Assessment of a Non-Invasive Approach for Pressure Volume Loop Prediction in Mice

Liliana Jelú Reyes[1#], Maria Emilia Alfaro[2#], Janet Akoth Kireta[2], Michele Lynn Joyner[2], Soumya Ullas[3], Brianna LaViolette[3], Dinesh Hirenallur-Shanthappa[3], and Nessy Tania[1*]

[1]Translational Clinical Sciences, Pfizer Research and Development, Cambridge MA 02139
[2]Department of Mathematics and Statistics, East Tennessee State University, Johnson City, 37614
[3]Drug Safety Research & Development, Pfizer Research and Development, Cambridge MA 02139
*Corresponding Author: nessy.tania@pfizer.com
[#]Equal contribution, joint first authorship

Supplementary Information

Time-Varying Elastance Model

Time-varying elastance, *E(t), is* defined as the ratio of the left ventricular pressure to volume [13],

$$\boldsymbol{E(t)} = \frac{\boldsymbol{P(t)}}{\boldsymbol{V(t) - V_0}} \tag{1}$$

Stergiopulos et al. [19] has proposed that time varying elastance can be modeled by the Double Hill function. Following the definition in Mynard et. Al. [28],

$$\boldsymbol{E(t) = k\left[\frac{g_1}{1+g_1}.\ \frac{1}{1+g_2}\right] + E_{min}} \tag{2}$$

where

$$\boldsymbol{g_1 = \left(\frac{t}{\tau_1}\right)^{\eta_1}} \quad \boldsymbol{g_2 = \left(\frac{t}{\tau_2}\right)^{\eta_2}}, \quad \text{and} \quad \boldsymbol{k = \frac{E_{max} - E_{min}}{\max\left[\frac{g_1}{1+g_1}.\ \frac{1}{1+g_2}\right]}}$$

In this equation, the first term in the brackets $\left(\frac{g_1}{1+g_1}\right)$ models the ascending part of the function and the second term in the brackets $\left(\frac{1}{1+g2}\right)$ models the descending part of the function (refer to Figure 2). In the equation, η_1 and η_2 determine the steepness, τ_1 and τ_2 define the relative appearance time of each curve within the cardiac period T , and E_{max} and E_{min} are the maximum and minimum elastance values, respectively, defined as

$$\boldsymbol{E_{max}} = \mathbf{max}\left(\frac{\boldsymbol{P(t)}}{\boldsymbol{V(t)-V_0}}\right) \tag{3}$$

$$\boldsymbol{E_{min}} = \mathbf{min}\left(\frac{\boldsymbol{P(t)}}{\boldsymbol{V(t)-V_0}}\right) \tag{4}$$

The end diastolic pressure volume relationship (EDPVR) is where the minimum elastance occurs and the end systolic pressure volume relationship (ESPVR) is where elastance reaches its maximum (refer to Figure 1 in the main manuscript). Kass et. al. [2] have defined E_{max} to occur at end systole and E_{min} at end diastole.

Experimental Validation

Stroke Work Theory

The area of a general two-dimensional region D can be found using a double integral

$$A = \int \int_D dA \tag{6}$$

which can be written as

$$\oint_c x\ dy = -\oint_c y\ dx \tag{7}$$

by Green's theorem, where C is the boundary of the curve of the region. Therefore, stroke work is calculated as

$$SW = \oint_c V\ dP = -\oint_c P\ dv \tag{8}$$

where C is the bounding curve of the PV loop.

Fitting Elastance Curve Without Including Emax and Emin

We implemented the approach described in Seemann et al. [3] of fitting only four parameters, $\eta_1, \eta_2, \tau_1, \tau_2$, on the normalized elastance curve and setting the amplitude parameters to

$$E_{max} = \frac{LVP_{systole}}{V(T_{LVPmax})-V_0} \qquad E_{min} = \frac{LVP_{diastole}}{V(T_{ED})-V_0}$$

$LVP_{systole}$ is obtained using peak LV pressure over one cardiac cycle (and $V(T_{LVPmax})$ the LV volume at the time that peak pressure is reached). $LVP_{diastole}$ is determined by estimating first and higher derivatives of LV Pressure data and the value is determined by locating the maximum of the peak of the second derivative. Identifications were verified by visual inspection for each animal data. Using this approach, we consistently obtained an under-estimation of peak elastance (Emax). To obtain a better estimator, we allowed Emax and Emin to be fitted directly. Note that Seemann et al. utilized a Newton-Raphson iteration to determine Emax value. Our approach is similar by simultaneously finding parameter values for least square error minimization.

Additional Figures

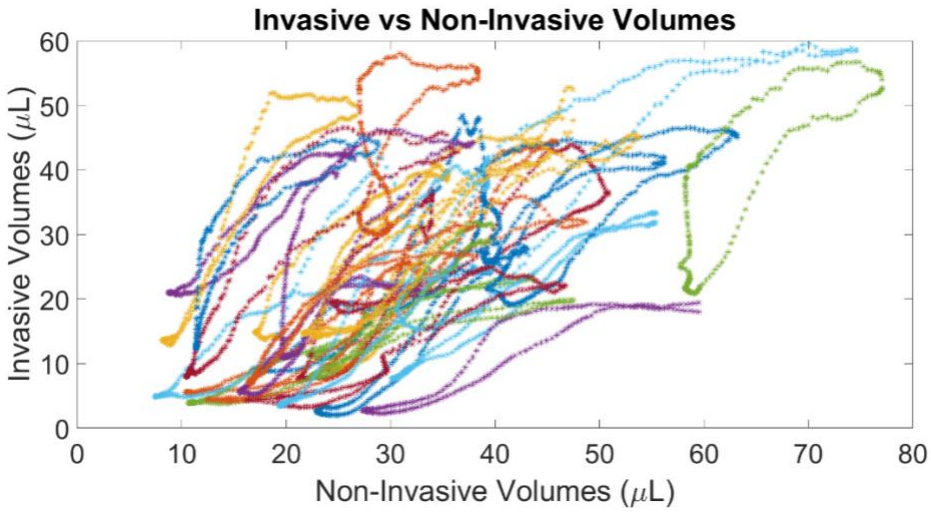
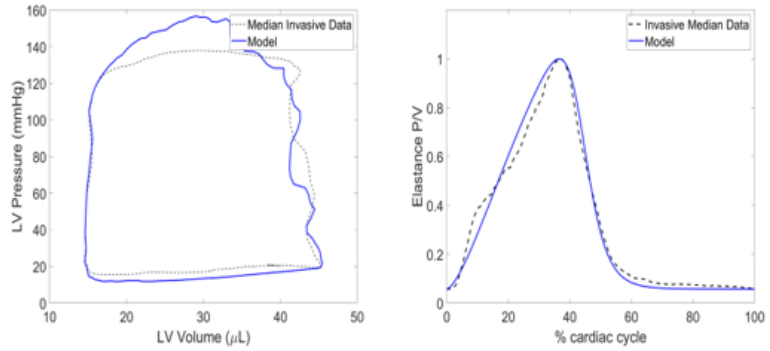


Figure S1 – Comparison of LV volume obtained from invasive procedure and non-invasive 4D echocardiography. Each color shows a different animal and each closed curve traces one cardiac cycle.

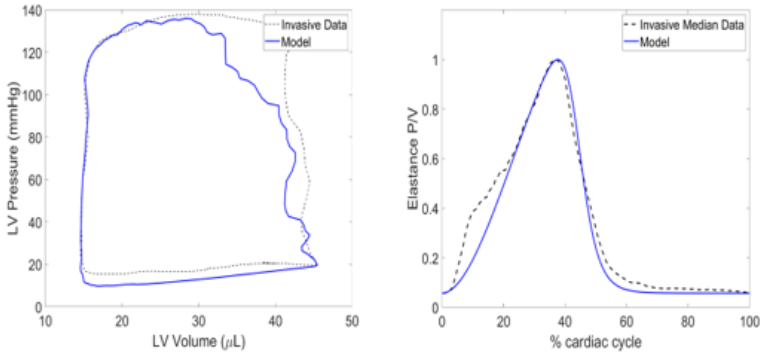
Animal 9 – Individually Optimized Parameters



η_1	η_2	τ_1	τ_2
2.32	13.64	17.85	43.88

Stroke Work Data (mJ)	0.4
Stroke Work Model (mJ)	0.5
% Difference	8%

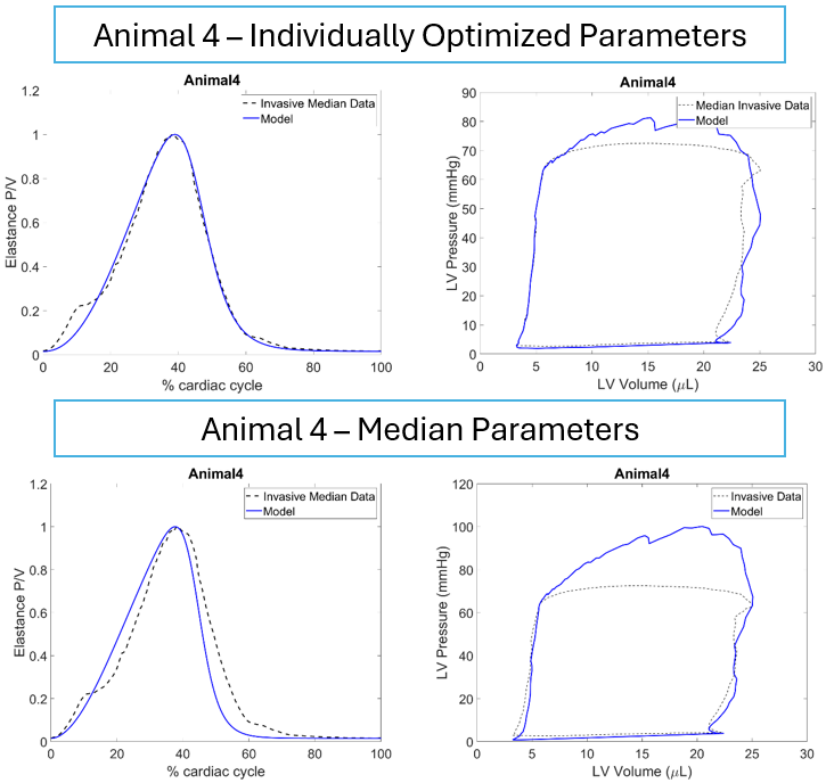
Animal 9 – Median Parameters



η_1	η_2	τ_1	τ_2
2.26	16.78	8.94	43.32

Stroke Work Data (mJ)	0.4
Stroke Work Model (mJ)	0.4
% Difference	9%

Figure S2 – Comparison between invasively-obtained PV loop data and model projection using individually fitted parameters or median parameters shown for a different animal than in Figure 5.



η_1	η_2	τ_1	τ_2
3.81	12.66	22.42	49.39

Stroke Work Data (mJ)	0.2
Stroke Work Model (mJ)	0.2
% Difference	12%

η_1	η_2	τ_1	τ_2
2.18	14.77	11.19	49.27

Stroke Work Data (mJ)	0.2
Stroke Work Model (mJ)	0.2
% Difference	30%

Figure S3 – Additional comparison between invasively-obtained PV loop data and model projection using individually fitted parameters or median parameter shown for a different animal than in Figure 5.