The Step Response of Left Ventricular Pressure to Ejection Flow: A System Oriented Approach

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Left ventricular pressure is dependent on both ventricular volume and ventricular ejection flow. These dependencies are usually expressed by ventricular elastance, and resistance, respectively. Resistance is a one-valued effect only, when ejection flow either is constant or increases. Decreasing ejection flow elicits a third effect: a decrease of elastance. The effects of elastance, resistance and elastance depression were modeled in a three-compartment model consisting of a dead-volume compartment, an elastance compartment, and a second series-elastance compartment connected to the elastance compartment by a resistance. This model was identified with the pressure response determined experimentally by imposing pumped constant-flow ejection epochs on isolated rabbit hearts. The experimental flow epochs consisted of two phases of constant flow separated by an increasing or decreasing flow step. It was found that elastance is not changed after the flow step if this is positive or zero. Negative flow steps induced a deactivation of elastance that is linearly dependent on the difference between isovolumic pressure that would be developed at the volume existing at the time of measurement and actual pressure. The parameters found from the identification procedure are ventricular active volume, nondepressed elastance, series-elastance, resistance, and the elastance deactivation factor. The first four parameter values were found in agreement with other results reported in literature. The elastance depression factor is a new parameter that could be of physiological or clinical significance since it may be related to the inability of the force generators in the heart muscle to be restored to their full number, after being inactivated or decoupled by filament sliding associated with ejection. On the basis of the results, an alinear state-model of the ventricle, for arbitrary, including physiological flow patterns is proposed.

Keywords— *Ventricular elastance, Resistance, Ventricular state models.*

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INTRODUCTION

In the last decades much effort has been invested in the search for ventricular indices that could represent the pumping quality of the left ventricle (24,107). Such indices reflect a state, usually called the contractile state of the ventricle. Several lines of research were followed. In one it was realized that ventricular state variables reflect a corresponding state of the ventricular myocardium in its interaction with the complex and variable geometry of the ventricle. A number of papers have been published (6,10,17,70,94,111) describing models of ventricular pressure generation based on a detailed inventory of cardiac muscle mechanics and ventricular anatomy. Global and measurable ventricular phenomena could thus be described; but no useful new definitions of ventricular performance arose from them. One reason is that not only should an index merely be defined by the model, but it also should be possible to actually derive it from physiological or clinical measurements. This would imply an inverse procedure with the detailed physiological model under study. Inverse procedures tend to be unstable if the model used is complicated.

An alternative approach, therefore, has been to start with the physiological measurements proper, using models derived from the data. Campbell *et al.* (21) discuss the interaction between the ventricle and the loading arterial tree on the basis of "global" concepts like elastance and resistance. They could thus define a ventricular state equation as part of a state model that could be identified from experiments.

Such models can very easily be made complex and could accurately describe ventricular phenomena. However, there is a general agreement that such models should be as simple as possible in order to optimally compress information present in the measurements into useful empirical relationships (2,5,7,14,20,25,26,29,48,85,87,108,109). This parametrization, which has a long history (39,82,100), has led to the proposal of a number of contractility indices (3,40,63,68), several of which enjoyed some physiological and even clinical popularity for some time.

An index widely accepted is *ventricular elastance*, introduced by Suga, 1969 (93), who concluded a longer history of investigations (67,100). Its usefulness is based on the fact that under certain restrictions, during ventricular ejection, there is a unique, instantaneous, nearly linear relation between ventricular volume and ventricular pressure (95); according to the equation:

$$P(t) = e \cdot f(t) \cdot [B(t) - B_d] \quad (1)$$

where $P(t)$ is ventricular pressure as a function of time, $B(t)$ is ventricular volume, and B_d is a constant. $e \cdot f(t) = E(t)$ is ventricular elastance. It was demonstrated that the value of e did not change if the contractile conditions within the myocardial muscle did not change. Also, e increased and decreased with positive and negative inotropic interventions (95).

In engineering terms, (1) can be considered as the definition of a ventricular state model (Fig. 1a). The state vector consists of one component, e . Input is $B(t)$, output is normalized pressure $P(t)/f(t)$. In this way, clinically determining elastance is a system identification process. Simple, even trivial as this system is, it is not linear, since the output is not a linear combination of the components of the state vector and the input vector.

Global and empirical models have a limited area of validity. One way of dealing with deviations encountered experimentally consists of defining additional state vec-

FIGURE 1. Ventricular state models. The ventricle is designated by a black box, in which one or more variables define the state. Input: $B_i(t) - B_d$: "active" volume; B_d : "dead volume". Output: $p(t)/f(t)$: time normalized pressure depends on both state and input. Panel (a) Rudimentary state model containing one state variable e which is constant ($\dot{e} = 0$) during systole. Output given by: $p(t)/f(t) = e \cdot [B_i(t) - B_d]$. Since the output is a multiplication of state variable and input $B_i - B_d$, this trivial model is nevertheless a linear. Panel (b) Extended ventricular state model. Elastance e is not constant during systole, satisfying a differential equation to be found from the present study. X : one or more additional state variables to be derived from experimental data.

tor components and thus making the model more accurate. As to the elastance model, it was shown in isolated ventricles (97), as well as in the intact animal (8,20,28,58,91), that deviations occur for greater stroke volumes and ejection fractions. This was also shown for extreme conditions on contractile state by Burkhoff *et al.* (19).

Subsequent work showed that apart from ventricular elastance at least the following effects can be discerned on ventricular pressure during the systolic ejection phase:

(a) During ejection, pressure is attenuated by an amount related to flow intensity being pumped out, and thus to the rate of ventricular volume decrease. This was shown by Campbell *et al.* (20), Hunter *et al.* (47), Shroff *et al.* (87), and Vaartjes and Boom (102). So next to elastance also a resistance is operative in the ventricular model.

(b) Stepwise increasing ejection flow was shown by Boom (13), Campbell *et al.* (23), Covell *et al.* (27), Schiereck and Boom (85,86), Templeton *et al.* (99), Vaartjes and Boom (102), and Yasumura *et al.* (112) to cause a lag in the corresponding pressure drop. This was compatible with the presence of a second, stiffer elastance which appears in series with the primary elastance.

(c) In addition to (b) stepwise decreasing flow exerts an effect on pressure comparable to a decrease of elastance as demonstrated by Boom and Wijkstra (15), and Wijkstra and Boom (109,110).

Analyzing the relationship between ventricular flow and pressure has proved to be complicated by the understandable inclination of researchers to use physiologic flow patterns. Thus, the influence of flow changes, and especially the difference between increasing and decreasing flow, was obscured. Vaartjes and Boom (102), and later Wijkstra and Boom (109) used *constant flow* pulses in analogy with the *constant volume* situation, which in the past clarified basic phenomena in the generation of ven-

tricular pressure (39). In particular, in studying what happens at the start and at the end of the constant flow epochs, that is, by studying the flow step response, the findings of (b) and (c) arose.

For a linear system the flow step response would suffice to derive the transfer function of the system from flow to pressure. However, the response for positive and negative flow steps was not symmetrical, showing that the system is not linear. The present paper starts from the concept that physiological flow can be thought of as a succession of infinitesimally small flow steps. Such steps differ from those used for (b) and (c) in that they do not step from relatively large flow to zero or vice versa. Therefore, the response of pressure to constant flow epochs, stepping from one value to another, is studied. On the basis of the results, it will be proposed how the state model of Fig. 1b can be expanded in order to arrive at a model that quantitatively describes pressure as a function of time for various volume and, hence, flow-time functions.

THEORY

Use will be made of a three-compartment model (Fig. 2). Total ventricular volume B_t is assumed to be composed of three compartments. One, the elastance compartment, with volume B_e obeys

$$P_e(t) = E_e(t) \cdot B_e = \epsilon \cdot e \cdot B_e(t) \cdot f(t) \quad (2)$$

where P_e is pressure in the elastance compartment. Constant e is a scale factor of elastance allowing $f(t)$ to have amplitude 1. Decrease of elastance, as it occurs during ejection, is indicated by $\epsilon < 1$. The time function $f(t)$ has the same meaning as in Eq. 1.

FIGURE 2. Three compartment model of the left ventricle. An active elastant compartment, volume B_e , elastance $E_e(t)$, combined with a constant "dead" volume compartment, volume B_d , is connected to a stiffer series-elastant compartment, volume B_s , elastance $E_s(t)$, by way of a Resistance $R(t)$. The series-elastant compartment communicates freely with the output. Therefore, output pressure $P(t)$ is equal to series-elastant pressure. During ejection, flow through $R(t)$ causes a pressure difference resulting in elastant pressure P_e to be higher than $P(t)$. During isovolumic contraction the pressure difference between B_e and B_s can be equilibrated. Elastances and resistance are all time variable in constant mutual proportions: $\epsilon \cdot R(t) = \mu \cdot E_e(t)$, and $\epsilon \cdot E_s(t) = \sigma \cdot E_e(t)$.

A dead volume compartment as indicated in Eq. 1 is represented by a compartment with volume B_d . A third compartment, the series-elastic, communicates freely with the output of the model and has a volume B_s according to

$$P(t) = \sigma \cdot e \cdot B_s(t) \cdot f(t) = \sigma \cdot e \cdot (B_t - B_e - B_d) \cdot f(t) \quad (3)$$

where $P(t)$ denotes ventricular output pressure. According to Schiereck and Boom (85), $\sigma \gg 1$ so that the series-elastic compartment is appreciably stiffer than the primary elastic compartment. During isovolumic contraction, compartment B_s can be in equilibrium with B_e : $P_e = P_s$, or, $\sigma \cdot B_s = \epsilon \cdot B_e$. In that case no flow occurs through the connection between the compartments. Therefore, flow introduces an additional pressure difference between the compartments given by

$$P(t) - P_e(t) = R(t) \cdot \frac{dB_e}{dt} = \mu \cdot e \cdot \frac{dB_e}{dt} \cdot f(t) \quad (4)$$

where $R(t)$ is resistance, which similarly to series-elastance has been found to be instantaneously proportional to E_e (87,101,102). Quantities σ and μ are thus constants.

Isovolumic (preejection) pressure $P_{iso}(t)$ is given by

$$P_{iso}(t) = \frac{\sigma \cdot \epsilon}{\sigma + \epsilon} \cdot e \cdot (B_t - B_d) \cdot f(t) \quad (5)$$

As can be easily found, by substituting Eqs. 2 and 3 into Eq. 4, B_e is subject to the differential equation

$$\dot{B}_e + \frac{\epsilon + \sigma}{\mu} \cdot B_e = \frac{\sigma}{\mu} \cdot (B_t - B_d) \quad (6)$$

which shows that the primary state model of the ventricle is expanded by B_e which also becomes a state variable.

For the case that ϵ is a constant (which will be shown to be true for constant or increasing flow), and $B_t(t)$ is a linear function of time (constant flow), Eq. 6 can be solved straightforwardly. For instance, in Laplace representation, if $B_t(0)$ is ventricular volume at the start of ejection, and ϕ (constant) is ejection flow; for the constant flow epoch

$$b_t(s) = \frac{B_t(0)}{s} - \frac{\phi}{s^2} \quad (7)$$

Thus

$$b_e(s) = \frac{s^2 \cdot B_e(0) + s \cdot \omega_s \cdot \{B_t(0) - B_d\} - \omega_s \cdot \phi}{s^2 \cdot (s + \omega_t)} \quad (8)$$

where small letters imply variables in the Laplace domain and s is the Laplace variable. Frequencies ω_s and ω_t are reciprocal time constants given by

$$\omega_s = \frac{\sigma}{\mu} \quad \text{and} \quad \omega_t = \frac{\sigma + \epsilon}{\mu}, \quad (9)$$

respectively. The three terms on the right side of Eq. 8 represent a negative exponential, an ascending exponential, and an ascending exponential plus a decreasing linear function, respectively. The linear function corresponds to the linear decrease of volume as results from constant ejection flow.

The Laplace transform of output variable $P(t)/f(t)$ is found from

$$\mathcal{L}\left[\frac{P(t)}{f(t)}\right] = \sigma \left(b_t - b_e - \frac{B_d}{s} \right) \cdot e \quad (10)$$

where $\mathcal{L}[F(t)]$ denotes the Laplace transform of function $F(t)$.

Ventricular pressure can be calculated by substituting suitable starting conditions for $B_t(0)$ and $B_e(0)$ into Eq. 8, and the result for $b_e(s)$ into Eq. 10. We are interested in the response of pressure to flow steps from one value to another. Such steps occur at t_1 in Fig. 3. In this figure the end of the isovolumic contraction phase is at t_0 . Thus, taking first $t_0 = 0$

FIGURE 3. Volume time courses during pumped flow interventions on the ventricle. The epochs between either t_0 and t_1 or t_1 and t_2 , uniformly decrease volumes and thus, imply constant ejection. From t_1 until t_2 , trajectories 1 through 5, have identical time courses. Any difference in developed pressure during this interval is uninfluenced by volume, flow or time differences. Volume-time course 2: positive flow step at t_1 . Volume-time courses 4 and 5: negative step t_1 . Volume-time course 3: $\phi_1 = \phi_2$, no flow switching. Volume-time course 1: $\phi_1 = 0$. Volume-time course 6: $\phi_2 = 0$. Courses 1 and 6 single are constant flow epochs. Equation 13 describes pressure development after a flow step at which $t = 0$ is defined. Since the equation is invariant for starting time it can be applied at either t_0 or t_1 . Application of Eq. 13 with $t_0 = 0$ at volume-time courses 2 through 5 yields a description of the pressure response *during* a constant flow epoch. Application with $t_1 = 0$ at time course 6 ($\phi_2 = 0$) likewise describes the pressure response *following* a constant flow epoch.

$$B_e(0) = \frac{\sigma}{\sigma + \epsilon} \{B_t(0) - B_d\} . \quad (11)$$

This is substituted into Eq. 8 after this equation has been transformed back to the time domain. Thus, the volume of the elastic compartment at t_1 , the time of the flow step in Fig. 4b, is

$$B_e(t_1) = \frac{\sigma}{\epsilon_1 + \sigma} \cdot \{B_t(t_0) - B_d\} + \frac{1}{\omega_{t1}} \left[\frac{\omega_s}{\omega_{t1}} (1 - E) - \omega_s \cdot (t_1 - t_0) \right] \cdot \phi_1 \quad (12)$$

where ϵ_1 is relative elastance during the first constant flow epoch from t_0 to t_1 , and ω_{t1} is the corresponding reciprocal time constant, according to Eq. 9. E denotes an exponential given by $E = \exp\{-\omega_{t1} \cdot (t_1 - t_0)\}$.

Now, Eq. 8 is applied for another time, taking for $B_e(0)$, the value of $B_e(t_1)$ given by Eq. 12. Then, also

$$B_t(t_0) = B_t(t_1) + \phi_1 \cdot (t_1 - t_0) .$$

This is substituted into Eq. 12, and the result together with, again, Eq. 7 into Eq. 8. This leads to an expression for $b_e(s)$ for the condition $t_1 = 0$. This expression is substituted into Eq. 10. After some straightforward algebra we obtain

$$\mathcal{L} \left[\frac{P(t)}{f(t)} \right] = e \cdot \frac{\epsilon_1 \cdot \sigma}{\epsilon_1 + \sigma} \cdot \left[\left\{ 1 + \frac{\epsilon_2 - \epsilon_1}{\epsilon_1} \cdot \frac{\omega_s}{s + \omega_{t2}} \right\} \cdot \left(b_t - \frac{B_d}{s} \right) - \sigma \cdot \frac{\frac{1-E}{\omega_{t1}} \phi_1 + \frac{\phi_2}{s}}{\epsilon_1 \cdot (s + \omega_{t2})} \right] . \quad (13)$$

The time domain equivalent of Eq. 13 consists of four terms on the right hand side

$$\frac{P(t)}{f(t)} = H_1(t) - H_2(t) - Z_1(t) - Z_2(t) . \quad (14)$$

The first term

$$H_1(t) = e \cdot \frac{\epsilon_1 \cdot \sigma}{\epsilon_1 + \sigma} \cdot \{B_t(t) - B_d\} \quad (15)$$

is the primary elastance term. According to Eq. 4, it equals isovolumic pressure at volume b_t . The second term is

$$H_2(t) = e \cdot \frac{\epsilon_1 \cdot \sigma}{\epsilon_1 + \sigma} \cdot \frac{\epsilon_1 - \epsilon_2}{\epsilon_1} \cdot \omega_s \cdot e^{-\omega_{t2}(t-t_2)} * \left(b_t - \frac{B_d}{s} \right) \quad (16)$$

where $*$ denotes convolution over the time interval from t_1 to t . H_2 is unequal to zero only when $\epsilon_2 \neq \epsilon_1$. As will be shown in results, this is the case for $\phi_2 < \phi_1$. Equa-

FIGURE 4. Pressure recordings during single and dual flow epochs. (a) Single flow epochs. From t_m on for the five time courses shown, volume and time are equal, eliminating instantaneous effect of volume and time. Pressure curve 1 is an isovolumic recording: at t_m resistance effect is zero. Time courses 2–5 show increasing constant flow values and increasing flow effects in the pressure tracings at t_m . After t_m time courses 1–5 show a deficit with respect to isovolumic pressure, implying that pressure is deactivated by the stepwise flow decrease occurring at t_m . This deactivation relates uniquely and linearly to the resistance effect at t_m , irrespective of volume history. (b) Dual flow epochs. Time course 1: positive flow step at t_m . Time course 2: no flow step at t_m (single flow epoch as a reference). Time course 3, 4, 5: negative flow steps at t_m . From t_m on, pressure tracings 1 and 2 are at the same pressure value, which is lower than isovolumic pressure. Since for pressure tracing 2 there is no deactivation, the equally lower value also for tracing 1 is due to the resistance effects only. Pressure tracings 3, 4, and 5 are progressively lower which can be ascribed to the negative, deactivating flow steps at t_m . Therefore, generally, at t_o , pressure is depressed as a combination of resistance and deactivation effects. In contrast, at t_m , pressure tracings are affected by resistance effects only.

tion 16, then, represents a low pass filtered step in elastance occurring at t_1 . The filtering occurs with a cut-off frequency of ω_{t2} .

A single flow epoch can be represented by taking either ϕ_1 or ϕ_2 equal to zero. In the first case, (volume time course 1 in Fig. 3) Eq. 13 describes the pressure response *during* a single flow step. In the second case, corresponding to time course 6, the equation represents the pressure response during the isovolumic period immediately after the single flow step. Then b_t represents a constant volume: $b_t = B_t/s$. Accordingly, using Eq. 5

$$\Delta\Pi_d = \frac{H_2(t)}{P_{iso}} = \frac{\epsilon_1 - \epsilon_2}{\epsilon_1} \cdot \frac{\omega_s}{\omega_{t2}} \cdot \{1 - e^{-\omega_{t2}(t-t_1)}\} \quad (17)$$

In Eq. 17 $H_2(t)$ has been normalized with respect to isovolumic pressure, eliminating the influence of volume differences.

In the situation immediately following a constant flow epoch it is expected that $\epsilon_2 < \epsilon_1$ (see results). Thus $\Delta\Pi_d$ is, then, positive and Eq. 17 indicates a pressure deficit in Eq. 14 to build up exponentially to a value equal to the coefficient: $[(\epsilon_1 - \epsilon_2)/\epsilon_1] \cdot (\omega_s/\omega_{t2})$.

Normalizing the third term in Eq. 14 leads to

$$\Delta\Pi_f = \frac{Z_1(t)}{P_{iso}} = \frac{\sigma}{\epsilon_1} \cdot \frac{1 - E}{\omega_{t1}(B_t - B_d)} \cdot e^{-\omega_{t2}(t-t_1)} \cdot \phi_1 \quad (18)$$

Thus, flow ϕ_1 during the first constant flow epoch, after it has been switched to ϕ_2 at t_1 , elicits a switching transient during $t_1 \rightarrow t_2$. This effect has an amplitude $\Delta\Pi(t_1)$ at t_1 equal to the coefficient of the exponential in Eq. 18. Because of the presence of E in Eq. 18, first flow epochs (from t_0 to t_1), not long with respect to $1/\omega_{t1}$, will elicit smaller switching transients.

The combined effect $\Delta\Pi_d + \Delta\Pi_f$, ($\phi_2 = 0$), also is an exponential with a time constant ω_{t2} decaying from a negative value equal to $\Delta\Pi_f$ at $t = t_1$ to the deactivation deficit $\Delta\Pi_d$ at $t \gg t_1$. Actually, Wijkstra and Boom (109,110) showed the normalized pressure transient response following a constant flow in the isolated rabbit heart epoch to be exponential with an asymptotic pressure deficit.

The fourth term in Eq. 14 is given by

$$Z_2 = e \cdot \frac{\sigma^2}{\epsilon_1 + \sigma} \cdot \frac{1}{\omega_{t2}} \cdot \{1 - e^{-\omega_{t2}(t-t_1)}\} \cdot \phi_2 \quad (19)$$

showing how, during the second flow epoch, the flow effect of ϕ_2 builds up to a steady value.

The exponentials in Eqs. 16, 18, and 19 are the result of redistribution of volume between the main and the series-elastic compartments caused by changes in pressure differences across the resistance. These, in turn, were elicited by the flow steps. The exponentials will be referred to as "flow switching effects."

Equation 13 will be validated experimentally, also as its normalized time domain equivalent $\Pi(t)/P_{iso}(t)$. The use of normalized pressure is advantageous since: First, it can be obtained experimentally if steady state isovolumic pressure is known. Secondly, its value is not influenced by effects introduced by the intrinsic time variability $f(t)$, and by differences in volume.

METHODS

Experimental Setup

The effect of stepwise changes in ejection flow was studied in isolated rabbit hearts. Details of the physiological preparation, and the experimental set up have been described in detail elsewhere (102,109). The hearts were quickly removed from the anesthetized animal (Hypnorm) and connected to a perfusion system, supplying oxygenated, Tyrode-like perfusion solution to the coronary arteries. For this, the arteries were cannulated by narrow catheters, which were glued to the cardiac tissue with tissue adhesive (Histoacryl blue). The aortic valves were glued shut in the same way.

The atria were removed from the heart and the ventricle was connected to a pump which was driven by a computer controlled, linear motor. The motor was powered by a high-power output amplifier, which received a fed-back position signal originating from a position transducer attached to the piston rod of the pump. The connection between ventricle and pump was made through a cannula sutured into the mitral orifice. The assembly consisting of ventricle, pump, linear motor, and power electronics had a volume step time of 2 ms.

To stabilize the contraction frequency of the heart, it was stimulated artificially by supplying rectangular current pulses of 2-10 ms duration, and 2-10 A amplitude to two silver electrodes of 10×10 cm. Usually stimulation frequency was 1 Hz. This low frequency was made possible by destroying the A-V node, and thus, inducing a very low spontaneous contraction frequency of the ventricle.

Intraventricular pressure was measured with a catheter tip transducer (Honeywell/Philips Type 9815-156-1,000) positioned deep in the left ventricle and adjusted in such a way that "artifacts" resulting from Bernoulli effects (53,75,76,77) were minimal. Pressure and position signals were sampled with a 12 bit A-D converter at 1 kHz.

Single and dual constant-flow epochs were imposed on the ventricle by corresponding constant velocity movements of the pump piston, according to Fig. 3. Flow patterns were either stepwise increasing or decreasing constant-flow epochs. Starting volumes

$$B_t(t_0) = B_t(t_m) + \phi_1 \cdot (t_1 - t_0)$$

epoch lengths $t_m - t_s$ and $t_e - t_m$, as well as flow intensities ϕ_1 and ϕ_2 during those epochs, could independently be varied, including the case that $\phi_2 = 0$. Within each protocol these variations were always realized in such a way that the volume time course during ϕ_2 stayed unchanged. In this way, any differences in pressure response during ϕ_2 were considered uncontaminated by influences of differing volume, time or flow, during the interval $t_m \rightarrow t_e$.

System Identification

Left ventricular pressure before, during, and after dual flow epochs was also computed by Eqs. 4 and 13. The computed pressures were then fitted to measured data as described previously (109). For the basic time function, $f(t)$, isovolumic pressure also measured, was utilized, and scaled to some suitable amplitude (see results). Using the SIMPLEX method according to Nelder and Mead (71) for the fitting procedure,

iterations were continued until the difference between successive mean RMS errors of calculated pressure, with respect to measured pressure, was less than 10^{-10} . The computations were performed on a time interval including the physiologic ejection period. Parameter values found by the fitting procedure were compared with values obtained by other methods.

RESULTS

Ventricular Pressure During Single and Dual Flow Epochs

Figure 4 shows representative examples of recorded single and dual-flow experiments as announced theoretically by Eq. 13 and Fig. 3. Pressure values of both single- and dual-flow epoch registrations are clearly affected by the changing volumes, and nonzero flow values during the flow intervals. As was explained in the Methods section, piston movements were arranged in such a way that from t_m onwards, during the contraction cycle, volume time courses for different contraction cycles were identical. Hence, differences then observed in pressure time courses could be assumed uninfluenced by instantaneous volume, flow, and time differences.

For the single-flow epoch registration (Fig. 4a) the pressure-time course during $t_s \rightarrow t_m$ is described by Eq. 13 with $\phi_1 = 0$, $t_1 = t_s$, and $t_2 = t_m$, corresponding to volume time course 1 in Fig. 3. From t_m onwards the same equation can be used with $\phi_2 = 0$, $t_0 = t_s$, and $t_1 = t_m$, volume time course 6. During the $t_s \rightarrow t_m$ interval a pressure deficit develops. Pressure stays lower than isovolumic pressure values that would have been generated by the ventricle at volume $B(t_m)$. According to Eq. 13 there are at least two components expected to be superposed in the pressure deficit. First, there is an increasing elastance effect according to Eq. 15. The second component is a resistance effect expected to grow exponentially to a value given by Eq. 19.

At the end of a single constant ejection epoch (t_m), these effects can be separated by examining constant-flow epochs with equal flow but different epoch durations as shown by Vaartjes and Boom (102), (not shown here). This was done by applying Eq. 13 with $\phi_2 = 0$, $t_0 = t_s$, $t_1 = t_m$, and $\epsilon_1 = 1$, varying E by varying $t_m - t_s$. Thus, for the isolated rabbit heart at 37°C , a value for the time constant $1/\omega_{t1}$ could be established of $10.35 \pm 0.26 \text{ ms}$.

After the single flow epoch, immediately following t_m (Fig. 4), according to Eq. 13, there is no resistance effect from ϕ_2 expected: $Z_2 = 0$ since $\phi_2 = 0$. Wijkstra and Boom (109) showed that this part of the pressure response, after normalizing by dividing the signal by isovolumic pressure, is exponential with an asymptotic value staying below 1. This was interpreted as the effects of $\Delta\Pi_d + \Delta\Pi_f$ from Eqs. 17 and 18, respectively. Indeed, the time constant was found equal to $1/\omega_{t2} = 10.44 \pm 0.09 \text{ ms}$, in good agreement with the above mentioned value for $1/\omega_{t1}$. Thus, redevelopment of normalized pressure $\Pi(t) = P(t)/P_{\text{iso}}(t)$ was found to be incomplete as predicted theoretically by Eq. 13. The result agreed quantitatively with Eq. 13 with a nonzero H_2 term. Thus, $\epsilon_2 < \epsilon_1$, and it could be concluded that in the isovolumic phase, following a constant ejection flow epoch, a depression of elastance occurs. In accordance with prevailing literature (for instance Hunter [48]), this depression will be referred to as "deactivation."

According to Wijkstra and Boom (109), the single flow epoch deactivation after t_m is related uniquely and linearly to the resistance effect that was developed at t_m , that is, the value of $\Delta\Pi_f$ in Eq. 18 for $t = t_1$. This equation predicts $\Delta\Pi_f(t = t_1)$ to

depend on flow intensity (ϕ_1) as well as, for the shorter flow epochs, on duration of the interval $t_s \rightarrow t_m$ (because of the flow-switching effect, represented by E). It was observed that deactivation did not depend on flow intensity (ϕ_1) or flow duration (E) separately, but only their combined influence in Eq. 13 at $t = t_1$.

In Fig. 4a the deficit, growing for increasing values of ϕ_1 , ($\phi_2 = 0$), in isovolumic pressure after t_m is clearly visible. The selective dependence of deactivation on the resistance effect at t_m ($= t_1$), allowed the conclusion that there was an intimate link of deactivation with the conditions existing at the negative flow step at t_m , and that no further influence of the flow and volume history of the constant-flow epoch existed.

Thus, *negative* flow steps, like those occurring at t_m (Fig. 4a) induce deactivation. The analysis was based on the predictive validity of Eq. 13 with $\epsilon_1 = 1$, both during the interval $t_s \rightarrow t_m$ as well as during the isovolumic contraction phase before t_s . This implies, that following the *positive* flow step at t_s , there was no deactivation.

Generalizing, we now hypothesize that following any positive flow step, starting at any flow value, deactivation fails to occur. As a corollary, we have to assume that deactivation occurs as a result of negative flow steps.

Turning to Fig. 4b, the depression of pressure at t_e , at the end of a dual constant flow epoch, is thus, not necessarily a mere resistance effect for all flow interventions involved. This is in contrast to the situation at t_m in both Fig. 4a and Fig. 4b. At t_e two flow steps have occurred, one positive at t_s , similar to that in Fig. 4a, and one that was either positive/zero, or negative. Figure 4b shows that for the one increasing step at t_m as well as for the nonstepping flow epoch (which is identical to a single-flow epoch), pressure depressions both at t_m and t_e equal. This is in accordance with the assumption that for those two experiments pressure depressions at t_e do constitute a pure resistance effect. In contrast, the two decreasing flow steps at t_m elicit greater pressure deficits at t_e . Those negative flow steps at t_m are therefore associated with deactivation observable at t_e .

A difference between negative flow steps occurring at either t_m and t_e is that at the latter instant flow steps to zero, leaving the value of ϕ_2 as the only degree of experimental freedom. A possible relationship between deactivation after t_e , and the flow effect at t_e could, therefore, be straightforwardly established for deactivation following single flow epochs, in the same way as it was done at t_m by Wijkstra and Boom (109). In contrast, in Fig. 4b, at t_m flow steps from one nonzero value to another, so that two parameters are involved, both ϕ_1 and ϕ_2 . Consequently, the ensuing depression of pressure cannot be expected to be as simply related to the previous flow effect.

Wijkstra and Boom (109) showed that deactivation brought about by stepping to zero-flow stayed unchanged during the remaining systolic phase. Also, the amount of deactivation elicited by a given amount of flow effect, if imposed at different times during systole, was independent of that time. We will assume that this constancy also holds for the effect of nonzero stepping flow during the interval $t_m \rightarrow t_s$, while flow is ϕ_2 . We will also assume that the additional pressure deficit resulting from the negative flow stepping at t_m can be interpreted as deactivation, that is: a decrease of elastance, as it was elicited at t_m . The amount of deactivation may be related to the flow step parameters at t_m . For this, again, normalized pressure $\Pi(t) = P(t)/P_{\text{iso}}$ will be calculated by dividing relevant pressure values by corresponding values of the isovolumic pressure signal for the same volume.

Depression of Elastance After a Stepped Flow Epoch

After a constant-flow, epoch redevelopment of normalized pressure $\Pi(t)$ is exponential (109) with time constant $1/\omega_{t1}$, and a deactivated value of ϵ . For single constant-flow pulses, the amount of deactivation following the zero-flow step at t_m could be identified in this way.

This procedure can be followed in principle whenever redevelopment of pressure $P(t)$ occurs isovolumically. Then B_t is constant: $B_t = s \cdot b_t$, and the convolution in Eq. 16 reduces to a simple multiplication. This is the case *after* the dual-flow pulse response of Fig. 4b. The quality of an exponential fit of the isovolumic phase following t_e is shown in Fig. 5. It also demonstrates that in the case of a dual flow pulse history redevelopment of $\Pi(t)$, values are exponential.

The asymptotic value of $\Pi(t)$ appears to be well defined since the quality of the fit is high. Similarly to the single flow epoch situation, at the end of the exponential, a plateau is reached of normalized pressure. This can thus be associated with a state of permanently depressed elastance. Figure 6 shows that the level of the plateau values as a function of normalized pressure at t_e . These are the values, which for single-flow responses would correspond to the resistance effect. However, for step-wise decreasing dual-flow responses, after t_e are contaminated with deactivation, elicited at t_m by the negative flow step occurring there.

From Fig. 6 three conclusions were drawn. First, the relation between deactivation, and end-ejection normalized pressure is linear and independent of the flow-step parameters. Second, positive flow steps at t_m elicit a deactivation at t_e independent of their flow step parameters and equal to the deactivation found for a single-flow epoch. Clearly, as discussed above, the deactivation that is brought about in that case results from the negative flow step to zero at t_e only. The third conclusion is drawn from the fact that each of the two protocols shown in Fig. 6 contains one beat with equal flow before and after the step at t_m . Accordingly, the relation between deactivation and the end-systolic resistance effect, as represented by $\Pi(t)$ being unequal to 1, is equal for constant-flow epochs and flow-switching epochs. This strongly suggests, that after either a step, or a constant-flow, elastance is deactivated according to a similar mechanism.

The relation depicted by Fig. 6 is not sufficient to calculate ventricular pressure for any (discretized) variable flow. For this, deactivation *during* changing flow, not only at the end of it, has to be examined.

Depression of Elastance Caused by a Flow Step During Ejection

For assessing deactivation during the interval $t_m \rightarrow t_e$, the method of exponential fitting cannot be applied since volume then is changing, and Eq. 16 does not predict an exponential. The full convolution would then have to be dealt with. However, as stated above, it could be assumed that deactivation induced by the negative flow step at t_m lasted throughout the second constant flow phase and was constant. Figure 7 shows normalized pressure at t_e as a function of the flow of the first flow phase ϕ_1 . For values of $\phi_1 > \phi_2$, thus for those ϕ_1 corresponding with a negative flow step at t_m , normalized pressure at t_e , or $\Pi(t_e)$, decreases for increasing step size. The decrease is stronger if the interval $t_s \rightarrow t_m$ is longer, causing the resistance effect at t_m to be greater. (In the case of Fig. 7, the length of $t_s \rightarrow t_m$ was not large with respect

FIGURE 5. Redevelopment of pressure after a dual flow step. (a) Pressure and volume tracings with negative flow steps at t_m . (b) Normalized pressure calculated by dividing actual measured pressure values by corresponding isovolumic pressure values, as a function of time during and following dual constant-flow epochs. The isovolumic recovery phase following t_m was fitted by an exponential which made the determination of a plateau value possible. This plateau was assumed to reflect deactivation. Nondeactivated values would correspond to a plateau value = 1. For the exponential regression analysis all sampled points between the start of the exponential (t_m) and the end of the plateau (estimated "by eye") were used. The end of the plateau was found to be at 193 ± 25 ms (mean $\pm$ SD), which is well after the end of the physiological ejection period. The total averaged RMS difference between fitted exponential and measured normalized pressure values was calculated to be 0.0077 ± 0.0036 (mean $\pm$ SD), which has to be compared to the nondeactivated value, which = 1. This indicates excellent fit and allows the conclusion that normalized pressure recovers exponentially from a dual-flow epoch, and that deactivation established in this way is well defined.

FIGURE 6. Deactivation represented by the parameter ϵ_2 during the interval $t_m \rightarrow t_o$ (Fig. 5) as a function of normalized pressure at t_m . Filled squares: $\phi_2 = 10$ ml/s, $t_o - t_m = 12$ ms. Open squares: $\phi_2 = 10$ ml/s, $t_o - t_m = 31$ ms. The different parameters for ϕ_2 result in different resistance effects at t_m , reflected by different normalized pressure values Π . Despite this, ϵ_2 values have the same relationships to normalized pressure. In both protocols one flow epoch does not step, and thus is a single flow epoch. It falls on the same relation. Therefore, after both dual and single flow epochs, the relation between deactivation and normalized pressure is unique.

FIGURE 7. Deactivation at t_o caused by flow steps at t_m . Normalized pressure at t_o , representing both the resistance effect and possible deactivation resulting from a (negative) flow step at t_m , as a function of the value of the flow of the first flow phase of a dual flow epoch. Shaded area corresponds to increasing or zero flow steps. For negative flow steps, normalized pressure decreases for increasing flow step magnitude. Since the second flow value is equal for all steps, resistance effects are equal and the difference in normalized pressure at t_o is due to different values of deactivation. Open squares: $t_m - t_s = 15$ ms. Crosses: $t_m - t_s = 22$ ms, $t_o - t_m = 30$ ms, $\phi_2 = 6$ ml/s.

FIGURE 8. Deactivation elicited by step wise changes of ejection flow as a function of normalized pressure. On the vertical axis the resistance effect measured during 12 protocols from 5 experiments at t_m (see Fig. 4b) is plotted. The pressure depressions at t_e were corrected for the resistance effect occurring for positive flow steps. Positive flow steps were shown not to elicit deactivation in this study and thus to exhibit a pure resistance effect only. All dual flow epochs had equal second flow phases regarding volume, flow and time, and, therefore, also had equal resistance effect (see Fig. 2). The resulting deactivation expressed by the value of ϵ at t_e was assumed to be equal to deactivation at t_m (see text). Deactivation is shown to be linearly dependent on normalized pressure regardless of values of absolute pressure, ϕ_1 , $t_m - t_s$, or the ventricle under study. Drawn line: best fitting straight line "by eye." Broken line: the same relation for $\phi_2 = 0$, according to Fig. 7.

to the time constant $1/\omega_t$ of the flow switching effect at t_s , causing the factor containing the exponential in Eq. 19 to be nonzero.) In contrast, both positive and zero-flow steps at t_m result in a pressure decrease at t_e of the equal magnitude. As was reasoned earlier, this represents the resistance effect caused by flow ϕ_2 only.

Since the resistance effect at t_e is different for different ϕ_1 values and also for different ventricles, plots like Fig. 7 are difficult to compare for different situations. Therefore, data as shown in Fig. 7, were replotted so as to compensate for the resistance effect given by the coefficient of the exponent in Eq. 19. For the experiments of Fig. 7, generally, $t - t_1 \gg 1/\omega_{t2}$.) We are looking for a relation between elastance depression at t_m and ejection parameters at that same instant. Since up to this point deactivation depended uniquely on normalized pressure at t_m , this quantity was tried as the independent variable also in the present case. Figure 8 shows the result. Clearly, for determining the amount of deactivation at t_e , and thus at t_m as well, for the ϕ_2 value involved, $\Pi(t_m)$ is the essential determining variable. Again, as at t_e , elastance depression is determined by the value of normalized pressure at the time the depression is elicited. It is not influenced by either ϕ_1 or the length of the interval $t_s \rightarrow t_m$ separately. Only their combined influences on $\Pi(t_m)$ as expressed by the coefficient of the exponential in Eq. 18 appear to be relevant. The relation between deactivation

and normalized pressure is linear for those values of $\Pi(t_m)$ that correspond to negative flow steps at t_m .

The relation shown in Fig. 8 can be represented algebraically by

$$\begin{aligned}\epsilon &= \alpha \Pi & (\phi_1 > \phi_2) \\ \epsilon &= 1 & (\phi_1 \leq \phi_2) .\end{aligned}\tag{20}$$

In (20) α is the slope of the linear part of the relation shown in Fig. 8. It is dependent on ϵ as well as on the horizontal offset in Fig. 8. The offset is not equal to 1 since, for all positive flow steps at t_1 , $\epsilon = 1$. The range of this is dependent on ϕ_2 , since for the largest value of ϕ_1 , for which there is no deactivation, it holds that $\phi_1 = \phi_2$.

System Identification

The pressure generated by the left ventricle was simulated using the three-compartment model introduced in the Theory Section by Eqs. 4-22. Following Wijkstra and Boom (110), the time function $f(t)$ was derived from measured isovolumic pressure by

$$f(t) = \frac{P_{\text{iso}}}{B_t - B_d} .\tag{21}$$

Implying that

$$\frac{\sigma \cdot \epsilon_1}{\sigma + \epsilon_1} e = 1\tag{22}$$

taking for B_t the volume at t_e , and for ϵ_1 undeactivated elastance before t_m : $\epsilon_1 = 1$. Flow ϕ_1 was taken as the experimental variable. The computation was started with educated guesses for $B_t - B_d$, σ , μ , and ϵ_2 , deactivated elastance between t_m and t_e . Elastic volume B_e was calculated for the first constant flow phase of a dual flow epoch. At the moment of the flow step (t_m), ϵ_1 was replaced by a tentative value ϵ_2 , and the computation of B_e was continued. Thus, $B_e(0)$ for the second constant-flow phase was equal to the value of B_e calculated at the end of the first.

Ventricular pressure until t_e was computed by the time-domain equivalent of Eq. 13. Following t_e , a third deactivation elastance was computed from $\epsilon_3 = a \cdot \Pi(t_e) + b$, and the computation of pressure was continued until 200 ms after stimulation. The RMS deviation of the calculated $P(t)$ from the experimental was computed and the process was iterated until minimal RMS error. In order to test the sensitivity of the model for the presence of deactivation in the model, two more cases were investigated in this way. In one case, elastance was assumed constant, both during flow stepping, and at the end of the dual-flow pulse: $\epsilon_3 = \epsilon_2 = 1$. In a second case, deactivation was assumed to be elicited at the end of the dual-flow pulse only. A representative example of the comparison of the experimental, and the fitted result is shown in Fig. 9. The estimated values of the model parameters are given in Table 1. Figure 9 shows that the three-compartment model gives satisfactory fitting results, be it only when, at all negative flow steps, deactivation is assumed to occur. Table 1 shows that RMS

FIGURE 9. Fitting of the three-compartment model on experimental dual-flow epochs. All panels: $\phi_2 = 6$ ml/s, $t_o - t_m = 6$ ml/s. The fitting was performed in the interval 55–200 ms after stimulation of the ventricle. P_{iso} : isovolumic pressure; P_{fit} : simulated pressure; P_{exp} : measured pressure; ΔP : absolute difference between simulated and experimental pressure. (a1), (b1), (c1): $\phi_1 = 3$ ml/s, $t_m - t_s = 15$ ms. (a2), (b2), (c2): $\phi_1 = 21$ ml/s, $t_m - t_s = 15$ ms. (a1), (a2): model without deactivation. (Figure continued on following two pages.)

errors are higher if such deactivation is not incorporated. Also, parameter values found for that case are different from those found with the complete model. For instance, series-elasticity would be underestimated without deactivation while resistance would be overestimated.

FIGURE 9 continued. (b1), (b2): model with activation elicited at end systole only.

DISCUSSION

Contrary to that proposed in the present study, global models of the left ventricle containing elastances and resistance only, are not capable to accurately describe ventricular pressure generation. Campbell *et al.* (22) examined a number of such models and concluded that all had shortcomings during the second half of the ejection phase. The results of the present study explain this finding. The physiologic flow time course has a triangular shape. During the first third of ejection, flow is increasing to

FIGURE 9 continued. (c1), (c2): model with activation elicited both at end-systole (t_e) and at the time of the flow step (t_m). A good fit is obtained with (c1) and (c2) only, demonstrating the necessity of deactivation in the model as well as its correctness.

a crest value (88). No deactivation is expected during this ascending phase and elastance-resistance models can be adequate. In contrast, in the second two thirds of systole, flow decreases, and according to the results of the present study, *elastance depression* will manifest itself. This phenomenon is not accounted for by pure

TABLE 1. Parameter values of the model found after fitting two dual-flow epochs with different flow parameters to experimental results.

Condition	Parameter							RMS error (mmHg)
	$B_t - B_d$ (ml)	e	σ (s)	μ	ϵ_3		ϵ_2	
					a	b		
$\epsilon = 1$	1.76	1.40	2.48	0.075	0	1	1	3.19
$\epsilon < 1$ after t_e	1.53	1.27	3.73	0.051	0.83	0.26	1	1.71
$\epsilon < 1$ after t_m	1.48	1.17	5.8	0.035	0.77	0.30	0.91	1.24

Symbols used: $B_t - B_d$, e , σ , μ (see text); ϵ_3 : deactivation factor after the end of ejection. a and b are the parameters in: $\epsilon_3 = a \cdot \Pi(t_e) + b$. First row: no deactivation; second row: deactivation after t_e ; third row: deactivation after both t_e and t_m . In the third row the RMS error is minimal, indicating optimal fit. Estimated active volume $B_t - B_d$ has a realistic value for the rabbit ventricle. Leaving out deactivation from the model underestimates series-elasticity and overestimates resistance in the ventricle.

elastance-resistance models. On the cellular (59), as well as on the muscular (16,18, 33,73) level, it has long been known that the capability to redevelop force after fiber shortening, is negatively affected. The present study, however, indicates that it is the shortening itself, rather than the state of having shortened that is associated with deactivation.

Others have found that elastance amplitude in the intact ventricle is not constant during systole. A number of ejection parameters were claimed to influence the time course of elastance. Increasing stroke volume and/or ejection fraction (8,97), as well as the preload to the ventricle (8,28), were shown to result in a decrease of elastance. In contrast, after increasing afterload, the opposite occurred (8,31,84). These findings were confusing since, for instance, preload, either to heart muscle (38,44), or to the intact ventricle (61,84), as well as afterload (84), were found to enhance the contractile state. The results of the present study suggest how at least parts of this seeming contradiction can be resolved. Deactivation is associated with flow decrease, to an extent closely linked to the level of the flow effect measurable at the instant that flow actually changes. Interventions that result in higher flow will also result in a greater flow effect (consisting partly of resistance and partly of deactivation accumulated as a result of earlier flow decreases). A higher flow also implies a more pronounced flow decrease in the latter phase of ejection. This stronger decrease, together with the greater flow effect, yield a greater deactivation. Afterload or preload increases results in smaller or greater ejection flow, respectively.

The conclusion of the present paper could not have been drawn by the above authors, since they applied physiological flow patterns, in an almost self-evident approach. The study of the present paper, showing that it is flow decrease that is necessary to make deactivation manifest, was based on the reasoning that if flow is expected to have influence on elastance, flow epochs consisting of one or more constant flow phases, would reveal the dependence more readily. This reasoning is analogous to the approach in the past, when it was felt that since ventricular volume

probably was the prime determinant of pressure, studying the ventricle under constant volume conditions would be illuminating (39,82). As it turned out, a constant flow epoch is the only flow pattern eliciting elastance depression at one instant only; at the very end.

Whereas, it is clear that the decreased capability of the ventricle to regenerate pressure after a negative flow step is compatible with a change in elastance, it might be questioned to what extent parameters other than elastance are also in play. Within the scope of the global three-compartment model posed in the present study, one or more of the parameters *primary elastance*, *resistance*, or *series elastance* are candidates for change after a negative flow step. If none of them changed, this would be a reason for rejecting the model. During the isovolumic recovery phase, after a constant-flow step, normalized pressure accurately follows an exponential time course (109,110). Its time constant did not significantly differ from the time constant measured for the switching-on effect observed directly following the positive flow step at the beginning of the constant-flow epoch. This latter, positive flow step does not induce deactivation. The time constant, according to the model is given by

$$\tau = \frac{1}{\omega_t} = \frac{\mu}{\sigma + \epsilon} . \quad (23)$$

Series-elastance σ is appreciably greater than depressed elastance ϵ . Therefore, the only two possibilities which do not affect τ appreciably are: a change in both μ and σ keeping their ratio approximately constant, or a change of ϵ . The simulations were done to check this point, among others. It was shown that a satisfactory model fit resulted when assuming that μ was not changed by the negative flow steps at t_m . If μ is not changed, σ cannot be changed without changing the time constant. It is therefore concluded that also during flow, a negative flow step results in a depression of elastance ϵ .

A global model such as that proposed in the present study gives no direct clues as to the physiological significance of its structure and its parameters. A primary aim of global models of the ventricle is to serve as a tool for the definition and the experimental derivation of ventricular performance indices that may be of clinical or physiological significance. For instance, the way in which the ventricle matches its performance to the properties of the arterial tree can be expressed in terms of a global model (106). Nevertheless, the response of the ventricle to step-wise flow changes is so conspicuously transparent (see for instance Fig. 8), that it is tempting to interpret it in terms of physiologic functioning of myocardial muscle. The way to do so would be through the construction of a detailed ventricular model, based on actin-myosin filament interaction (36,42,49,56,78), and ventricular geometry (17,30,41,46,54,65,66,79,81), as well as anatomy (4,81,90,92,104), and electrophysiology (10). However, such studies seldom attempt to quantitatively predict ventricular performance in terms of compressed data models as the present three-compartment model. Usually, a force-velocity relation for heart muscle is built in (6,10,17), but then it is not explained how ventricular pressure-flow relations are linear (87,102), whereas force-velocity relations for cardiac muscle are hyperbolic (24,89). One reason for the difference might be that ventricular geometry, both with respect to muscle fiber orientation and complexity

of shape, has not been accounted for in sufficient detail. Without a global model available this discrepancy would not have been detected.

The same holds true for deactivation of elastance in the ventricle. This phenomenon plausibly corresponds with a depressed force-length relation in cardiac muscle (18,33). It is interesting to note that Edman and Nilsson (33) found that in cardiac muscle, after constant velocity shortening contraction, force is decreased to an amount related to the shortening velocity. However, in the simpler geometrical models, the relationship between shortening velocity and ejection flow is not linear, so that the transformation is quantitatively not self-evident.

The remarkable link between pressure depression during flow and the inability of the ventricle to regenerate full isovolumic pressure, suggests that the two phenomena are an expression of the same myocardial mechanism. Also, here a simple translation to myocardial events is difficult. Force and pressure are thought to be generated by discrete molecular force generators, the number of which determines the amount of force, or pressure (34). Shortening of muscle fibers is thought to couple generators to an amount closely linked to shortening velocity, a mechanism that can quantitatively explain the force-velocity relation (9,35,51). Elastance depression, then, corresponds to the property that the muscle is not capable of regenerating the same amount of force generators as before decoupling. It is not implausible that the more force generators were decoupled, the more recouplable generators were lost.

One way to account for the link between flow effect and elastance depression consists in the assumption that it is decoupling itself that introduces the depression of elastance. Each force generator that is decoupled, then, would naturally cause a fixed amount of depression of regeneration capability. This view implies that elastance depression occurs during flow instead of after the end of it. Moreover, decoupling of force generators is a reversible process. More generators are decoupled than, at the end, correspond with the number of generators left, since during flow a number are recoupled as well (35,51). The implication would be that part of resistance, as measured during the present study, is identical with elastance depression after the end of ejection. However, no definitive conclusions can be drawn on the basis of the material presented in the present study. It may also be questioned whether this distinction would be observable in a global model of the ventricle.

The results summed up in Fig. 8 now make it possible to propose a complete state model of the generation of left ventricular pressure for arbitrary, including physiologic flow patterns. Such a model should take into account the observation reported on in the present paper. Of these, the dependence of deactivation, ϵ , on instantaneous normalized pressure, $\Pi(t)$, (or flow effect, which is equivalent) is the most essential. This relationship is illustrated by Fig. 8, and expressed by Eq. 20. However, this complicates Eq. 6 because therein ϵ was introduced as a constant. If we admit, nevertheless, ϵ to be variable, while requiring that Eq. 6 retains its validity, this would change Eq. 6 into an ailinear differential equation.

Furthermore the findings of Eq. 20 have to be expanded since, in the present study, only one nonzero ϕ_2 value was studied extensively. However, Fig. 4 shows that for the case $\phi_2 = 0$ (isovolumic recovery condition) the relation between elastance depression ϵ and Π is steeper than for ϕ_2 not equal to zero. This makes an estimation of $d\epsilon/d\phi \approx \Delta\epsilon/\Delta\phi$ possible. The estimated values of $\Delta\epsilon$ and $\Delta\phi$ are indicated in Fig. 8.

Thus

$$\frac{d\epsilon}{dt} = \frac{d\epsilon}{d\phi} \cdot \frac{d\phi}{dt} \approx \frac{\Delta\epsilon}{\Delta\phi} \cdot \frac{d\phi}{dt} \quad (24)$$

and Eq. 20 for negative values of $d\phi/dt$:

$$\frac{d\epsilon}{dt} = \left[\beta \cdot \Pi + \alpha \cdot \frac{d\Pi}{d\phi} \right] \cdot \frac{d\phi}{dt}, \quad \frac{d\phi}{dt} < 0 \quad (25)$$

$$\frac{d\epsilon}{dt} = 0 \quad \frac{d\phi}{dt} \geq 0 \quad (26)$$

were $\beta = d\alpha/d\phi$.

In Fig. 8 the case $\phi_2 = 0$ is also indicated. It shows that $d\epsilon/d\phi$ depends much more on variations in α than on those in Π . Therefore the second term on the right in Eq. 25 will be neglected.

Although the value of $\beta = d\alpha/d\phi$, thus, could be estimated from Figs. 6 and 8, it is more realistic to consider it as an additional parameter to be estimated from measurements. Also, as yet, there are no further data available on how this parameter, that is expected to be closely linked to the contractile machinery of the cardiac muscle in various mammalian species, including humans, depends on various physiologic conditions.

Substituting Eqs. 3 and 5 into $\Pi(t) = P(t)/P_{\text{iso}}(t)$ and applying the result of this into Eq. 25 finally yields:

$$\frac{d\epsilon}{dt} = \beta \cdot (1 + \sigma) \cdot \left[1 + \frac{B_e}{B_t - B_d} \right] \cdot S \left\{ \frac{d\phi}{dt} \right\} \quad (27)$$

$$\frac{dB_e}{dt} = -\frac{\epsilon + \sigma}{\mu} \cdot B_e + \frac{\sigma}{\mu} \cdot (B_t - B_d) \quad (28)$$

The function $S(f)$ being defined as a multiplication by the value of its argument if this is positive, otherwise by zero.

Equations 27 and 28 constitute the description of an alinear state model of the left ventricle with state variables B_e and ϵ . Output $P(t)$ can be determined from the state variables by (3). The states are controlled by inputs $B_t - B_d$ and $d\phi/dt$. Parameter β is a candidate for investigation regarding its clinical significance. Identification of alinear state models, currently, is an area of intensive study in systems engineering. The field has been reviewed by Nijmeijer and Van der Schaft (72).

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