Supplemental Material for: Phenotyping heart failure using model-based analysis and physiology-informed machine learning

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This supplementary material provides further details on the model formulation, reassessment of ejection fraction, calculation of nominal parameters, methods used to estimate initial volume distribution in the cardiovascular system, residual expression used to evaluate parameter sensitivity and optimize parameters, cluster classification for each patient using clinical data and optimized parameters, and additional figures not included in the main manuscript that might be of interest to the reader.

S1. MODEL EQUATIONS

The cardiovascular systems model used for this studied is a reduced version of the Smith et al. model [1]. Multiple reduced forms were investigated and the final reduced version balances the degree of model complexity with the informational content of the clinical data. In this reduced form the venetricular-ventricular interaction and pericardium were omitted and all zero pressure volumes in each compartment were set to zero. The equations of this reduced model are given below.

S1.1. Time-varying elastance

The elastance function driving heart systole and diastole depends on a periodic τ that is the time from the beginning of the current cardiac cycle is given as

$$e_\tau = \exp\left\{ -\mathrm{HR}\Big(\tau - \frac{1}{2\mathrm{HR}}\Big)^2 \right\}. \tag{S1}$$

S1.2. Pressures

Left (lv) and right (rv) pressure development from end-systolic (es) and end-diastolic (ed) pressure-volume relationships are

$$P_{es,lv} = E_{lv}\, V_{lv}, \tag{S2}$$
$$P_{ed,lv} = P_{0,lv}\, (\exp\{\lambda_{lv}\, V_{lv}\} - 1), \tag{S3}$$

$$P_{lv} = e_\tau P_{es,lv} + (1 - e_\tau) P_{ed,lv}, \tag{S4}$$
$$P_{es,rv} = E_{rv}\, V_{rv}, \tag{S5}$$
$$P_{ed,rv} = P_{0,rv}\, (\exp\{\lambda_{rv}\, V_{rv}\} - 1), \quad \text{and} \tag{S6}$$
$$P_{rv} = e_\tau P_{es,lv} + (1 - e_\tau) P_{ed,rv}, \tag{S7}$$

where V_i is the compartment volume, E_i is an elastance parameter, $P_{0,i}$ is a reference pressure, and λ_i is a stiffness parameter. The systemic arterial (sa), systemic venous (sv), pulmonary arterial (pa), and pumonary venous (pv) pressures are

$$P_{sa} = E_{sa} V_{sa}, \tag{S8}$$
$$P_{sv} = E_{sv} V_{sv}, \tag{S9}$$
$$P_{pa} = E_{pa} V_{pa}, \quad \text{and} \tag{S10}$$
$$P_{pv} = E_{pv} V_{pv}. \tag{S11}$$

S1.3. Flows

Blood flow is modeled using Ohm's law. Flow through the systemic (*sys*) and pulmonary (*pul*) circulations are

$$Q_{sys} = \frac{P_{sa} - P_{sv}}{R_{sys}} \quad \text{and} \tag{S12}$$

$$Q_{pul} = \frac{P_{pa} - P_{pv}}{R_{pul}}. \tag{S13}$$

Flows through the heart values (mitral (*mt*), aortic (*av*), tricuspid (*tc*), and pulmonary (*pv*) are treated as diodes to prevent backflow, that is,

$$Q_{mt} = \begin{cases} \dfrac{P_{pv} - P_{lv}}{R_{mt}} & \text{if } P_{pv} > P_{lv} \\ 0 & \text{otherwise,} \end{cases} \tag{S14}$$

$$Q_{av} = \begin{cases} \dfrac{P_{lv} - P_{sa}}{R_{av}} & \text{if } P_{lv} > P_{sa} \\ 0 & \text{otherwise,} \end{cases} \tag{S15}$$

$$Q_{tc} = \begin{cases} \dfrac{P_{sv} - P_{rv}}{R_{tc}} & \text{if } P_{sv} > P_{rv} \\ 0 & \text{otherwise,} \end{cases} \tag{S16}$$

and

$$Q_{pv} = \begin{cases} \dfrac{P_{rv} - P_{pa}}{R_{pv}} & \text{if } P_{rv} > P_{pa} \\ 0 & \text{otherwise.} \end{cases} \tag{S17}$$

S1.4. Differential equations

This model conserves volume by formulating differential equations in terms of volumes and flows using Kirchoff's Law, that is,

$$\frac{\mathrm{d}V_{lv}}{\mathrm{d}t} = Q_{mt} - Q_{av}, \tag{S18}$$

$$\frac{\mathrm{d}V_{sa}}{\mathrm{d}t} = Q_{av} - Q_{sys}, \tag{S19}$$

$$\frac{\mathrm{d}V_{sv}}{\mathrm{d}t} = Q_{sys} - Q_{sv}, \tag{S20}$$

$$\frac{\mathrm{d}V_{rv}}{\mathrm{d}t} = Q_{sv} - Q_{rv}, \tag{S21}$$

$$\frac{\mathrm{d}V_{pa}}{\mathrm{d}t} = Q_{rv} - Q_{pul}, \tag{S22}$$

and

$$\frac{\mathrm{d}V_{pv}}{\mathrm{d}t} = Q_{pul} - Q_{mt}. \tag{S23}$$

Table S1. Parameter descriptions and values for the reduced Smith et al. ([1]) model.

Symbol	Value	Description	Units
Left ventricle (LV)			
E_{lv}	1.32	LV active contractility	mmHg mL^{-1}
$P_{0,lv}$	0.12	LV reference pressure	mmHg
λ_{lv}	0.02	LV passive stiffness	mL^{-1}
Right ventricle (RV)			
E_{rv}	0.70	RV active contractility	mmHg mL^{-1}
$P_{0,rv}$	0.22	RV reference pressure	mmHg
λ_{rv}	0.02	RV passive stiffness	mL^{-1}
Pulmonary arteries (PA) and veins (PV)			
E_{pa}	0.26	PA stiffness	mmHg mL^{-1}
E_{pv}	0.01	PV stiffness	mmHg mL^{-1}
R_{pv}	0.13	Pulmonary resistance	mmHg s mL^{-1}
Systemic arteries (SA) and veins (SV)			
E_{sa}	0.90	SA stiffness	mmHg mL^{-1}
E_{sv}	0.01	SV stiffness	mmHg mL^{-1}
R_{sys}	1.28	Systemic resistance	mmHg s mL^{-1}
Heart valve resistances			
R_{mt}	0.016	Mitral valve	mmHg s mL^{-1}
R_{av}	0.018	Aortic valve	mmHg s mL^{-1}
R_{tc}	0.024	Tricuspid valve	mmHg s mL^{-1}
R_{pv}	0.006	Pulmonary valve	mmHg s mL^{-1}

S1.5. Parameterization

Table S1 defines all model parameters and gives values that result in normal cardiovascular function. This normal set of parameters prescribes a patient with roughly 120/80 mmHg systemic pressure, 20/9 mmHg pulmonary artery pressure, left ventricular diastolic volume of 85 mL, left ventricular stroke volume of 57mL (for an ejection fraction of 67%) and cardiac output of 4.6 L/min. These values vary from the original Smith model parameters because we have reduced their model and then adjusted the remaining parameters to produce cardiovascular function similar to the full Smith model normal CV function.

S2. REASSESSMENT OF EJECTION FRACTION

When we asked a cardiologist to return to the transthoracic echocardiogram (TTE) images to get an estimate using the method of discs (MOD) of the left ventricular (LV) systolic and diastolic end volumes [3], the new volume estimates resulted in a new ejection fraction (EF). In some cases, there was little or no change in EF from the value recorded in the original diagnosis. In others, the change was significant enough that a third evaluation from another cardiologist was performed to determine if the reported EF, the new EF, or some combination of the two measures should be used as the patient's "official" EF, as outlined in the manuscript (Manuscript Figure 2). Table S2 outlines the EF calculations for each patient: EF from MOD (EF-MOD),

Table S2. Ejection fraction (EF) calculation method for each heart failure (HF) patient.

Patient	Method	Patient	Method
HFrEF			
1	EF-MOD	6	EF-MOD
2	EF-MOD	7	EF-Teichholz
3	EF-MOD	8	EF-MOD
4	EF_2	9	EF_3
5	EF_2	10	EF-MOD
HFpEF			
11	EF-MOD	22	EF-Teichholz
12	EF_3	23	EF_3
13	EF-Teichholz	24	EF-MOD
14	EF-Teichholz	25	EF-MOD
15	EF-Teichholz	26	EF-MOD
16	EF-MOD	27	EF-MOD
17	EF-Teichholz	28	EF-Teichholz
18	EF-Teichholz	29	EF-Teichholz
19	EF-MOD	30	EF-MOD
20	EF-MOD	31	EF-MOD
21	EF-Teichholz		

MOD - method of discs [3].
Teichholz - Teichholz's equation [2].
EF_2 - Manuscript Equation (1).
EF_3 - Manuscript Equation (2).

Table S3. Clinical measures used for calculation of nominal parameter values

Symbol	Description
$V_{lv,syst}$	LV systolic volume
$V_{lv,diast}$	LV diastolic volume
$P_{rv,syst}$	RV systolic pressure
$P_{rv,diast}$	RV diastolic pressure
$P_{sa,syst}$	SA systolic pressure
$P_{sa,diast}$	SA diastolic pressure
$P_{pcw,ave}$	Average PCW pressure
$P_{pa,syst}$	PA systolic pressure
$P_{pa,diast}$	PA diastolic pressure
$P_{sv,pp}$	SV pulse pressure
CO_{RHC}	Right heart catheter cardiac output

PCW - pulmonary capillary wedge.

EF from Teichholz's equation (EF-Teichholz) [2], EF_2 calculated using Manuscript Equation (1), and EF_3 calculated using Manuscript Equation (2).

S3. CALCULATION OF NOMINAL PARAMETERS

Nominal values for all 16 parameters in the model are specified for each patient using a combination of each patient's clinical measures, the model equations, and values from the literature. The equations below are a summary of the NomParam_Calc function from the code. The left and right ventricular end-diastolic reference pressures ($P_{0,lv}$ and $P_{0,rv}$) are set at nominal values from the Smith et al. study so the ventricular end-diastolic stiffness exponents can be estimated explicitly from the model equations.

When dealing with clinical data, some measurements are not consistent with each other. For example, the pulmonary arterial systolic pressure ($P_{pa,syst}$) is sometimes greater than the right ventricular systolic pressure ($P_{rv,syst}$) likely because these two measurements are made serially instead of simultaneously. In this case, computation of the nominal pulmonary valve resistance (R_{pv}) value is made differently than if $P_{rv,sys}$ is greater than $P_{pa,syst}$. All special cases similar to this example that arise from the clinical data are discussed in the sections below.

For the nominal right ventricular passive stiffness parameter (λ_{rv}), when the right ventricular diastolic pressure ($P_{rv,diast}$) is measured to be negative or zero, a positive nonzero value is calculated from the estimate of the pulse pressure in the systemic veins ($P_{sv,pp}$) to use in our nominal parameter calculation.

For the nominal pulmonary resistance (R_{pul}), calculating R_{pul} from the clinical data led to three different scenarios that we had to account for. In most cases, adding 2/3 of the estimated pulmonary venous pulse pressure ($P_{pv,pp}$) to the measured pulmonary capillary wedge pressure ($P_{pcw,ave}$) resulted in a pressure that was smaller than average pulmonary arterial pressure ($P_{pa,ave}$). In some cases, this is not true but this sum is still less than the pulmonary arterial systolic pressure ($P_{pa,syst}$), so we substitute $P_{pa,syst}$ for $P_{pa,ave}$ in the calculation. In a small number of cases, the $P_{pcw,ave}$ is actually measured to be much larger than the upstream $P_{pa,syst}$, which is not physiologically possible. In this case, we estimate the pulmonary venous systolic pressure ($P_{pv,syst}$) from the average ratio of the two pressures from all other patients in our study.

For the nominal tricuspid valve resistance (R_{tc}), when the right ventricular diastolic pressure ($P_{rv,diast}$) is measured to be negative or zero, a positive nonzero value is calculated from the estimate of $P_{sv,pp}$.

For the nominal pulmonary valve resistance (R_{pv}), when the measured $P_{pa,syst}$ is larger than the $P_{rv,syst}$, a pressure drop of 2.5% across the pulmonary valve is assumed to generate a nonnegative estimate of R_{pv}.

S3.1. Estimating patient-specific model pressures and volumes from clinical measures

The following equations calculate estimates for pressures and volumes in systole and daistole from the clinical data. The bar notation ($\bar{\cdot}$) indicates a nominal estimate whereas no bar indicates a clinical measure, which are found in Table S3.

S3.1.1. Volume estimates

Right ventricular compartment volume estimates are assumed to be 90% of the left ventricular volumes, that is,

$$\bar{V}_{rv,syst} = 0.90\ V_{lv,syst}, \quad \text{and} \tag{S24}$$

$$\bar{V}_{rv,diast} = 0.90\ V_{lv,diast}. \tag{S25}$$

S3.1.2. Pressure estimates

$$\bar{P}_{lv,syst} = 1.025\ P_{sa,syst} \tag{S26}$$

$$\bar{P}_{lv,diast} = 0.975\ \bar{P}_{pv,diast} \tag{S27}$$

$$\bar{P}_{pv,pp} = 0.20\ (P_{pa,syst} - P_{pa,diast}) \tag{S28}$$

$$\bar{P}_{sv,pp} = 0.05\ (P_{sa,syst} - P_{sa,diast}) \tag{S29}$$

$$\bar{P}_{pv,diast} = P_{pcw,ave} - \frac{1}{3}\ \bar{P}_{pv,pp} \tag{S30}$$

$$P_{pa,ave} = \frac{1}{3}\ P_{pa,syst} + \frac{2}{3}\ P_{pa,diast} \tag{S31}$$

$$P_{sa,ave} = \frac{1}{3}\ P_{sa,syst} + \frac{2}{3}\ P_{sa,diast} \tag{S32}$$

$$\bar{P}_{rv,diast} = \begin{cases} \frac{1}{2}\ \bar{P}_{sv,pp} & \text{if } P_{rv,diast} \leq 0 \\ P_{sv,pp} & \text{otherwise} \end{cases} \tag{S33}$$

$$\bar{P}_{sv,diast} = \begin{cases} 1.025\ \bar{P}_{rv,diast} & \text{if } P_{rv,diast} \leq 0 \\ 1.025\ P_{rv,diast} & \text{if } P_{rv,diast} > 0 \end{cases} \tag{S34}$$

$$\bar{P}_{sv,syst} = \bar{P}_{sv,diast} + \bar{P}_{sv,pp} \tag{S35}$$

$$\bar{P}_{pu,syst} = \begin{cases} P_{pcw,ave} + \frac{2}{3}\ \bar{P}_{pv,pp} \\ \quad \text{if } 0.975 P_{pa,syst} \geq P_{pcw,ave} + \frac{2}{3}\ \bar{P}_{pv,pp} \\ 0.4854\ P_{pa,syst} \\ \quad \text{if } 0.975\ P_{pa,syst} < P_{pcw,ave} + \frac{2}{3}\ \bar{P}_{pv,pp} \end{cases} \tag{S36}$$

For the nominal values of $\bar{V}_{pa,syst}$, $\bar{V}_{pu,syst}$, $\bar{V}_{sa,syst}$, and $\bar{V}_{sv,syst}$, see nominal/initial volume calculation in Section S4 below.

S3.2. Calculating nominal parameters from pressure and volume estimates

S3.2.1. Left ventricle parameters

$$\bar{E}_{lv} = \frac{\bar{P}_{lv,syst}}{V_{lv,syst}} \tag{S37}$$

$$\bar{P}_{0,lv} = 0.1203\,\text{mmHg} \tag{S38}$$

$$\bar{\lambda}_{lv} = \frac{\ln(\bar{P}_{lv,diast}/\bar{P}_{0,lv})}{V_{lv,diast}} \tag{S39}$$

S3.2.2. Right ventricle parameters

$$\bar{E}_{rv} = \frac{P_{rv,syst}}{\bar{V}_{rv,syst}} \tag{S40}$$

$$\bar{P}_{0,rv} = 0.2157\,\text{mmHg} \tag{S41}$$

$$\bar{\lambda}_{rv} = \begin{cases} \frac{\ln(\bar{P}_{rv,diast}/\bar{P}_{0,rv})}{\bar{V}_{rv,diast}} & \text{if } P_{rv,diast} \leq 0 \\ \frac{\ln(P_{rv,diast}/\bar{P}_{0,rv})}{\bar{V}_{rv,diast}} & \text{if } P_{rv,diast} > 0 \end{cases} \tag{S42}$$

S3.2.3. Pulmonary parameters

$$\bar{E}_{pa} = \frac{P_{pa,syst} - P_{pa,diast}}{\bar{V}_{pa,syst}} \tag{S43}$$

$$\bar{E}_{pv} = \frac{\bar{P}_{pv,pp}}{\bar{V}_{pv,syst}} \tag{S44}$$

$$\bar{R}_{pul} = \begin{cases} \frac{P_{pa,ave} - \bar{P}_{pu,syst}}{\text{CO}_{\text{RHC}}} \\ \quad \text{if } 0.975\ P_{pa,ave} \geq P_{pcw,ave} + \frac{2}{3}\bar{P}_{pu,pp} \\ \frac{P_{pa,syst} - \bar{P}_{pu,syst}}{\text{CO}_{\text{RHC}}} \\ \quad \text{if } 0.975\ P_{pa,ave} < P_{pcw,ave} + \frac{2}{3}\ \bar{P}_{pu,pp} \end{cases} \tag{S45}$$

S3.2.4. Systemic parameters

$$\bar{E}_{sa} = \frac{P_{sa,syst} - P_{sa,diast}}{\bar{V}_{sa,syst}} \tag{S46}$$

$$\bar{E}_{sv} = \frac{\bar{P}_{sv,pp}}{\bar{V}_{sv,syst}} \tag{S47}$$

$$\bar{R}_{sys} = \frac{P_{sa,ave} - \bar{P}_{sv,syst}}{\text{CO}_{\text{RHC}}} \tag{S48}$$

S3.3. Heart valve resistances

$$\bar{R}_{mt} = \frac{\bar{P}_{pu,diast} - \bar{P}_{lv,diast}}{\text{CO}_{\text{RHC}}} \tag{S49}$$

$$\bar{R}_{av} = \frac{\bar{P}_{lv,syst} - \bar{P}_{sa,syst}}{\text{CO}_{\text{RHC}}} \tag{S50}$$

$$\bar{R}_{tc} = \begin{cases} \frac{\bar{P}_{sv,diast} - \bar{P}_{rv,diast}}{\text{CO}_{\text{RHC}}} & \text{if } P_{rv,diast} \leq 0 \\ \frac{\bar{P}_{sv,diast} - P_{rv,diast}}{\text{CO}_{\text{RHC}}} & \text{if } P_{rv,diast} > 0 \end{cases} \tag{S51}$$

$$\bar{R}_{pv} = \begin{cases} \frac{P_{rv,syst} - \bar{P}_{pa,syst}}{\text{CO}_{\text{RHC}}} & \text{if } P_{pa,syst} \geq P_{rv,syst} \\ \frac{P_{rv,syst} - P_{pa,syst}}{\text{CO}_{\text{RHC}}} & \text{if } P_{pa,diast} < P_{rv,syst} \end{cases} \tag{S52}$$

Table S4. Blood volume distributions in mL adapted from Beneken [4].

Stressed		Unstressed		Total	
Systemic arteries (SA)					
$V_{s,B,sa}$	160	$V_{u,B,sa}$	425	$V_{t,B,sa}$	585
Systemic veins (SV)					
$V_{s,B,sv}$	219	$V_{u,B,sv}$	2697	$V_{t,B,sv}$	2916
Pulmonary arteries (PA)					
$V_{s,B,pa}$	69	$V_{u,B,pa}$	50	$V_{t,B,pa}$	119
Pulmonary veins (PV)					
$V_{s,B,pv}$	54	$V_{u,B,pv}$	460	$V_{t,B,pv}$	514
Left ventricle (LV)					
$V_{s,B,lv}$	125	$V_{u,B,lv}$	0	$V_{t,B,lv}$	125
Left atrium (LA)					
$V_{s,B,la}$	50	$V_{u,B,la}$	30	$V_{t,B,la}$	80
Right ventricle (RV)					
$V_{s,B,rv}$	125	$V_{u,B,rv}$	0	$V_{t,B,rv}$	125
Right atrium (RA)					
$V_{s,B,ra}$	50	$V_{u,B,ra}$	30	$V_{t,B,ra}$	80
Totals					
$V_{s,B,tot}$	852	$V_{u,B,tot}$	3692	$V_{t,B,tot}$	4544

Table S5. New blood volume distributions in mL with 30% volume.

Stressed		Unstressed		Total	
Systemic arteries (SA)					
$V^*_{s,B,sa}$	230	$V^*_{u,B,sa}$	355	$V^*_{t,B,sa}$	585
Systemic veins (SV)					
$V^*_{s,B,sv}$	662	$V^*_{u,B,sv}$	2554	$V^*_{t,B,sv}$	2916
Pulmonary arteries (PA)					
$V^*_{s,B,pa}$	77	$V^*_{u,B,pa}$	42	$V^*_{t,B,pa}$	119
Pulmonary veins (PV)					
$V^*_{s,B,pv}$	130	$V^*_{u,B,pv}$	384	$V^*_{t,B,pv}$	514
Left ventricle (LV)					
$V^*_{s,B,lv}$	88	$V^*_{u,B,lv}$	37	$V^*_{t,B,lv}$	125
Left atrium (LA)					
$V^*_{s,B,la}$	40	$V^*_{u,B,la}$	40	$V^*_{t,B,la}$	80
Right ventricle (RV)					
$V^*_{s,B,rv}$	88	$V^*_{u,B,rv}$	37	$V^*_{t,B,rv}$	125
Right atrium (RA)					
$V^*_{s,B,ra}$	40	$V^*_{u,B,ra}$	40	$V^*_{t,B,ra}$	80
Totals					
$V^*_{s,B,tot}$	1355	$V^*_{u,B,tot}$	3692	$V^*_{t,B,tot}$	4544

S4. RECALCULATION OF INITIAL VOLUME DISTRIBUTIONS

A current theory with regards to HFpEF is that there is some dysfunction in the ability to adjust volume distribution in the cardiovascular system. Our model can take into consideration different percentages of total stressed volume in the cardiovascular system which might vary across patients. Even though we have this option for the purpose of discriminating HFpEF phenotypes, we have fixed the total stressed volume at 30% of total blood volume. This still leaves us with the problem of how to estimate the initial volume distribution across compartments in this model and the percentages of stressed volume in each compartment to sum up to be 30% of total blood volume.

We start with the nominal values of stressed, unstressed, and total blood volume in each compartment from Beneken [4]. The difference here is that Beneken's stressed volume distributions add up to be only 18.75%, which is now generally taken to be too low. In the code, we recalculate an initial stressed volume distribution to a 30% stressed volume that is appropriate. Table S4 is a summary of the Table 1-1 values we use as a starting point from Beneken.

The total blood volume in Beneken is 4544, mL which is different than the blood volume calculated for each patient. Therefore, we will estimate the percentages of stressed and unstressed volumes for different total stressed volume percentages with respect to the Beneken volumes and then use those percentages to calculate the inital volume distributions for the patient-specific total blood volume. We start by adjusting what volumes are stressed and unstressed in the heart. Beneken assumes 100% stressed volume in the ventricles and 60% stressed volume in the atria, which we change to 70% and 50% respectively. To adjust this we will calculate new volumes in the heart as

$$V^*_{s,B,lv} = 0.70\ V_{t,B,lv} \tag{S53}$$

$$V^*_{s,B,la} = 0.50\ V_{t,B,la} \tag{S54}$$

$$V^*_{s,B,rv} = 0.70\ V_{t,B,rv} \tag{S55}$$

$$V^*_{s,B,ra} = 0.50\ V_{t,B,ra} \tag{S56}$$

We need to recruit volume over the Beneken values, and we assume that this recruited volume will come from only the systemic and pulmonary circulations and not from the heart. So, we take the Beneken stressed volumes and then subtract off the heart chamber stressed volumes as

$$V_{s,B,nh} = V_{s,B,tot} - V_{s,B,lv} - V_{s,B,la} - V_{s,B,rv} - V_{s,B,ra}, \tag{S57}$$

where the subscript nh denotes "no heart".

But now assume we have the total stressed volume fraction specified in this patient (i.e. 30%) with the now new stressed volumes calculated above based on the Beneken total blood volume and we subtract off our new hart chamber stressed volumes as

$$V^*_{s,B,tot} = 0.30\ V_{t,B,tot} \tag{S58}$$

$$V^*_{s,B,nh} = V^*_{s,B,tot} - V^*_{s,B,lv} - V^*_{s,B,la} - V^*_{s,B,rv} - V^*_{s,B,ra}. \tag{S59}$$

The difference between these stressed volumes is the amount that we have to recruit over and above the Beneken stressed volumes, which we now call the recruited volume

$$V_{s,R,tot} = V^*_{s,B,nh} - V_{s,B,nh}. \tag{S60}$$

We now have to decide where to recruit this from. If we take a straight percentage based on total volume in each compartment, we run the risk of recruiting all of the volume in the compartments that have little left to give (e.g., pulmonary arteries) before we run out of volume anywhere else. So this recruited volume in each compartment should be calculated based on the fraction of the unstressed volume in each compartment with respect to the total unstressed volume, $V_{u,B,tot}$. Hence, all compartments would approach 0% unstressed volume equally as the stressed volume approaches 100%, that is,

$$V_{s,B,R,,sa} = V_{s,R,tot}\,(V_{u,B,sa}/V_{u,B,tot}), \tag{S61}$$
$$V_{s,B,R,sv} = V_{s,R,tot}\,(V_{u,B,sv}/V_{u,B,tot}), \tag{S62}$$
$$V_{s,B,R,pa} = V_{s,R,tot}\,(V_{u,B,pa}/V_{u,B,tot}), \quad \text{and} \tag{S63}$$
$$V_{s,B,R,pu} = V_{s,R,tot}\,(V_{u,B,pu}/V_{u,B,tot}). \tag{S64}$$

Adding these recruited volumes to the Beneken Table 1-1 values will give the volumes with the desired 30% total stressed volume as

$$V^*_{s,B,sa} = V_{s,B,sa} + V_{s,B,R,sa}, \tag{S65}$$
$$V^*_{s,B,sv} = V_{s,B,sv} + V_{s,B,R,sv}, \tag{S66}$$
$$V^*_{s,B,pa} = V_{s,B,pa} + V_{s,B,R,pa}, \quad \text{and} \tag{S67}$$
$$V^*_{s,B,pu} = V_{s,B,pu} + V_{s,B,R,pu}. \tag{S68}$$

Dividing these new volumes by the total compartment volumes from Benenken Table 1-1 gives the fraction of stressed volume for each compartment, that is,

$$f_{VsB,sa} = V^*_{s,B,sa}/V_{t,B,sa}, \tag{S69}$$
$$f_{VsB,sv} = V^*_{s,B,sv}/V_{t,B,sv}, \tag{S70}$$
$$f_{VsB,pa} = V^*_{s,B,pa}/V_{t,B,pa}, \quad \text{and} \tag{S71}$$
$$f_{VsB,pu} = V^*_{s,B,pu}/V_{t,B,pu}. \tag{S72}$$

These fractions can be used for the patient-specific V_{tot} to get an initial stressed volume distribution across compartments assuming a 30% total stressed volume.

S5. RESIDUAL EQUATION USED FOR SENSITIVITY ANALYSIS AND OPTIMIZATION

A residual function was used to assess parameter sensitivity in our global sensitivity analysis and optimize model parameters to patient data. The change in this residual with changes in parameter values over a sampling of the entire parameter space is used to rank the sensitivity of each parameter with respect to each other. For optimization, a set of parameter values is found that minimizes the residual function producing a patient-specific model that most closely represents a given set of patient data. Two simulation runs are made to compute the residual: one at the RHC heart rate and the second at the TTE heart rate. The eleven pressures, volumes, and cardiac output measures from these two simulations are used to compute the eleven residuals between the simulation and clinical measures using an appropriate normalization for each residual.

$$P^{res}_{rv,syst} = \frac{|\,P^{sim}_{rv,syst} - P^{data}_{rv,syst}\,|}{P^{data}_{sa,syst}}, \tag{S73}$$

$$P^{res}_{rv,diast} = \frac{|\,P^{sim}_{rv,diast} - P^{data}_{rv,diast}\,|}{P^{data}_{sa,sys}}, \tag{S74}$$

$$P^{res}_{pa,syst} = \frac{|\,P^{sim}_{ps,syst} - P^{data}_{pa,syst}\,|}{P^{data}_{sa,syst}}, \tag{S75}$$

$$P^{res}_{pa,diast} = \frac{|\,P^{sim}_{pa,diast} - P^{data}_{pa,diast}\,|}{P^{data}_{sa,sys}}, \tag{S76}$$

$$P^{res}_{sa,syst} = \frac{|\,P^{sim}_{sa,syst} - P^{data}_{sa,syst}\,|}{P^{data}_{sa,syst}}, \tag{S77}$$

$$P^{res}_{sa,diast} = \frac{|\,P^{sim}_{sa,diast} - P^{data}_{sa,diast}\,|}{P^{data}_{sa,sys}}, \tag{S78}$$

$$P^{res}_{pcw,ave} = \frac{|\,P^{sim}_{pcw,ave} - P^{data}_{pcw,ave}\,|}{P^{data}_{sa,sys}}, \tag{S79}$$

$$\mathrm{CO}^{res}_{\mathrm{RHC}} = \frac{|\,\mathrm{CO}^{sim}_{\mathrm{RHC}} - \mathrm{CO}^{data}_{\mathrm{RHC}}\,|}{\max\left(\mathrm{CO}^{data}_{\mathrm{RHC}}, \mathrm{CO}^{data}_{\mathrm{TTE}}\right)}, \tag{S80}$$

$$V^{res}_{lv,syst} = \frac{|\,V^{sim}_{lv,syst} - V^{data}_{lv,syst}\,|}{V^{data}_{lv,syst}}, \tag{S81}$$

$$V^{res}_{lv,diast} = \frac{|\,V^{sim}_{lv,diast} - V^{data}_{lv,diast}\,|}{V^{data}_{lv,sys}}, \tag{S82}$$

and

$$\mathrm{CO}^{res}_{\mathrm{TTE}} = \frac{|\,\mathrm{CO}^{sim}_{\mathrm{TTE}} - \mathrm{CO}^{data}_{\mathrm{TTE}}\,|}{\max\left(\mathrm{CO}^{data}_{\mathrm{RHC}}, \mathrm{CO}^{data}_{\mathrm{TTE}}\right)}. \tag{S83}$$

The eleven residuals are then averaged with no additional weighting terms being used as

$$Res = \frac{\sum_{i=1}^{7} P^{res}_i + \sum_{j=1}^{2} \mathrm{CO}^{res}_j + \sum_{k=1}^{2} V^{res}_k}{11} \tag{S84}$$

where $i = \{rv,syst\ \ rv,diast\ \ pa,syst\ \ pa,diast\ \ sa,syst\ \ sa,diast\ \ pcw,ave\}$, $j = \{\mathrm{RHC\ \ TTE}\}$, and $k = \{lv,syst\ \ lv,diast\}$. To calculate P_{pcw} from the simulation, the average value of P_{pv} over the last five beats of the simulation is taken. Similarly, for the cardiac output, the flow is averaged over the last five cardiac cycles.

S6. PATIENT SUBGROUPS FROM CLINICAL MEASURES

The method used to determine patient subgroups is summarized in the manuscript. Table S6 details which PCA hull, *k*-means cluster, and hierarchical cluster each patient falls into based on the clinical measures alone.

Table S6. Clinical data cluster classification.

Patient	Hull Location	*k*-means Cluster	Hierarchical Cluster	Group
HFrEF				
1	HFrEF	A	A	HFrEF
2	HFrEF	A	B	NCC
3	HFrEF	A	A	HFrEF
4	HFrEF	A	B	NCC
5	HFrEF	B	B	NCC
6	HFrEF	A	A	HFrEF
7	HFrEF	A	B	NCC
8	HFrEF	A	A	HFrEF
9	HFrEF	A	B	NCC
10	HFrEF	A	B	NCC
HFpEF				
11	HFrEF	A	B	NCC
12	HFpEF	B	B	HFpEF
13	HFpEF	B	B	HFpEF
14	HFpEF	B	B	HFpEF
15	HFpEF	B	B	HFpEF
16	HFpEF	A	A	NCC
17	HFpEF	A	B	NCC
18	HFrEF	A	B	NCC
19	HFpEF	B	B	HFpEF
20	HFpEF	A	A	NCC
21	HFpEF	A	A	NCC
22	HFpEF	B	B	HFpEF
23	HFpEF	A	A	NCC
24	HFrEF	B	B	NCC
25	HFpEF	B	B	HFpEF
26	HFpEF	B	B	HFpEF
27	HFpEF	A	A	NCC
28	HFpEF	B	B	HFpEF
29	HFpEF	B	B	HFpEF
30	HFpEF	B	B	HFpEF
31	HFpEF	B		HFpEF

NCC - not consistently clustered.

Table S7. Optimized parameter cluster classification

Patient	Hull Location	*k*-means Cluster	Hierarchical Cluster	Group
HFrEF				
2	HFrEF	A	B	HFrEF
3	HFrEF	A	A	HFrEF
4	HFrEF	A	A	HFrEF
5	HFrEF	A	A	HFrEF
7	HFrEF	A	A	HFrEF
8	HFrEF	A	A	HFrEF
9	HFrEF	A	A	HFrEF
10	HFrEF	A	A	HFrEF
HFpEF				
11	HFrEF	A	A	HFpEF1
12	HFpEF	A	A	NCC
13	HFpEF	B	B	HFpEF2
14	HFpEF	B	B	HFpEF2
15	HFpEF	A	A	NCC
16	HFpEF	B	B	HFpEF2
17	HFrEF	A	A	HFpEF2
18	HFrEF	A	A	HFpEF2
19	HFpEF	B	B	HFpEF2
20	HFpEF	B	B	HFpEF2
21	HFpEF	B	B	HFpEF2
22	HFpEF	B	B	HFpEF2
23	HFpEF	A	A	NCC
24	HFpEF	B	B	HFpEF2
25	HFpEF	B	B	HFpEF2
26	HFpEF	B	B	HFpEF2
27	HFpEF	A	B	NCC
28	HFpEF	A	B	NCC
29	HFrEF	A	A	HFpEF1
30	HFpEF	A	A	NCC
31	HFpEF	B		HFpEF2

NCC - not consistently clustered.

S7. PATIENT SUBGROUPS FROM OPTIMIZED PARAMETERS

The method used to determine patient subgroups is summarized in the manuscript. Table S7 details which PCA hull, *k*-means cluster, and hierarchical cluster each patient falls into based on the optimized parameters.

S8. SUPPLEMENTAL FIGURES

In the manuscript, the figures only include clinical measures and optimized parameters that had showed *p*-values at 0.05 or lower. The supplemental figures here are included for completeness. In Figure S1, we show the panels not included in Manuscript Figure 3 exhibiting differences in the clinical measures between our diagnosed subgroups of HFrEF and HFpEF. In Figure S2, we include all the optimized parameters not shown in Manuscript Figure 7 and how they vary across HFrEF, HFpEF1, HFpEF2 and NCC groups. In Figure S3, we include all the clinical measures not shown in Manuscript Figure 8 as we revisit the differences in the clinical measures between the HFrEF, HFpEF1, HFpEF2 and NCC groups.

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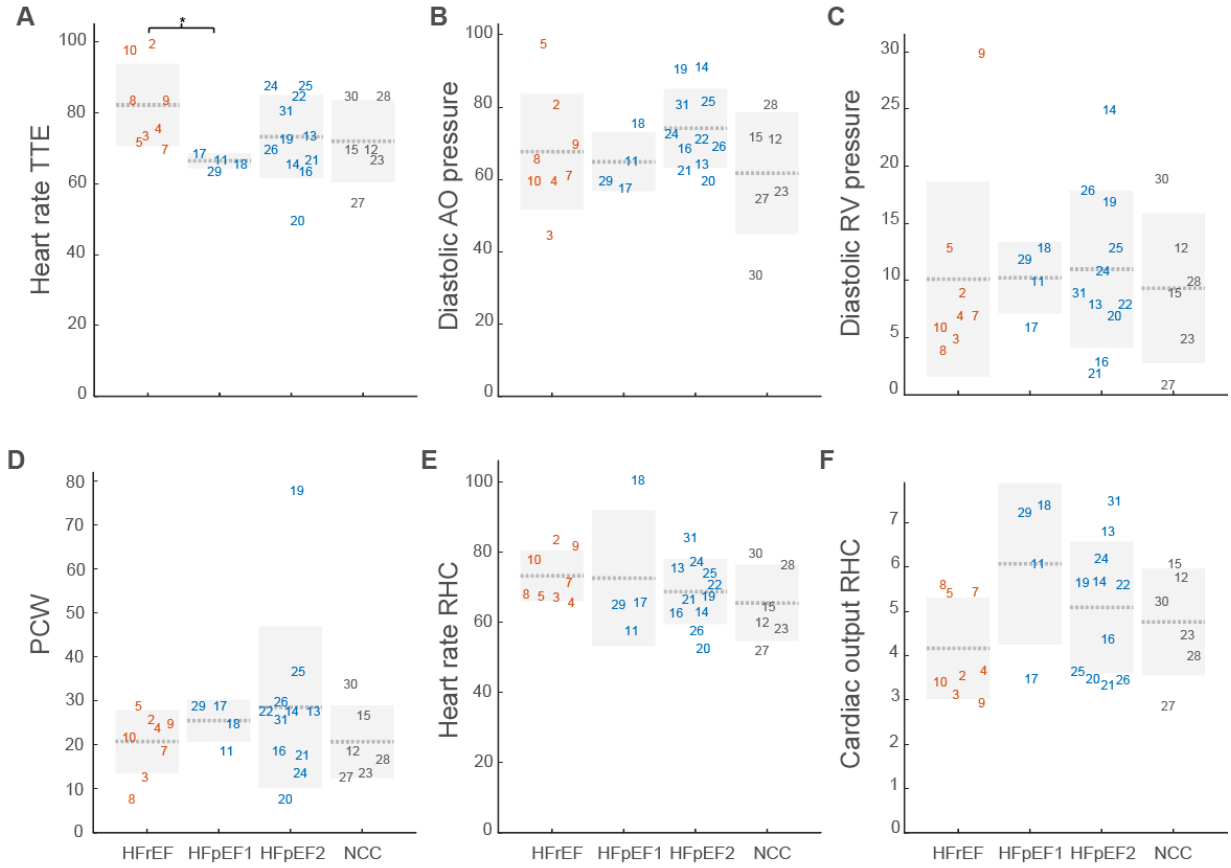

Fig. S1. Supplemental Figure 3. Box plots of clinical data. Heart rate TTE, diastolic systemic arterial (SA) pressure, diastolic right ventricular (RV) pressure, capillary wedge pressure (PCW), heart rate RHC, cardiac output RHC in clinical data between heart failure patients based on the HFrEF and HFpEF diagnosis. Light gray dashed line denotes the group average, and the grey box contains one standard deviation above and below the mean of each clinical value (*p-value <0.05, **p-value <.01, ***p-value <.001).

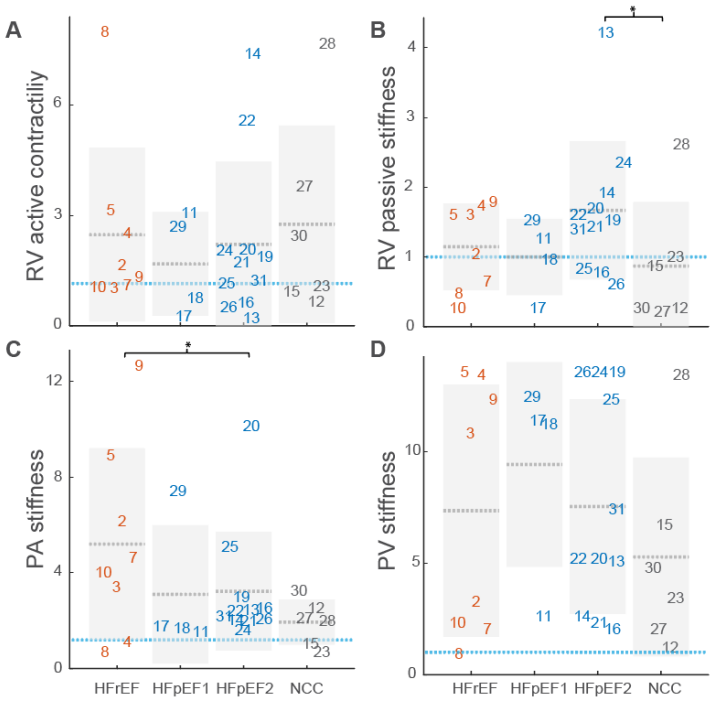

Fig. S2. Supplemental Figure 7.Box plots of the optimized parameter values with 4 heart failure groups. Analysis of the optimized parameters gives us an understanding of the mechanistic differences between the three HFpEF groups that cannot be seen by analyzing the clinical measures alone. A-D right ventricular (RV) active contractility, RV passive stiffness, pulmonary arterial (PA) stiffness and pulmonary venous (PV) stiffness are plotted relative to the normal Smith et al. model (Smith et al., 2004) parameter values indicated by the blue dashed line. Light gray dashed line denotes the average, and the gray box contains one standard deviation above and below the mean of each parameter value (*p-value <0.05, **p-value <0.01, ***p-value <0.001).

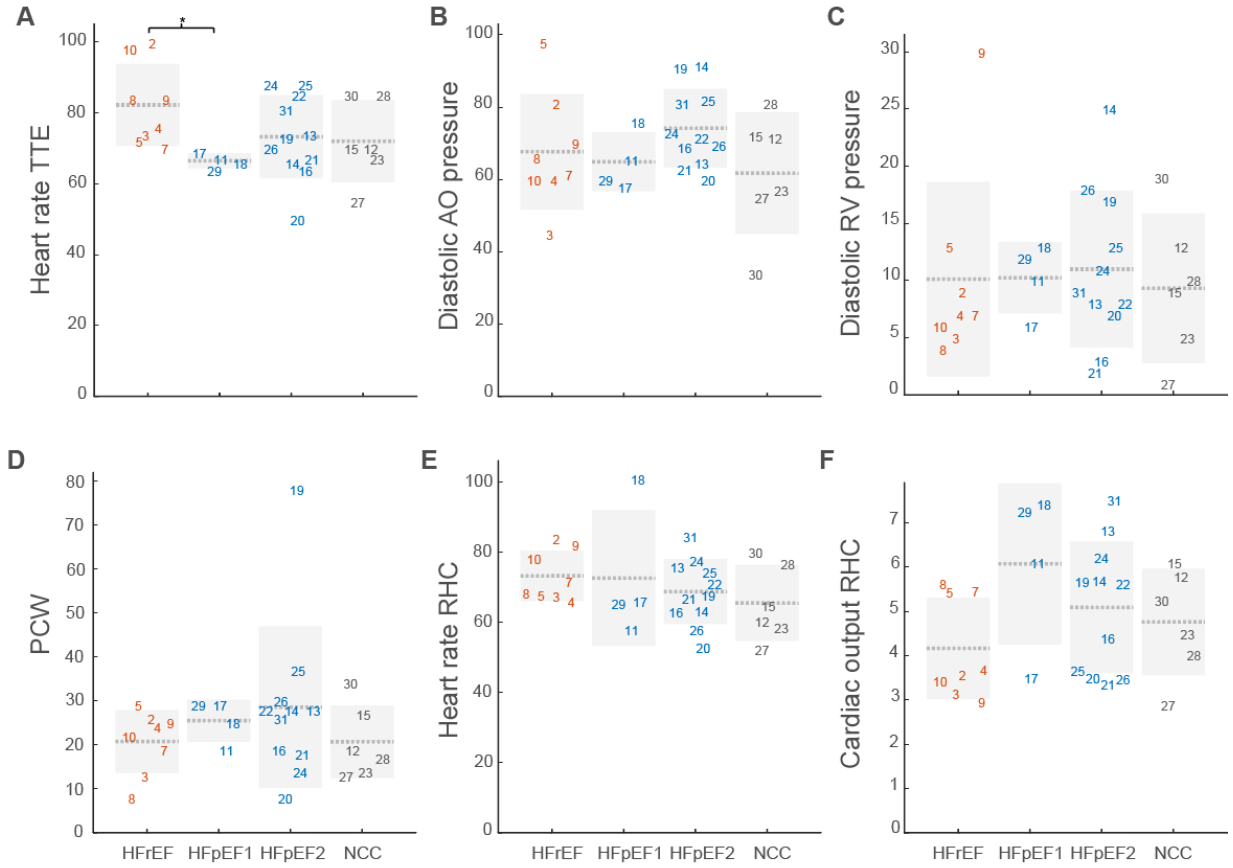

Fig. S3. Box plots of the clinical data with 4 heart failure groups. Heart rate TTE, diastolic systemic arterial (SA) pressure, diastolic right ventricular (RV) pressure, capillary wedge pressure (PCW), heart rate RHC, cardiac output RHC in clinical data between heart failure patients based on the 4 heart failure groups determined from our methodology. Light gray dashed line denotes the average, and the gray box contains one standard deviation above and below the mean of each clinical value (*p-value <0.05, **p-value <0.01, ***p-value <0.001).