for different end-diastolic volumes [2].

Ventricular pressure p_v is described as a function of time t and ventricular volume V_v according to [3], [1]:

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

Generated pressure results from the sum of passive and active components, shown on the left and right sides of the plus sign in eq. 1, respectively. The passive term, to the left of the plus sign, includes model parameters a and b, which are derived from ventricular diastolic pressure measurements. a is a measure of passive ventricular elastance. b corresponds to diastolic volume at zero pressure. These two terms correspond to the pressure resulting from stretch of the passive elastic ventricle filled with initial end-diastolic volume.

The active term, to the right of the plus sign, includes model parameters c and d, which are derived from ventricular systolic pressure measurements. This active term arises from the active generation of force by the underlying heart muscle. c, the volume dependent component, is directly related to the heart's contractile state, and varies with changes in inotropy. The volume independent term, d, is constant for a particular heart.

The function $f(t)$ describes the time course of active force generation, a product of contraction and relaxation exponen-

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TABLE I

MODEL PARAMETERS EXTRACTED FROM DOG 10.

Constant	Value
a	0.3887 [mmHg/ml^2]
b	5.857 [ml]
c	4.832 [mmHg/ml]
d	57.41 [mmHg]
τ_c	0.133 [s]
t_p	0.219 [s]
τ_r	0.216 [s]
α	2.88

tials 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 these processes. The denominator normalizes $f(t)$ between the values 0–1. The combination of diastolic and systolic terms yields an analytical function describing ventricular pressure as a function of both time and ventricular volume. t_b is a time constant derived from t_p, τ_c, τ_r and α:

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

Ventricular elastance, E_v, defined as $\partial p_v / \partial V_v$, may be computed as

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

III. RESULTS

Diastolic and systolic isovolumic pressures were measured for various values of fixed end-diastolic volume. Figure 1 shows end diastolic pressures (EDP) measured on dog 10 (lower curve) and the difference between peak systolic pressure and EDP, denoted peak developed pressure (PDP) above. EDP was fitted to the function $a(V_v - b)^2$ using MATLAB's nonlinear regression algorithm, giving the parameter values of a and b shown in Table I. PDP was fitted to the function $cV_v - d$ using MATLAB's linear regression algorithm, giving c and d. Both diastolic and systolic relations had regression coefficients of determination r^2 = 0.99, indicating a close match between measured data and the model.

The activation function $f(t)$ in eq. 1 is related to the buildup of crossbridge bonds during contraction and the dissolution of bonds during relaxation of the underlying cardiac muscle. The time constants τ_c and τ_r may be determined from experimental isovolumic curves by examining the rising and falling (respectively) phases of ventricular pressure plotted versus time. The time constant t_p is time to peak pressure and is directly measured from the isovolumic pressure curve. $f(t)$ measured from dog 10 is shown in Fig. 2. The shape of the isovolumic pressure curve, and consequently for $f(t)$, has

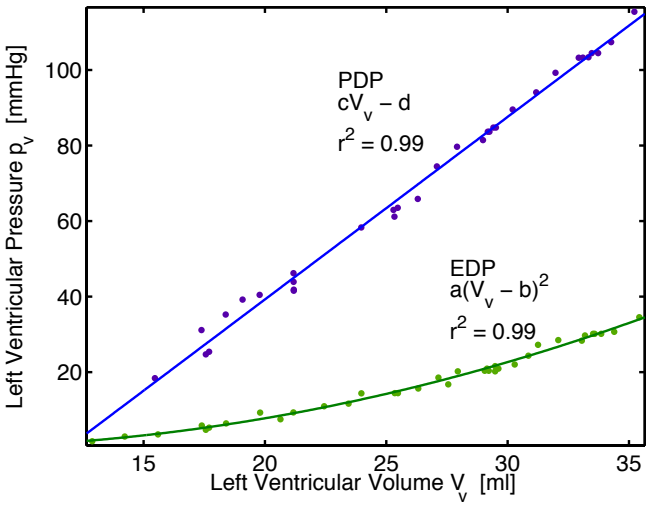

Fig. 1. Dog 10 peak developed pressure PDP and end diastolic pressure EDP measured as functions of initial isovolumic volume V_v. Measured pressures are shown with dots. Solid curves show linear PDP and nonlinear EDP curve fits.

been shown to be little affected by large changes in heart rate, contractility, contraction uniformity and impulse path [4]. At the same time, shape does vary from dog to dog, suggesting that these model time constants need be determined once for a particular heart.

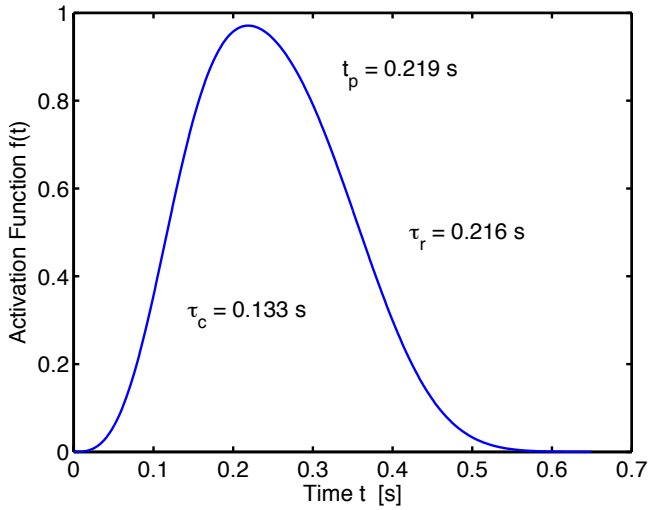

Fig. 2. Dog 10 activation function $f(t)$ and values of parameters τ_c, τ_r and t_p.

Figure 3 shows how well the model (eq. 1) and extracted model parameters (Table I) describe measured pressures for dog 10. Crosses denote measured pressures and solid lines are computed from the model. One equation and one set of parameters is able to well describe the entire set of isovolumic pressure curves. Although not shown, the same one equation and model parameters can describe a wide range of contraction phenomena, including ejecting beats,

isobaric beats, and cardiac work loops for both normal and pathological conditions [5].

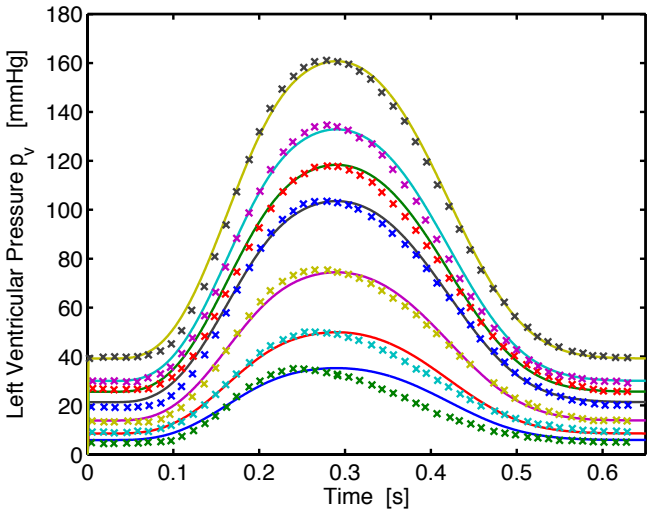

Fig. 3. Dog 10 left ventricular isovolumic pressure curves measured (crosses) and modeled with eq. 1 using the parameter values in Table I. Ventricular volumes range from 17–37 ml.

Heart models must allow for chronotropic interventions that alter heart rate, for example, the negative chronotropic effect of beta blockers, such as Metoprolol and the positive effect of atropine. Experiments show that increased heart rate narrows the time duration of isovolumic pressure and raises peak pressure [4]. A previous attempt at endowing this model with these properties obscured the physiological simplicity of the model by introducing a large number of unnecessary new functions and model parameters, with little physiological significance [6]. Heart rate variability may be modeled simply by scaling model parameter c and the time constants τ_c, τ_r and t_p, as shown in Fig. 4. A 10% increase in heart rate corresponds to a 10% increase in c and a 10% decrease in these time constants, consistent with the isovolumic pressure curves measured by [4].

Studies show that contraction duration of an ejecting beat is always less than that of an isovolumic beat, termed shortening deactivation [4], [7]. The responsible mechanism has been proposed to be calcium ion release from the myofilaments or uptake by the sarcoplasmic reticulum [4]. When the model of eq. 1 is subjected to isobaric contraction conditions this deactivation effect is manifest without separate model assumptions, as shown in Fig. 5. Plotted is an isovolumic beat using the model parameters of dog 10 for EDV = 37 ml and an isobaric beat for the same EDV. The isobaric ventricle ejected into a three-element modified windkessel arterial load.

Comparing initial ventricular outflow during isobaric conditions to the applied isobaric load yields the analog to Hill's force-velocity relation for skeletal muscle [9], as shown in Fig. 6. Initial ventricular outflow is inversely related to load, with a shape similar to the force-velocity relation measured on cardiac muscle strip by [8].

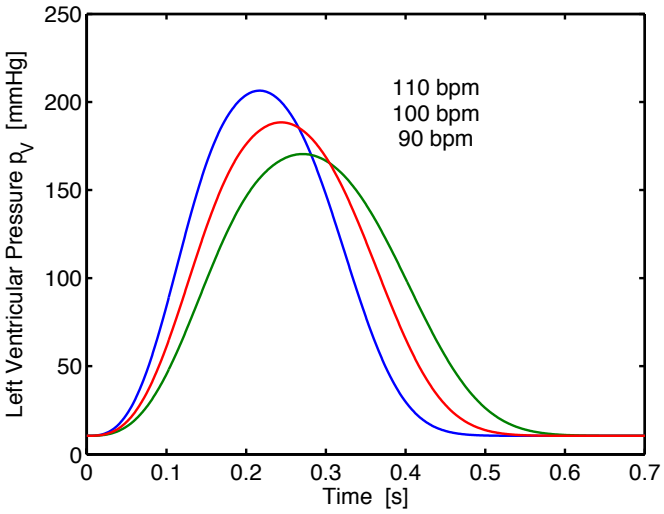

Fig. 4. Isovolumic heart beats computed from the model for three different heart rates. As heart rate increases, peak pressure increases by scaling model parameter c up, and beat duration decreases by scaling the model parameters t_p, τ_c and τ_r down by the same percentage. Results closely resemble those of [4].

Ventricular elastance computed via eq. 4 was found to be strongly sensitive to the heart's contractile state, but insensitive to preload or afterload (not shown). In contrast, defining ventricular elastance as the ratio of p_v/V_v gives time-varying elastance curves that vary considerably with preload, afterload, and contractile state [10].

IV. Discussion

The generalized pressure model (eq. 1) is built from isovolumic pressure curves, yet it possesses the extensive dynamic behavior of the ventricle. Since these mechanical properties arise from the underlying heart muscle, it is revealing to examine how muscle properties are embodied in the model. The Frank-Starling relation for the heart, including both increased isovolumic pressure and increased ventricular outflow during ejecting beats when the heart is filled more (EDV), arises from muscle's force-length relation. The model has both passive (related to a and b) and active (related to c and d) elastic properties that describe increased stretching of the elastic heart chamber, plus increased active generation of force due to formation of muscular crossbridge bonds. As preload of the heart increases, both passive and active terms contribute; the former from increased chamber stretch and the latter from muscle's force-length relation, believed to be due to more optimal myofilament overlap permitting formation of more crossbridge bonds [11].

Since the generalized pressure model is an analytical function, ventricular elastance may be computed by taking the partial derivative of pressure with respect to volume [10]. Equation 4 computed from the classic definition of elastance $\partial p/\partial V$ includes both passive and active terms, the former related to model parameters a and b, and the latter related to c, both of which vary with ventricular volume. Dividing

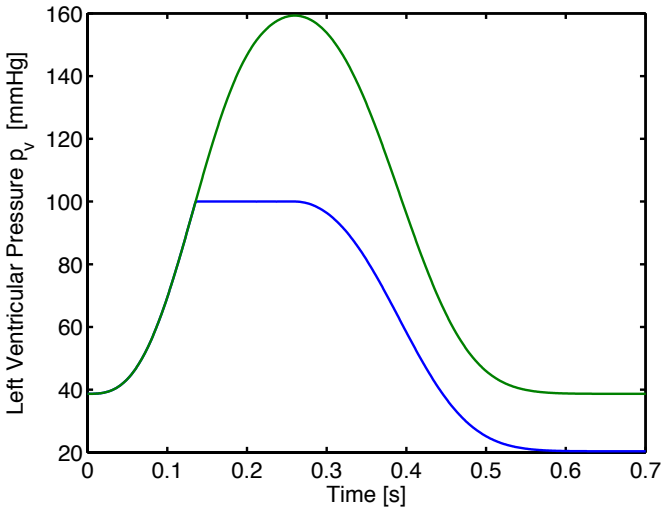

Fig. 5. Isovolumic pressure computed from eq. 1 using dog 10 model parameters (top curve) for EDV = 37 ml, and for isobaric conditions where the applied load is 100 mmHg. The isobaric contraction, which includes blood ejection, ends earlier than the isovolumic beat, denoted shortening deactivation. Results are in agreement with [4].

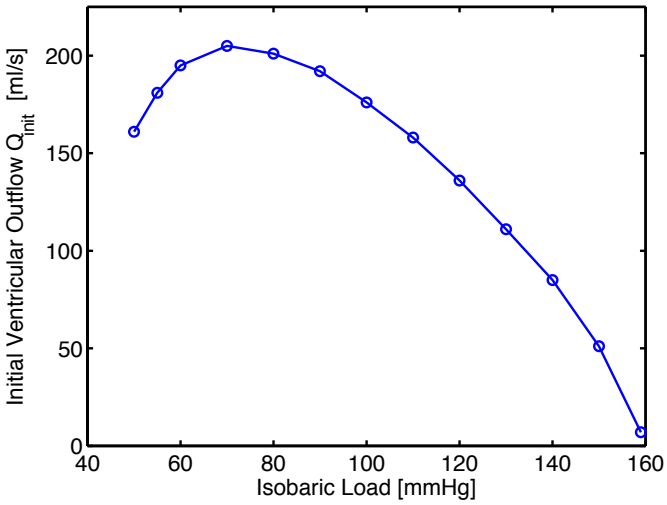

Fig. 6. Initial ventricular outflow during isobaric conditions plotted as a function of isobaric load demonstrates the analog to Hill's inverse force-velocity relation for muscle [9].

ventricular elastance into passive and active components has been proposed by other investigators [12]. The passive term corresponds to increased stretching of the passive elastic chamber and the active term to changes in stiffness associated with the active formation of crossbridge bonds.

Increased afterload (arterial pressure) requires the ventricle to operate at a higher pressure (force) and, therefore, with decreased outflow (velocity). Comparison of the isovolumic and isobaric beats in Fig. 5 suggests that the force-velocity relation is an energy issue. Since blood ejection requires work, less energy is available compared to the non-ejecting heart beat and the beat duration is shorter.

Inotropic changes are believed to influence calcium ion availability, which is thought to control the number of crossbridge bonds formed within the heart muscle. This property is dictated in the model by parameter c, which modifies the force-length relation in the model. As expected, ventricular elastance computed using eq. 4 is directly related to parameter c, reflecting the heart's contractile state [10].

Changes in heart rate have been shown to have two direct effects on isovolumic pressure [4]. When heart rate is increased peak ventricular pressure increases, enacted in the model by increasing the contractile parameter c. Also, the duration of the heart beat decreases, enacted by decreasing the time constants t_p, τ_c and τ_r in equal proportion.

V. Conclusions

The generalized pressure model describes the heart as a dynamic pump. Modeling a particular heart requires extraction of modal parameters from measured isovolumic pressure curves. The resulting model is a single equation that can describe normal and pathological hearts under isovolumic, ejecting, and isobaric conditions [5]. Changes in ventricular pressure associated with changes in heart rate were incorporated by scaling model time parameters. Since model parameters are directly related to heart muscle's contraction mechanism, this model is more dynamic than previous heart models based on time-varying elastance curves that are defined *a priori*. This model may be useful for characterizing the mechanical performance of an individual heart, or as a compact description of the heart in a larger physiological model.

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