Index for cardiac dysfunction of left-ventricular filling phase

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Abstract

Left ventricular (LV) diastolic dysfunction often precedes systolic dysfunction. Hence, the assessment of LV diastolic function is imperative for the early diagnosis of the disease, and this phase of the cardiac cycle has not been adequately analyzed. Thus, this study aims to develop a model of LV diastolic performance, in terms of LV compliance, resistance-to-filling and inertia, which are the indices of LV-pump's filling performance or behavior. Therefrom, we have developed a novel filling-phase index (*FLI*) as well as the diastolic pressure-time profile and provided the basis of their noninvasive determination. By evaluating the range of *FLI*, it is possible to differentially diagnose diastolic dysfunction.

1 Introduction

The human LV is the chamber of the heart that is responsible for pumping blood through the circulatory system to provide nutrition to the cells of the organ systems. LV diastolic dysfunction often precedes systolic dysfunction [1]. Thus, the assessment of LV diastolic function is useful for the early diagnosis of deteriorating LV function.

Traditionally, the major determinants of LV function have been end-diastolic pressure and volume, stroke volume & stroke power and ejection-fraction. However, these characteristics do not intrinsically assess LV pump function or dysfunction during the filling-phase in the form of LV compliance and resistance-to-filling. In addition, indices derived from the data of LV pressure require cardiac catheterization, which makes them less attractive for routine clinical applications. The development of high-resolution ultrasonic imaging and

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echocardiography has however made possible non-invasive measurement of trans-mitral flow, and has led to a geometrical growth of studies related to diastolic function [2].

Models based on a time-varying elastance or (its inverse) compliance have dominated characterization of the LV as a pump. Most current lumped ventricular models employ bulk compliance. The classical definition of compliance (*C*) relates differential volume *dV* and pressure *dP* [3]:

$$C = \frac{dV}{dP} \tag{1}$$

where V(t) & P(t) are LV volume and pressure with respect to start-of-filling values. On the other hand, we can define LV elastance [3] as

$$E = \frac{dP}{dV} \tag{2}$$

Noordergraaf et al [4] proposed the following functional relationship:

$$P = F[\frac{d^2V}{dt^2}, \frac{dV}{dt}, V] \tag{3}$$

wherein the coefficients of these volume-related quantities may also be regarded to be time-variant.

In the classic volume on "cardiac mechanics" [5], some pioneering rigorous works on LV performance were brought together, for the first time. Another pioneering advance in characterizing LV performance was made by evaluating in-vivo intra-LV flow velocity and pressure distributions in humans [6]. Our study may be deemed to contribute to noninvasive assessment of LV filling-phase (or diastolic dysfunction).

2 Modeling LV Filling-function

A. Governing Equation:

During diastolic-filling phase, the left atrium pumps blood into LV (refer Figure 1), and the LV pressure profile is the response to it. The associated governing differential equation can be put down as:

$$M\ddot{V} - LVP + LV \; Elastic\text{-}recoil \; pressure \; (P_e) = 0 \tag{4}$$

along with (i) $P_e = V / C + P_{eo}$; (ii) $LAP - P_2 = R\dot{V}$;

(iii) $LVP = P_3 = P_2 + \frac{\rho \dot{V}^2}{2}$.

where t represents the time variable (in *second*)

V represents volume of LV in *ml*

LVP represents pressure of the LV, in mmHg (hereafter symbolized by P)

P_{co} represents elastic recoil pressure at V=0

R represents resistance to filling due to flow in the mitral valvular (mv) orifice-tract

M the inertial term in $mmHg/(ml/s^2)$, corresponds to LV wall-density (ρ)/(LV surface-area/wall-thickness) ($= \rho h/4\pi R^2$, for a spherical LV model)

C represents the compliance term, in *ml/mmHg*. We have employed *mmHg* instead of *Pascal*, because in medicine it is customary to make pressure measurements in *mmHg*.
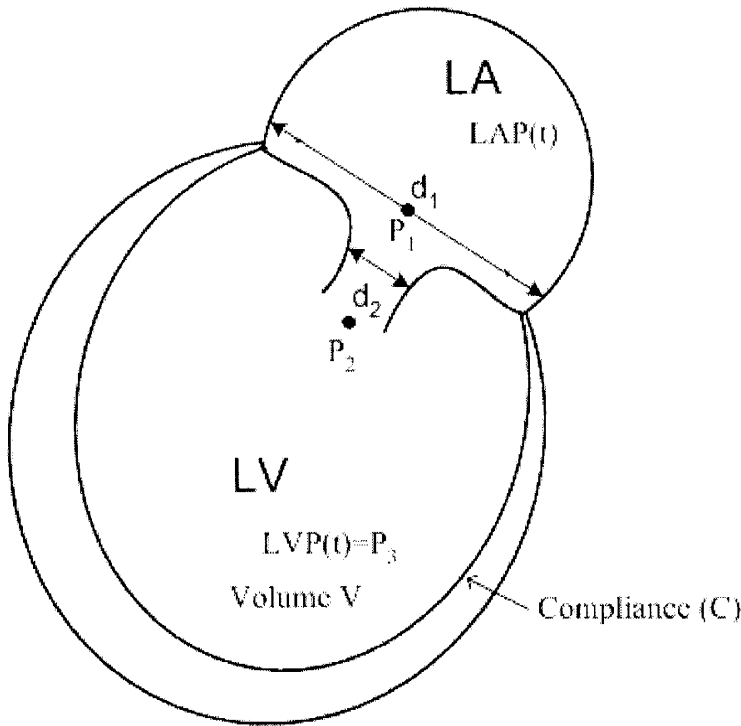

Figure 1: Schematic of the LV longitudinal cross-section, showing the mitral-valvular tract and the pressure P_1, P_2, P_3 locations.

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We can rewrite equation (4) as follows:

$$MV̈ + \frac{V}{C} = LVP(t) = P_3 - P_{co} = P_2 + \frac{\rho V_2^2}{2} - P_{co} = LAP(t) - R\dot{V} + \frac{\rho V_2^2}{2} - P_{co} \qquad (5)$$

or as

$$M\ddot{V} + R\dot{V} + \frac{V}{C} = LAP(t) + \frac{\rho V_2^2}{2} - P_{co} \qquad (6)$$

where $A_2 V_2 = \dot{V} = Q$, and R represents resistance-to-filling through the mitral-valve orifice.

At t=0 (at start of filling), because of no flow, we have $\dot{V} = 0$ (along with $\ddot{V} = 0$), therefore,

$$P_{co} = LAP(t = 0) + \rho V_2^2 / 2 \qquad (7)$$

and hence we obtain:

$$M\ddot{V} + R\dot{V} + \frac{V}{C} = LAP(t) - LAP(t = 0) \qquad (8)$$

Now, $\Delta P = LAP - LVP$, the pressure-difference in the mitral-valvular orifice tract, can be related to the echocardiographically-derived mitral-valvular orifice geometry (Figure 1) as:

$$\Delta P = P_1 - P_2 = LAP - P_2 = \rho V_2^2 / 2 - \rho V_1^2 / 2 + \rho k_c V_2^2 / 2$$
$$= \frac{\rho Q^2}{2} [\frac{1}{A_2^2} - \frac{1}{A_1^2} + \frac{k_c}{A_2^2}] \qquad (9)$$

wherein (i) A_1 & A_2 are cross-sectional areas, whose diameters d_1 & d_2 are depicted in Figure 1. (ii) k_c is the coefficient representing the pressure-loss due to retain of the mitral valvular orifice.

We can combine equations (5, 6 & 9) to yield:

$$M\ddot{V} + R\dot{V} + \frac{V}{C} = LAP(t) - LAP(t = 0)$$
$$= P_2 + \frac{\rho Q^2}{2} (\frac{1}{A_2^2} - \frac{1}{A_1^2} + \frac{k_c}{A_2^2}) - LAP(t = 0) \qquad (10)$$
$$\overset{or}{=} (P_3 - \frac{\rho Q^2}{2A_2^2}) + \frac{\rho Q^2}{2} (\frac{1}{A_2^2} - \frac{1}{A_1^2} + \frac{k_c}{A_2^2}) - LAP(t = 0)$$
$$= P_3 + \frac{\rho Q^2}{2} (-\frac{1}{A_1^2} + \frac{k_c}{A_2^2}) - LAP(t = 0)$$

Now, since t=0,

$$LAP(t=0) - P_2(t=0) = \rho V_2^2(t=0)/2 = \rho Q^2(t=0)/2A_2^2 = 0$$

$$\therefore \;\; LAP(t=0) = P_2(t=0) = P_3(t=0) \tag{11}$$

Equation (10) can here be rewritten as

$$M\ddot{V} + R\dot{V} + \frac{V}{C} - \frac{\rho \dot{V}^2}{2}(G) = P_3(t) \tag{12}$$

where the "G" (for geometry) term can be obtained from echocardiography.

B. Nonlinear Compliance

We can also express the LV compliance term in equation (4) and (12) in a different format, to incorporate increase in elastance (1/compliance) with increase in LV volume, as

$$P_e = C_1 e^{C_2 V} \tag{13}$$

$$E = \frac{1}{C} = \frac{dP_e}{dV} = C_1 C_2 e^{C_2 V} = C_2 P_e \tag{14}$$

which makes for time-varying elastance and compliance (C). So then, from a rigorous viewpoint, our governing equation becomes

$$M\ddot{V} + R\dot{V} - \frac{\rho \dot{V}^2}{2}(G) + C_1 e^{C_2 V} = P_3(t) = k_1 e^{k_2 t} \tag{15}$$

which we need to solve for V(t). However, for the sake of simplicity, we will:
  (i)   assume that the pressure drop in the mitral valve orifice tract is small;
  (ii) the $\frac{\rho \dot{V}^2}{2}(G)$ term is small in comparison with the $R\dot{V}$ term;
  (iii) the compliance term is $1/C$ (as in equation 9), and not $C_1 e^{C_2 V}$.

Then our simplified equation (12) is

$$M\ddot{V} + R\dot{V} + \frac{V}{C} = P_3(t) = k_1 e^{k_2 t} \tag{16}$$

where k_1 & k_2 are constants to be determined, so that P_3(t) can then be obtained.

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For a solution of equation (13), we can put down

$$V = c_1 e^{r_1 t} + c_2 e^{r_2 t} + c_3 e^{k_2 t} \tag{17-a}$$

in terms of the parameters (M, R, C, k_1, k_2) of equation (14), as:

$$r_1 = (-R + \sqrt{R^2 - 4M/C})/2M$$
$$r_2 = (-R - \sqrt{R^2 - 4M/C})/2M \tag{17-b}$$
$$c_3 = k_1/(k_2^2 M + k_2 R + 1/C)$$

3 Defining Novel Filling Index

The parameters in equation (17) have physiologic relevance, are independent of each other, and can help to differentiate between normal and disease states of LV filling. However, we can also formulate an index (containing these parameters), to totally characterize the performance of LV diastolic filling, as

$$FLI = \sqrt[3]{\frac{RM}{C}} \tag{18}$$

wherein a high value of *FLI* corresponds to the pathological state of the LV. All of the quantities in equation (18) can be calculated from clinical-data simulation of equations (17-a & 17-b). However, the volume can be measured non-invasively by echocardiography, and hence *FLI* can also be evaluated non-invasively.

4 Patient data acquisition

Herein, the LV geometry, volume and pressure data have been obtained from cineangiography measurements, in order to validate the model. This data is displayed in Figures 2 & 3. Therein, the LV is modeled as a sphere of radius R and wall-thickness h, so that (i) $4\pi R^3/3 = LV$ volume at any instant, and (ii) $4\pi R^2 h = LV$-*wall volume* = constant throughout the cardiac cycle.

In Figure 2, we present one set of cineangiographically-derived LV spherical-model dimensions, equivalent radius R and wall-thickness (h) of the LV, during a cardiac cycle. Additionally, we have also monitored: *HR (heart rate)*=75 beats/min, *CO (cardiac output)*=5.475 l/min and *EF (Ejection fraction)*=25.3%.

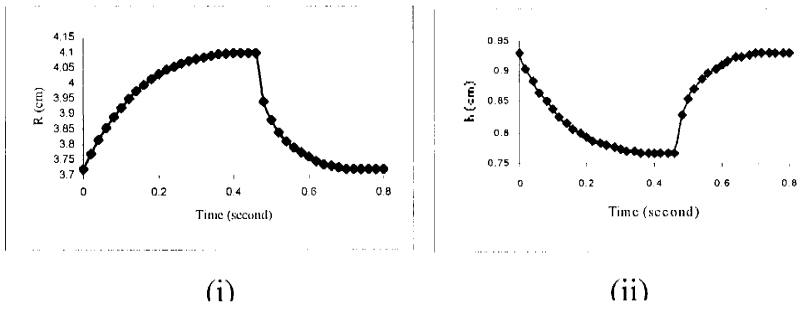(i)   (ii)

Figure 2: Cineangiography-derived data on LV geometrical parameters. (i) chamber equivalent-radius (R) with time and (ii) wall-thickness (h) with time of LV throughout the cycle; $R = \sqrt[3]{LV \text{ volume}/4\pi}$.

Figure 3 depicts LV pressure vs. time and volume vs. time. This data is employed in the application of the model-analysis.
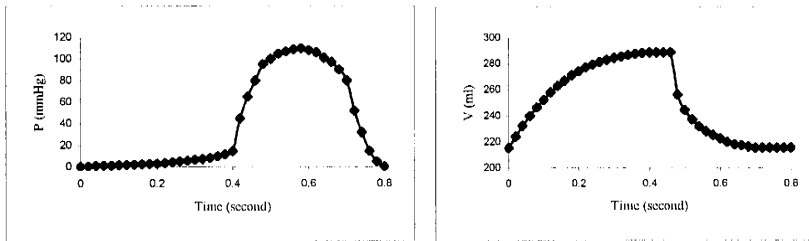

Figure 3: Cineangiography-derived data on LV pressure and volume vs. time.

5 Model application & case study

Figure 4 illustrates the monitored LV-volume data. This patient does not have stenosis or regurgitant mitral valve. Hence, we can justifiably neglect the term
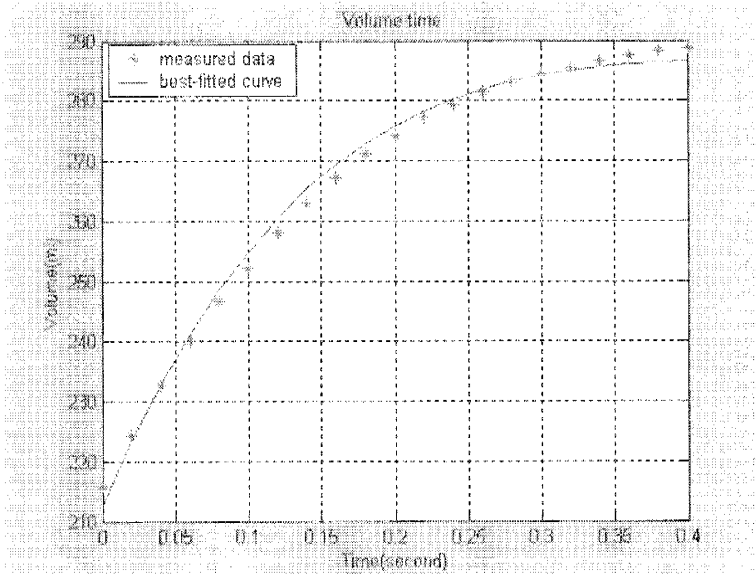
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Figure 4: Representative data of diastole-volume with time. Solid curve is the curve obtained by substituting the values of the computed parameters into equation (17). The clinically monitored LV-volume data is designated by *.

Table 1: Parameters related to case study

Parameters	Values	Unit
Inertia (M)	237×10^{-4}	$mmHg/(ml/s^2)$
Resistance (R)	1221×10^{-4}	$mmHg/(ml/s)$
Compliance (C)	17.6991	$ml/mmHg$
k_1	0.65	$mmHg$
k_2	7.92	s^{-1}
I	550×10^{-4}	$mmHg/(ml/s)$
RMS1	1.6235	ml
RMS2	0.5509	$mmHg$

of pressure drop across the mitral valve. We now simulate the solution (17) of the governing equation (16), to match this LV-volume data displayed in Figure 4, and evaluate the model parameters M, R & C as well as the index FLI. The resulting computed volume values, employing the parametric values (as listed in Table 1) into equation (17), matches the monitored LV volume in Figure 4. The values of these parameters and their RMS values are summarized in Table 1.

Upon computing the parameters M, R, & C, as well as k_1 & k_2, we determine and plot the LV pressure profile $P_3(t) = k_1 e^{k_2 t}$ (using k_1 & k_2 as listed in the Table 1), in Figure 5. It can be noted that we have been able to obtain an excellent fit of the computed LVP with the LVP(t) data.

The accuracy and stability between the model and the experiment data are expressed by means of the computed RMS values, listed in Table 1. The computed LV volume solution (14-a) has a fit with LV volume data, with RMS1 of 1.6235 ml. The computed pressure vs. time $P_3(t) = k_1 e^{k_2 t}$ (in equation 16) has a RMS2 of 0.5509 mmHg.
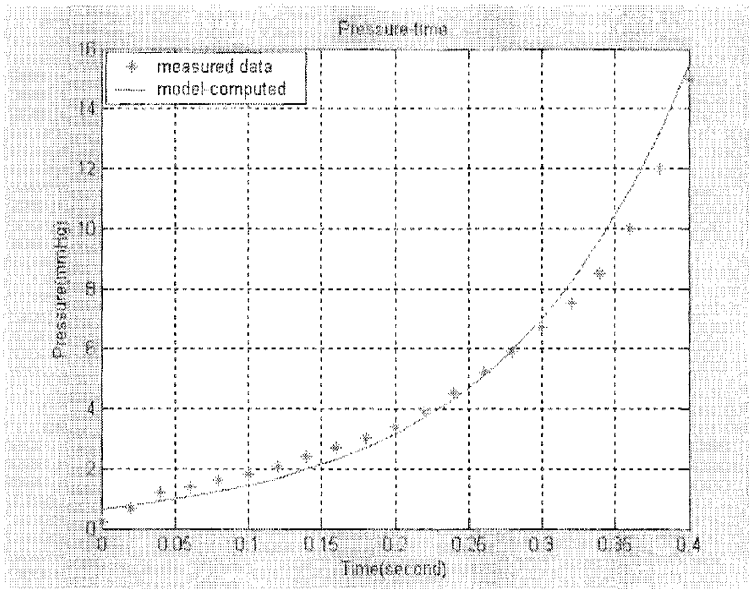

Figure 5: Plot of pressure model-computed vs. time during the diastolic phase of the LV. (*) represents the measured data, (-) represents the model-computed curve.

6 Conclusion

Our characterization of the LV diastolic performance is aimed to provide the basis for the formation and computation of the derived index (FLI), as well as the pressure-time profile, non-invasively during diastolic filling.

The LV volume solution equation (17) is associated with parameters, which have physiological implications. For a heart with different pathological conditions, these parameters would of course change.

With a big database for different patients, we can determine the distribution of *FLI*, from which we can categorize normal patients and dysfunctional patients (with various mitral-valvular and filling disorders). The distribution of the index *FLI* may eventually prove to be a clinical useful measure of LV filling performance &/or dysfunction.

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