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, estimation of initial volume distribution in the cardiovascular system, formulation of the residual expression used to determine 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 study is a reduced version of the Smith et al. model [3] adapted from our previous study [2]. This reduced version balances the degree of model complexity with the informational content of the clinical data. Further reduction was made by omitting the pericardium and all zero pressure volumes in each compartment were set to zero.

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

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

Left (LV) and right (RV) ventricular pressure from end-systolic (es) and end-diastolic (ed) pressure-volume relationships are

$$P_{es,LV} = E_{LV}\, V_{LV}, \tag{S2}$$
$$P_{ed,LV} = P_{0,LV}\,(e^{\lambda_{LV}\, V_{LV}} - 1) \tag{S3}$$
$$P_{LV} = e_\tau P_{es,LV} + (1 - e_\tau) P_{ed,LV}, \tag{S4}$$
$$P_{es,RV} = E_{RV}\, V_{RV}, \tag{S5}$$
$$P_{ed,RV} = P_{0,RV}\,(e^{\lambda_{RV}\, V_{RV}} - 1), \quad \text{and} \tag{S6}$$
$$P_{RV} = e_\tau P_{es,LV} + (1 - e_\tau) P_{ed,RV}, \tag{S7}$$

where V_i is the compartment volume, E_i is a stiffness parameter, $P_{0,i}$ is a reference pressure, and λ_i reflects the passive stiffness. The systemic arterial (SA), systemic venous (SV), pulmonary arterial (PA), and pumonary venous (PV) pressures are

$$P_{SA} = E_{SA} V_{SA}, \tag{S8}$$
$$P_{SV} = E_{SV} V_{SV}, \tag{S9}$$
$$P_{PA} = E_{PA} V_{PA}, \quad \text{and} \tag{S10}$$
$$P_{PV} = E_{PV} V_{PV}. \tag{S11}$$

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 valves (mitral ($mval$), aortic ($aval$), tricuspid ($tval$), and pulmonary ($pval$) are treated as diodes to prevent backflow, that is,

$$Q_{mval} = \begin{cases} \dfrac{P_{PV} - P_{LV}}{R_{mval}} & \text{if } P_{PV} > P_{LV} \\ 0 & \text{otherwise,} \end{cases} \tag{S14}$$

Table S1. Parameter descriptions, values for normal CV function, and typical parameter bounds for the reduced CV systems model

Symbol	Units	Description	Value	Lower bound	Upper bound
Left ventricle (LV)					
E_{LV}	mmHg mL^{-1}	LV active contractility	4.32	0.1	10
$P_{0,LV}$	mmHg	LV reference pressure	0.12	0.01	5
λ_{LV}	mL^{-1}	LV passive stiffness	0.02	0.005	0.1
Right ventricle (RV)					
E_{RV}	mmHg mL^{-1}	RV active contractility	0.70	0.05	5
$P_{0,RV}$	mmHg	RV reference pressure	0.22	0.01	5
λ_{RV}	mL^{-1}	RV passive stiffness	0.02	0.005	0.1
Pulmonary arteries (PA) and veins (PV)					
E_{PA}	mmHg mL^{-1}	PA stiffness	0.26	0.05	5
E_{PV}	mmHg mL^{-1}	PV stiffness	0.01	0.0005	0.1
R_{pul}	mmHg s mL^{-1}	Pulmonary resistance	0.13	0.005	1
Systemic arteries (SA) and veins (SV)					
E_{SA}	mmHg mL^{-1}	SA stiffness	0.90	0.05	5
E_{SV}	mmHg mL^{-1}	SV stiffness	0.01	0.0001	0.1
R_{sys}	mmHg s mL^{-1}	Systemic resistance	1.28	0.05	15
Heart valve resistances					
R_{mval}	mmHg s mL^{-1}	Mitral valve	0.016	0.005	0.5
R_{aval}	mmHg s mL^{-1}	Aortic valve	0.018	0.005	0.5
R_{tval}	mmHg s mL^{-1}	Tricuspid valve	0.024	0.005	0.5
R_{pval}	mmHg s mL^{-1}	Pulmonary valve	0.006	0.0005	0.25

$$Q_{aval} = \begin{cases} \dfrac{P_{LV} - P_{SA}}{R_{aval}} & \text{if } P_{LV} > P_{SA} \\ 0 & \text{otherwise,} \end{cases} \tag{S15}$$

$$Q_{tval} = \begin{cases} \dfrac{P_{SV} - P_{RV}}{R_{tval}} & \text{if } P_{SV} > P_{RV} \\ 0 & \text{otherwise,} \end{cases} \tag{S16}$$

and

$$Q_{pval} = \begin{cases} \dfrac{P_{RV} - P_{PA}}{R_{pval}} & \text{if } P_{RV} > P_{PA} \\ 0 & \text{otherwise.} \end{cases} \tag{S17}$$

This model conserves volume by formulating differential equations using Kirchoff's Law, that is,

$$\frac{\mathrm{d}V_{LV}}{\mathrm{d}t} = Q_{mval} - Q_{aval}, \tag{S18}$$

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

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

$$\frac{\mathrm{d}V_{RV}}{\mathrm{d}t} = Q_{tval} - Q_{pval}, \tag{S21}$$

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

and

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

S1.1. Normal cardiovascular function parameterization

Table S1 describes all model parameters and lists the nominal values that result in normal cardiovascular function. This set of parameters prescribes a patient with roughly 120/80 mmHg SA pressure, 20/9 mmHg PA pressure, 85 mL LV diastolic volume, 57 mL LV stroke volume (SV) (for an ejection fraction (EF) of 67%), and 4.6 L min^{-1} cardiac output (CO). These values vary from the original Smith model parameters because we have reduced their model

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

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

EF_{MOD} - EF from Method of Discs [5].
EF_T - EF from Teichholz's equation [4].
EF_2 - Manuscript Equation (1).
EF_3 - Manuscript Equation (2).

and then adjusted the remaining parameters to produce cardiovascular function similar to the full Smith model. Figure S5 shows the model predictions for normal cardiovascular 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 LV systolic and diastolic volumes [5], the new volume estimates resulted in a new EF. Manuscript Figure 2 shows the decision trees used to determine the appropriate EF calculation for each patient. Table S2 lists the EF calculation used for each patient: EF from MOD (EF_{MOD}), EF from Teichholz's equation (EF_T) [4], EF_2 calculated using Manuscript Equation (1), and EF_3 calculated using 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.

S3. CALCULATION OF NOMINAL PARAMETERS

Nominal values for 14 of the 16 parameters in the model are specified for each patient using a combination of each patient's clinical data, the model equations, and values from the literature. The equations below are a summary of the NomParam_Calc function from the code.

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 listed in Table S3. The bar notation ($\bar{\cdot}$) indicates a nominal estimate whereas no bar indicates a clinical measure.

RV compartment volume estimates are assumed to be 90% of the LV volumes in both systole (*syst*) and diastole (*diast*), that is,

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

$$\bar{V}_{RV,diast} = 0.90\, V_{LV,diast}. \tag{S25}$$

Pressure drop across the aortic and pulmonary valve is assumed to be ∼2.5%. Also, pulse pressure (pp) in the pulmonary veins is assumed to be ∼20% of the PA pulse pressure, whereas SV pulse pressure is ∼5% of the SA pulse pressure. The following summarize the pressure estimates:

$$\bar{P}_{LV,syst} = 1.025\, P_{SA,syst} \tag{S26}$$

$$\bar{P}_{LV,diast} = 0.975\, \bar{P}_{PV,diast} \tag{S27}$$

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

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

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

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

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

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

$$\bar{P}_{SV,diast} = \begin{cases} 1.025\,\bar{P}_{RV,diast} & \text{if } P_{RV,diast} \le 0 \\ 1.025\,P_{RV,diast} & \text{if } P_{RV,diast} > 0 \end{cases} \tag{S34}$$

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

$$\bar{P}_{PV,syst} = \begin{cases} P_{PCW,ave} + \frac{2}{3}\,\bar{P}_{PV,pp} \\ \quad \text{if } 0.975\,P_{PA,syst} \ge P_{PCW,ave} + \frac{2}{3}\,\bar{P}_{PV,pp} \\ 0.4854\,P_{PA,syst} \\ \quad \text{if } 0.975\,P_{PA,syst} < P_{PCW,ave} + \frac{2}{3}\,\bar{P}_{PV,pp} \end{cases} \tag{S36}$$

For the nominal values of $\bar{V}_{PA,syst}$, $\bar{V}_{PV,syst}$, $\bar{V}_{SA,syst}$, and $\bar{V}_{SV,syst}$, see nominal/initial volume calculation in Section S4 below.

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

The LV and RV end-diastolic reference pressures ($P_{0,LV} = 0.1203$ mmHg and $P_{0,RV} = 0.2157$ mmHg) are set at nominal values so the ventricular end-diastolic stiffness exponents (λ_{LV} and λ_{RV}) can be estimated explicitly from the model equations, i.e.,

$$\bar{\lambda}_{LV} = \frac{\ln(\bar{P}_{LV,diast}/P_{0,LV})}{V_{LV,diast}} \text{ and} \tag{S37}$$

$$\bar{\lambda}_{RV} = \begin{cases} \dfrac{\ln(\bar{P}_{RV,diast}/P_{0,RV})}{\bar{V}_{RV,diast}} & \text{if } P_{RV,diast} \le 0 \\ \dfrac{\ln(P_{RV,diast}/P_{0,RV})}{\bar{V}_{RV,diast}} & \text{if } P_{RV,diast} > 0 \end{cases} \tag{S38}$$

For the nominal RV passive stiffness (λ_{RV}), when the RV diastolic pressure ($P_{RV,diast}$) is nonpositive, a positive value is calculated from the estimate of the SV pulse pressure ($P_{SV,pp}$).

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 RV systolic pressure ($P_{RV,syst}$), likely due to the fact that these two measurements are made serially rather than simultaneously. In this case, computation of the nominal pulmonary valve resistance (R_{pval}) value is made differently than if $P_{RV,syst}$ is greater than $P_{PA,syst}$. For the nominal tricuspid valve resistance (R_{tval}), when the RV diastolic pressure ($P_{RV,diast}$) is nonpositive, a positive value is calculated from $P_{SV,pp}$. For the nominal pulmonary valve resistance (R_{pval}), when the measured $P_{PA,syst}$ is larger than $P_{RV,syst}$, a pressure drop of 2.5% across the pulmonary valve is assumed to generate a nonnegative estimate of R_{PV}. All heart valve resistances are computed as

$$\bar{R}_{mval} = \frac{\bar{P}_{PV,diast} - \bar{P}_{LV,diast}}{\mathrm{CO}_{\mathrm{RHC}}} \tag{S39}$$

$$\bar{R}_{aval} = \frac{\bar{P}_{LV,syst} - \bar{P}_{SA,syst}}{\mathrm{CO}_{\mathrm{RHC}}} \tag{S40}$$

$$\bar{R}_{tval} = \begin{cases} \dfrac{\bar{P}_{SV,diast} - \bar{P}_{RV,diast}}{\mathrm{CO}_{\mathrm{RHC}}} & \text{if } P_{RV,diast} \le 0 \\ \dfrac{\bar{P}_{SV,diast} - P_{RV,diast}}{\mathrm{CO}_{\mathrm{RHC}}} & \text{if } P_{RV,diast} > 0 \end{cases} \tag{S41}$$

$$\bar{R}_{pval} = \begin{cases} \dfrac{P_{RV,syst} - \bar{P}_{PA,syst}}{\mathrm{CO}_{\mathrm{RHC}}} & \text{if } P_{PA,syst} \ge P_{RV,syst} \\ \dfrac{P_{RV,syst} - P_{PA,syst}}{\mathrm{CO}_{\mathrm{RHC}}} & \text{if } P_{PA,diast} < P_{RV,syst} \end{cases} \tag{S42}$$

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

$$\bar{R}_{sys} = \frac{P_{SA,ave} - \bar{P}_{SV,syst}}{\mathrm{CO}_{\mathrm{RHC}}} \tag{S43}$$

$$\bar{R}_{pul} = \begin{cases} \dfrac{P_{PA,ave} - \bar{P}_{PV,syst}}{\mathrm{CO}_{\mathrm{RHC}}} \\ \quad \text{if } 0.975\,P_{PA,ave} \ge P_{PCW,ave} + \frac{2}{3}\bar{P}_{PV,pp} \\ \dfrac{P_{PA,syst} - \bar{P}_{PV,syst}}{\mathrm{CO}_{\mathrm{RHC}}} \\ \quad \text{if } 0.975\,P_{PA,ave} < P_{PCW,ave} + \frac{2}{3}\,\bar{P}_{PV,pp} \end{cases} \tag{S44}$$

All elastance parameters were approximated using the systolic pressure and stressed volume estimates as

$$\bar{E}_{LV} = \frac{\bar{P}_{LV,syst}}{V_{LV,syst}} \tag{S45}$$

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

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

$$\bar{E}_{RV} = \frac{P_{RV,syst}}{\bar{V}_{RV,syst}} \tag{S48}$$

$$\bar{E}_{PA} = \frac{P_{PA,syst} - P_{PA,diast}}{\bar{V}_{PA,syst}} \tag{S49}$$

$$\bar{E}_{PV} = \frac{\bar{P}_{PV,pp}}{\bar{V}_{PV,syst}} \tag{S50}$$

S4. RECALCULATION OF INITIAL VOLUME DISTRIBUTIONS

A recent 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 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 and to ensure the percentages of stressed volume in each compartment 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 [1]. 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 blood volume distributions 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 initial 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 calculate new volumes in the heart as

$$V^*_{s,B,LV} = 0.70\ V_{t,B,LV} \tag{S51}$$

$$V^*_{s,B,RV} = 0.70\ V_{t,B,RV} \tag{S52}$$

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

$$V_{s,B,nh} = V_{s,B,tot} - V_{s,B,LV} - V_{s,B,RV}, \tag{S53}$$

where the subscript *nh* denotes "non-heart".

To obtain a total stressed volume fraction of 30% for each patient, we have

$$V^*_{s,B,tot} = 0.30\ V_{t,B,tot}. \tag{S54}$$

Table S4. Blood volume distributions in mL adapted from Beneken [1].

Stressed		**Unstressed**		**Total**	
Left atrium (LA)					
$V_{s,B,LA}$	50	$V_{u,B,LA}$	30	$V_{t,B,LA}$	80
Left ventricle (LV)					
$V_{s,B,LV}$	125	$V_{u,B,LV}$	0	$V_{t,B,LV}$	125
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
Right atrium (RA)					
$V_{s,B,RA}$	50	$V_{u,B,RA}$	30	$V_{t,B,RA}$	80
Right ventricle (RV)					
$V_{s,B,RV}$	125	$V_{u,B,RV}$	0	$V_{t,B,RV}$	125
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
Totals					
$V_{s,B,tot}$	852	$V_{u,B,tot}$	3692	$V_{t,B,tot}$	4544

Then, we subtract off the new heart chamber stressed volumes as

$$V^*_{s,B,nh} = V^*_{s,B,tot} - V^*_{s,B,LV} - V^*_{s,B,RV}. \tag{S55}$$

The difference between these stressed volumes is the amount of *recruited* volume over and above the Beneken stressed volumes, that is,

$$V_{s,R,tot} = V^*_{s,B,nh} - V_{s,B,nh}. \tag{S56}$$

The recruited volume in each compartment is calculated based on the fraction of the unstressed volume in each compartment with respect to the total unstressed volume, $V_{u,B,tot}$, that is

$$V_{s,B,R,SA} = V_{s,R,tot}\ (V_{u,B,SA}/V_{u,B,tot}), \tag{S57}$$

$$V_{s,B,R,SV} = V_{s,R,tot}\ (V_{u,B,SV}/V_{u,B,tot}), \tag{S58}$$

$$V_{s,B,R,PA} = V_{s,R,tot}\ (V_{u,B,PA}/V_{u,B,tot}), \quad \text{and} \tag{S59}$$

$$V_{s,B,R,PV} = V_{s,R,tot}\ (V_{u,B,PV}/V_{u,B,tot}). \tag{S60}$$

Adding these recruited volumes to the Beneken values will give the volumes with the desired 30% total stressed

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

Stressed		Unstressed		Total	
Left atrium (LA)					
$V^*_{s,B,LA}$	40	$V^*_{u,B,LA}$	40	$V^*_{t,B,LA}$	80
Left ventricle (LV)					
$V^*_{s,B,LV}$	88	$V^*_{u,B,LV}$	37	$V^*_{t,B,LV}$	125
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	$V^*_{u,B,SV}$	2254	$V^*_{t,B,SV}$	2916
Right atrium (RA)					
$V^*_{s,B,RA}$	40	$V^*_{u,B,RA}$	40	$V^*_{t,B,RA}$	80
Right ventricle (RV)					
$V^*_{s,B,RV}$	88	$V^*_{u,B,RV}$	37	$V^*_{t,B,RV}$	125
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
Totals					
$V^*_{s,B,tot}$	1355	$V^*_{u,B,tot}$	3189	$V^*_{t,B,tot}$	4544

volume as

$$V^*_{s,B,SA} = V_{s,B,SA} + V_{s,B,R,SA}, \tag{S61}$$
$$V^*_{s,B,SV} = V_{s,B,SV} + V_{s,B,R,SV}, \tag{S62}$$
$$V^*_{s,B,PA} = V_{s,B,PA} + V_{s,B,R,PA}, \quad \text{and} \tag{S63}$$
$$V^*_{s,B,PV} = V_{s,B,PV} + V_{s,B,R,PV}. \tag{S64}$$

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

$$f_{VsB,SA} = V^*_{s,B,SA}/V_{t,B,SA}, \tag{S65}$$
$$f_{VsB,SV} = V^*_{s,B,SV}/V_{t,B,SV}, \tag{S66}$$
$$f_{VsB,PA} = V^*_{s,B,PA}/V_{t,B,PA}, \quad \text{and} \tag{S67}$$
$$f_{VsB,PV} = V^*_{s,B,PV}/V_{t,B,PV}. \tag{S68}$$

These fractions are used for the patient-specific total volume to get an initial stressed volume distribution across compartments assuming a 30% total stressed volume (see Table S5).

S5. RESIDUAL EQUATION USED FOR SENSITIVITY ANALYSIS AND OPTIMIZATION

A residual function was used to assess parameter influence 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 following equations show the eleven pressures, volumes, and cardiac output measures from these two simulations used to compute the eleven residuals between the simulation and clinical measures using an appropriate normalization for each residual:

$$P^{res}_{RV,syst} = \frac{\mid P^{sim}_{RV,syst} - P^{data}_{RV,syst} \mid}{P^{data}_{SA,syst}}, \tag{S69}$$
$$P^{res}_{RV,diast} = \frac{\mid P^{sim}_{RV,diast} - P^{data}_{RV,diast} \mid}{P^{data}_{SA,syst}}, \tag{S70}$$
$$P^{res}_{PA,syst} = \frac{\mid P^{sim}_{PA,syst} - P^{data}_{PA,syst} \mid}{P^{data}_{SA,syst}}, \tag{S71}$$
$$P^{res}_{PA,diast} = \frac{\mid P^{sim}_{PA,diast} - P^{data}_{PA,diast} \mid}{P^{data}_{SA,syst}}, \tag{S72}$$
$$P^{res}_{SA,syst} = \frac{\mid P^{sim}_{SA,syst} - P^{data}_{SA,syst} \mid}{P^{data}_{SA,syst}}, \tag{S73}$$
$$P^{res}_{SA,diast} = \frac{\mid P^{sim}_{SA,diast} - P^{data}_{SA,diast} \mid}{P^{data}_{SA,syst}}, \tag{S74}$$
$$P^{res}_{PCW,ave} = \frac{\mid P^{sim}_{PCW,ave} - P^{data}_{PCW,ave} \mid}{P^{data}_{SA,syst}}, \tag{S75}$$
$$\mathrm{CO}^{res}_{\mathrm{RHC}} = \frac{\mid \mathrm{CO}^{sim}_{\mathrm{RHC}} - \mathrm{CO}^{data}_{\mathrm{RHC}} \mid}{\max\left(\mathrm{CO}^{data}_{\mathrm{RHC}}, \mathrm{CO}^{data}_{\mathrm{TTE}}\right)}, \tag{S76}$$
$$V^{res}_{LV,syst} = \frac{\mid V^{sim}_{LV,syst} - V^{data}_{LV,syst} \mid}{V^{data}_{LV,syst}}, \tag{S77}$$
$$V^{res}_{LV,diast} = \frac{\mid V^{sim}_{LV,diast} - V^{data}_{LV,diast} \mid}{V^{data}_{LV,syst}}, \tag{S78}$$

and

$$\mathrm{CO}^{res}_{\mathrm{TTE}} = \frac{\mid \mathrm{CO}^{sim}_{\mathrm{TTE}} - \mathrm{CO}^{data}_{\mathrm{TTE}} \mid}{\max\left(\mathrm{CO}^{data}_{\mathrm{RHC}}, \mathrm{CO}^{data}_{\mathrm{TTE}}\right)}. \tag{S79}$$

The residuals are then averaged with no additional weights as

$$Res = \frac{\sum_{i=1}^{7} P^{res}_i + \sum_{j=1}^{2} \mathrm{CO}^{res}_j + \sum_{k=1}^{2} V^{res}_k}{11} \tag{S80}$$

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	HFrEF
3	HFrEF	A	A	HFrEF
4	HFrEF	A	B	HFrEF
5	HFrEF	B	B	HFrEF
6	HFrEF	A	A	HFrEF
7	HFrEF	A	B	HFrEF
8	HFrEF	A	A	HFrEF
9	HFrEF	A	B	HFrEF
10	HFrEF	A	B	HFrEF
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	B	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	HFpEF
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	B	HFpEF

NCC - not consistently clustered.

where $i = \{RV, syst\ RV, diast\ PA, syst\ PA, diast\ SA, syst\ SA, diast\ PCW, ave\}$, $j = \{\text{RHC TTE}\}$, 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. Note that HFpEF patients that fall in the overlap region are labeled as HFrEF for their hull location in Tables S6 and S7.

Table S7. Optimized parameter cluster classification

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

cluded for completeness. In Figure S1, we show the panels not included in Manuscript Figure 5 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 9 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 10 as we revisit the differences in the clinical measures between the HFrEF, HFpEF1, HFpEF2 and NCC groups. In Figure S4, we show the plot of the weighted loadings from the principal component analysis of the optimized parameters. The red circle indicates which parameters contribute the most to the total variance. In Figure S5, the model predictions for normal cardiovascular function are plotted using the parameters in Table S1. In Figures S6–S13, the model predictions for the patients with HFrEF are plotted. In Figures S14–S34, the model predictions for the patients with HFpEF are plotted.

REFERENCES

1. J. E. W. Beneken. A physical approach to hemodynamic aspects of the human cardiovascular system. Physical bases of circulatory transport: regulation and exchange. W. B. Saunders, PA, USA. 1979.
2. A. L. Colunga, K. G. Kim, N. P. Woodall, T. F. Dardas, J. H. Gennari, M. S. Olufsen. Deep phenotyping of cardiac function in heart transplant patients using cardiovascular system models. *JACC Heart Fail* 8: 172-184. 2020. DOI: 10.1113/JP279393.
3. B. W. Smith, J. G. Chase, R. I. Nokes, G. M. Shaw, and G. Wake. Minimal haemodynamic system model including ventricular interaction and vaLVe dynamics. *Med Eng Phys*, 26: 131-139. 2004. DOI: 10.1016/j.medengphy.2003.10.001.
4. L. E. Teichholz, T. Kreulen, M. V. Herman, and R. Gorlin. Problems in echocardiographic volume determinations: Echocardiographic-angiographic correlations in the presence or absence of asynergy. *Am J Cardiol*, 37: 7-11. 1976. DOI: 10.1016/0002-9149(76)90491-4.
5. H. L. Wyatt, M. K. Heng, S. Meerbaum, J. D Hestenes, J. M. Cobo, R. M. Davidson, and E. Corday. Cross-sectional echocardiography I. Analysis of mathematic models for quantifying mass of the left ventricle in dogs. *Circulation*, 60: 1104-1113. 1979. DOI: 10.1161/01.Cir.60.5.1104.

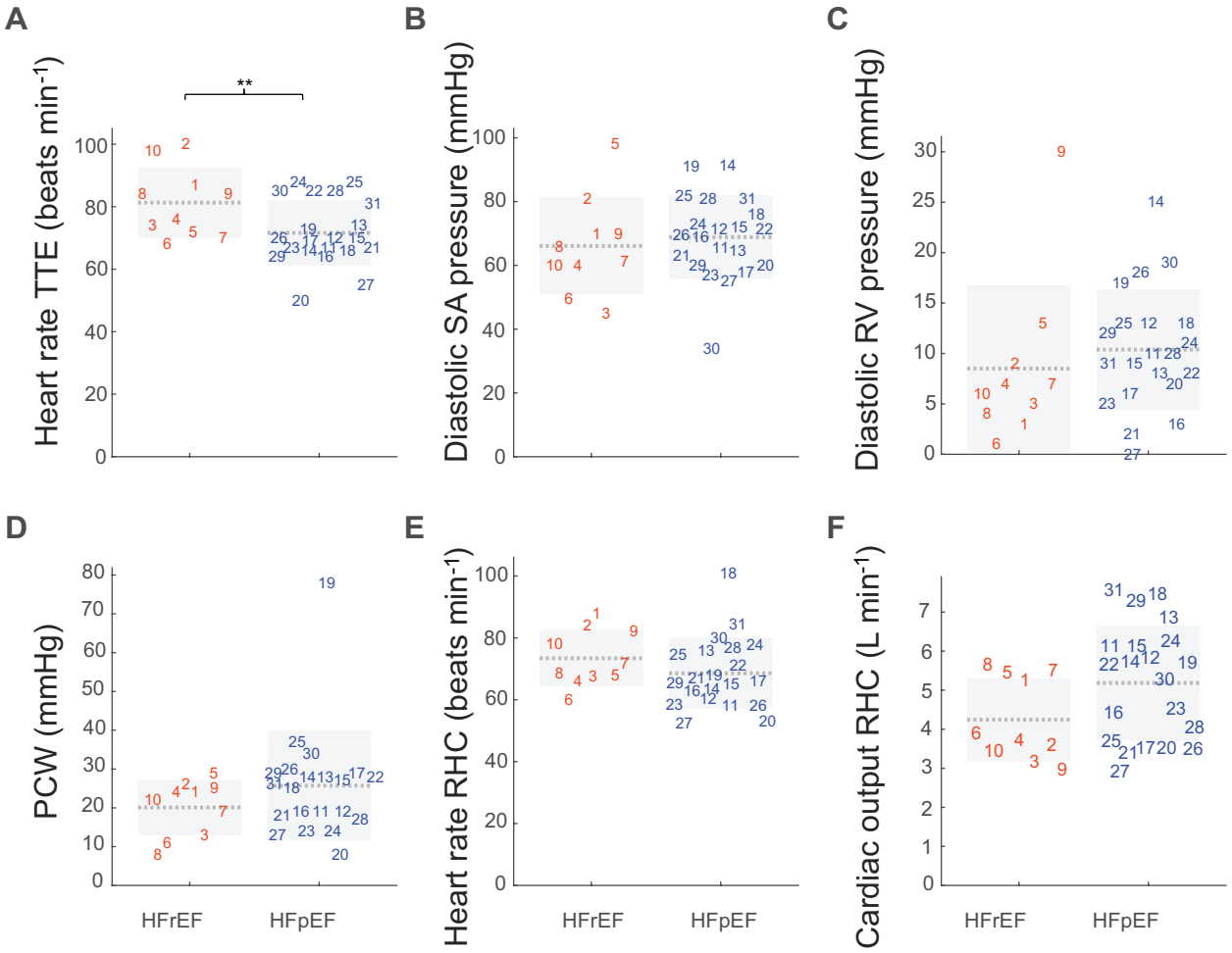

Fig. S1. Box plots of clinical data grouping heart failure patients based on their HFrEF and HFpEF diagnosis. A. Heart rate from the TTE (bpm). B. Diastolic systemic arterial (SA) pressure (mmHg) C. Diastolic right ventricular (RV) pressure (mmHg). D. Pulmonary capillary wedge (PCW) pressure (mmHg). E. Heart rate from the RHC (bpm) F. Cardiac output from the RHC (L min^{-1}). The 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).

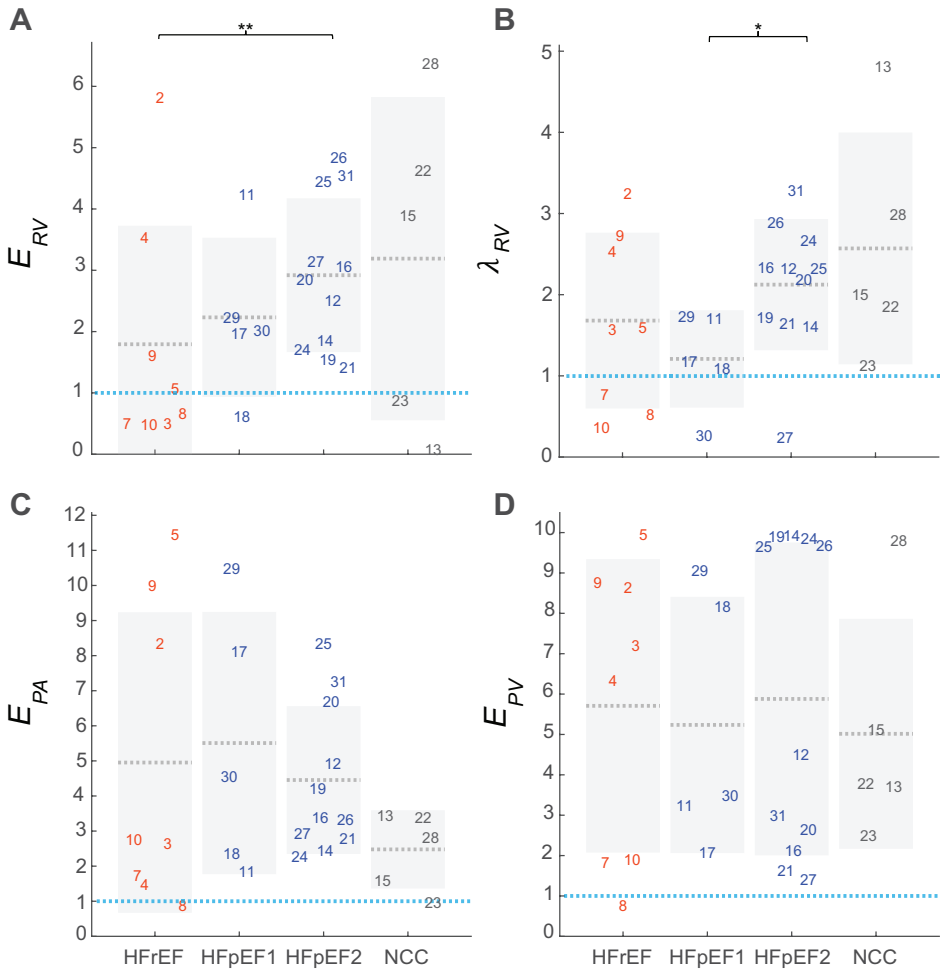

Fig. S2. Box plots of the optimized parameter values with 4 heart failure groups. Analysis of the optimized parameters gives us an understanding of the mechanistic differences between the three HFpEF groups that cannot be seen by analyzing the clinical data alone. A. Right ventricular (RV) active contractility (E_{RV}, mmHg mL^{-1}). B. RV passive stiffness (λ_{RV}, mL^{-1}). C. Pulmonary arterial (PA) stiffness (E_{PA}, mmHg mL^{-1}). D. PV stiffness (E_{PV}). All values are plotted relative to the normal model values given in Table S1, indicated by the horizontal dashed blue line. The 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).

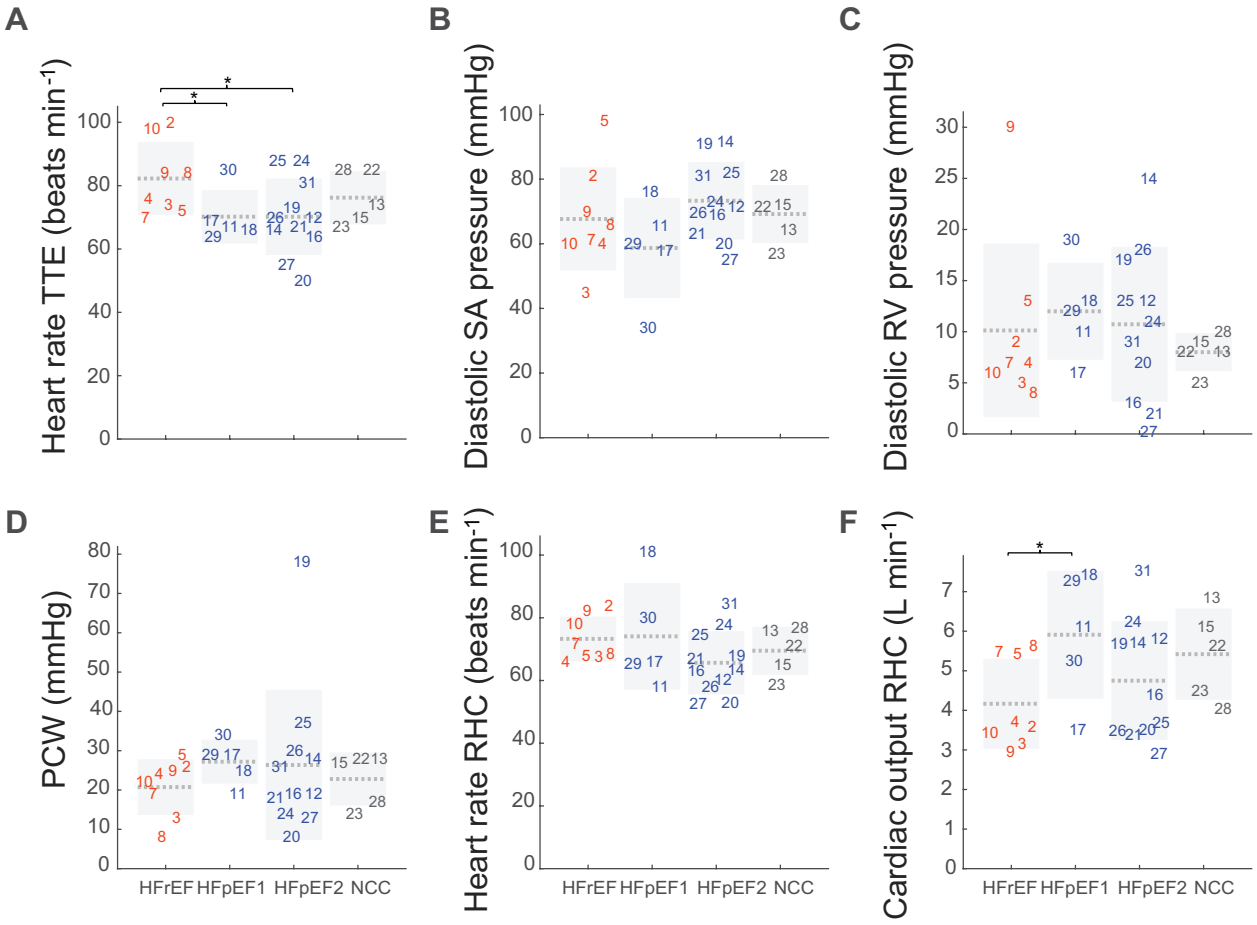

Fig. S3. Box plots of the clinical data with 4 heart failure groups with significant differences between heart failure patients based on their HFrEF and HFpEF diagnosis. A. Heart rate from the TTE (bpm) B. Diastolic systemic arterial (SA) pressure (mmHg). C. Diastolic RV pressure (mmHg). D. Pulmonary capillary wedge (PCW) pressure (mmHg). E. Heart rate from the RHC (bpm). F. Cardiac output from the RHC (L min^{-1}). The 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).

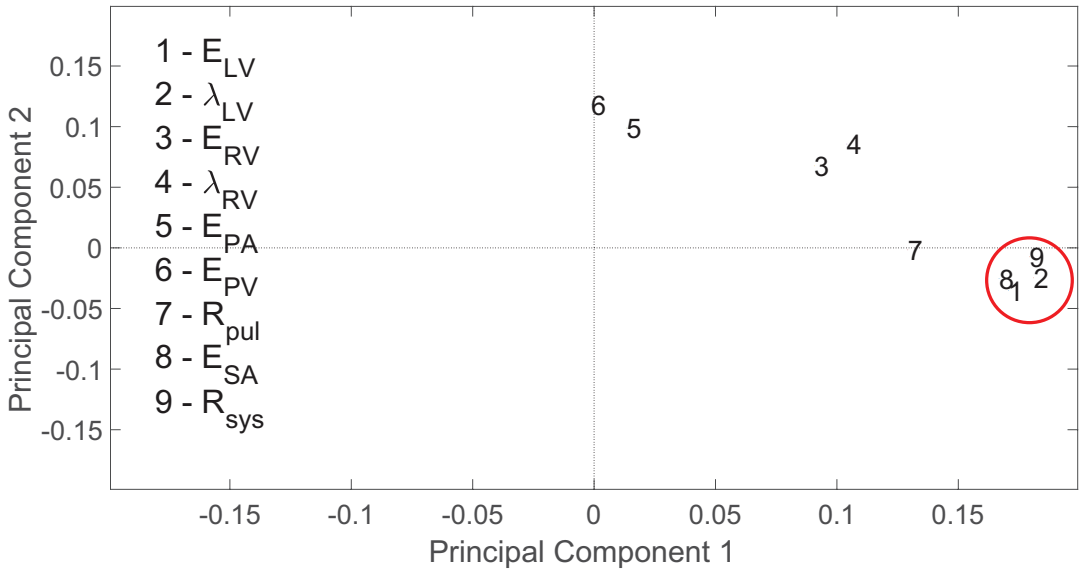

Fig. S4. Weighted loadings from the principal component analysis. The values in the red circle indicate the most influential parameters to the total variance.

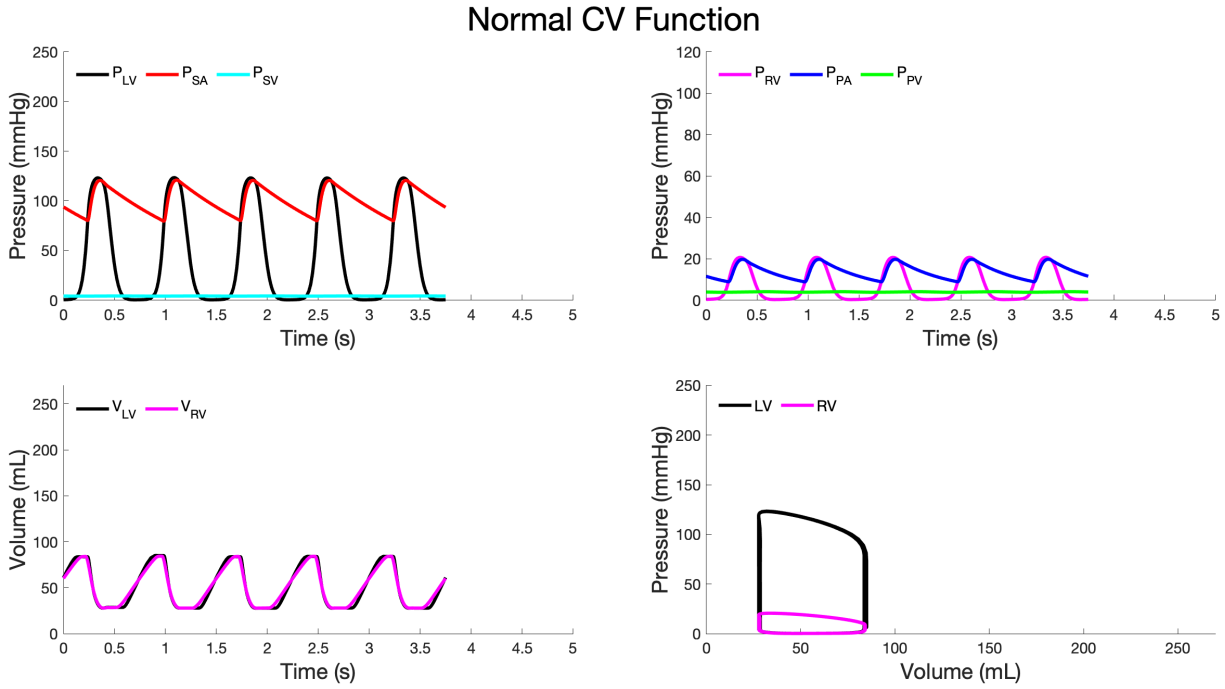

Fig. S5. Simulation of normal cardiovascular function using parameters from Table S1

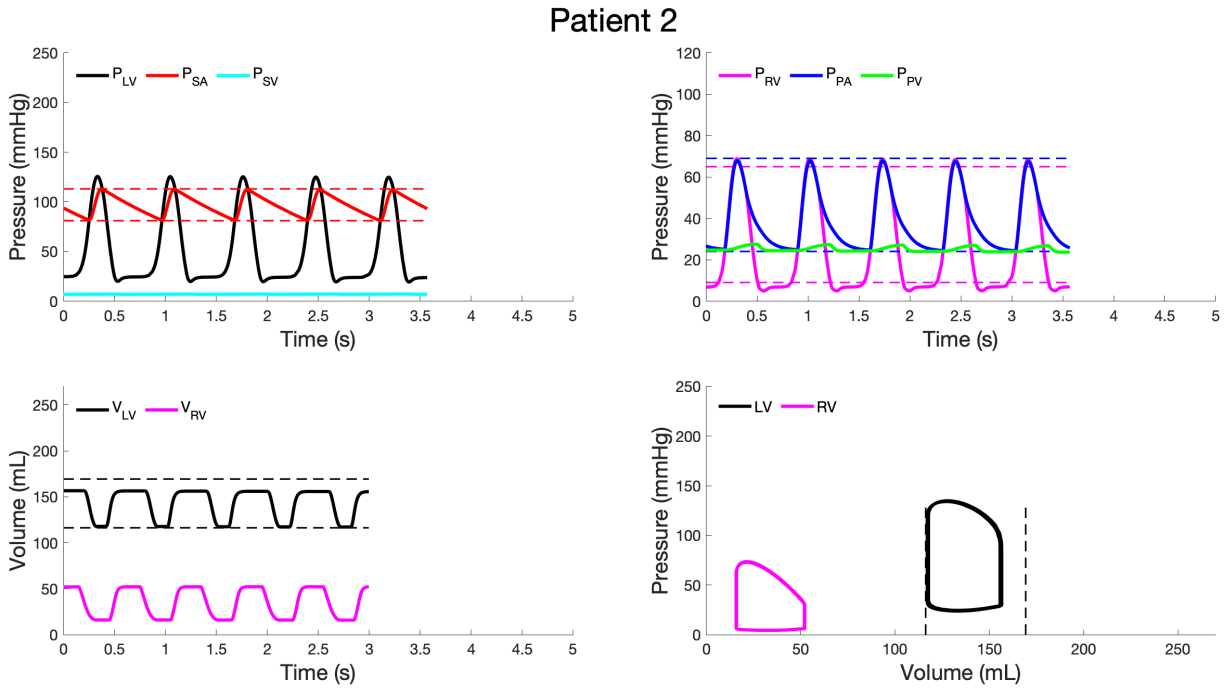

Fig. S6. Simulation fits to data for Patient 2 where dashed lines indicate the clinical measures and solid lines represent simulated cardiovascular function. CO is also matched during parameter optimization. For RHC: measured CO_{RHC} is 3.57 L/min and simulation CO is 3.55 L/min. For TTE: measured $CO_{MOD/T}$ is 5.30 L/min, measured CO_{LVOT} is 3.10 L/min and simulation CO is 3.95 L/min

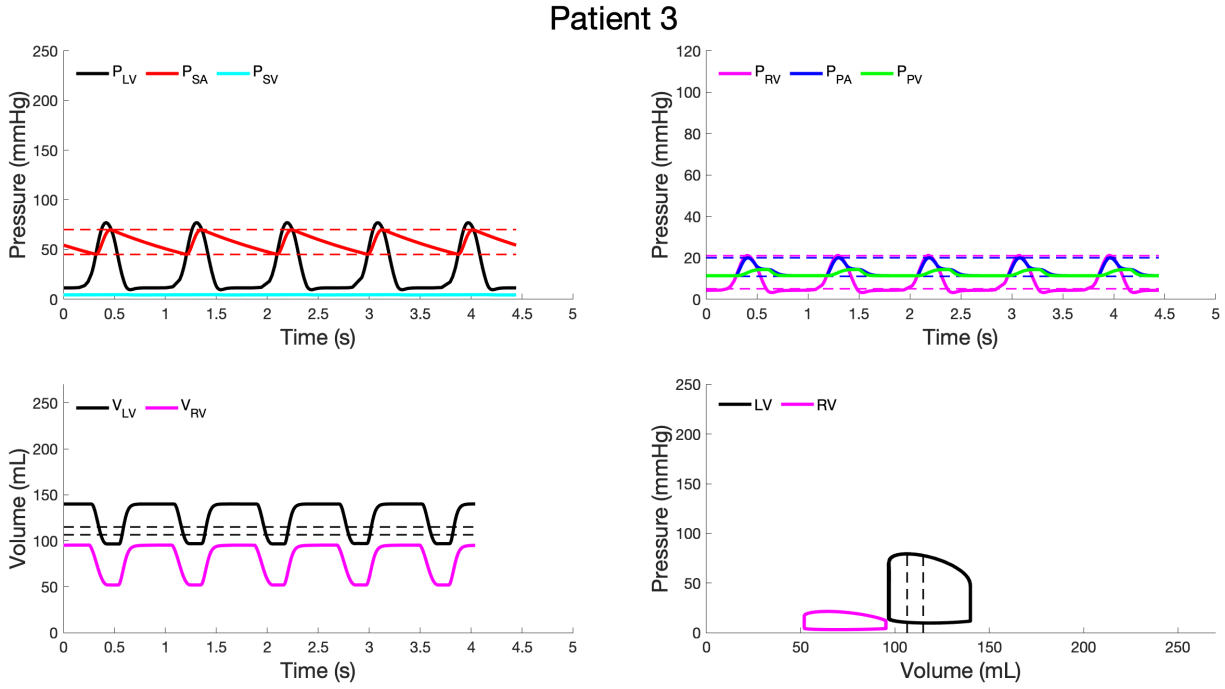

Fig. S7. Simulation fits to data for Patient 3 where dashed lines indicate the clinical measures and solid lines represent simulated cardiovascular function. CO is also matched during parameter optimization. For RHC: measured CO_{RHC} is 3.15 L/min and simulation CO is 3.07 L/min. For TTE: measured $CO_{MOD/T}$ is 0.63 L/min, measured CO_{LVOT} is 3.20 L/min and simulation CO is 3.22 L/min

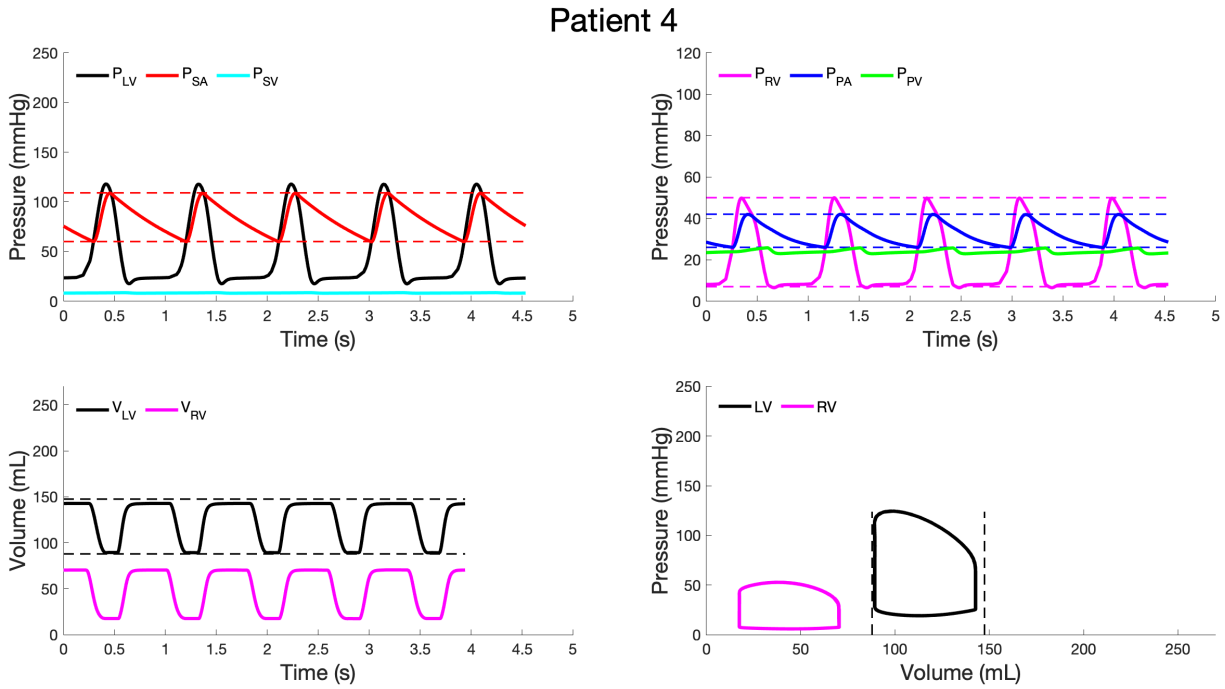

Fig. S8. Simulation fits to data for Patient 4 where dashed lines indicate the clinical measures and solid lines represent simulated cardiovascular function. CO is also matched during parameter optimization. For RHC: measured CO_{RHC} is 3.70 L/min and simulation CO is 3.71 L/min. For TTE: measured $CO_{MOD/T}$ is 4.53 L/min, measured CO_{LVOT} is 4.10 L/min and simulation CO is 4.08 L/min

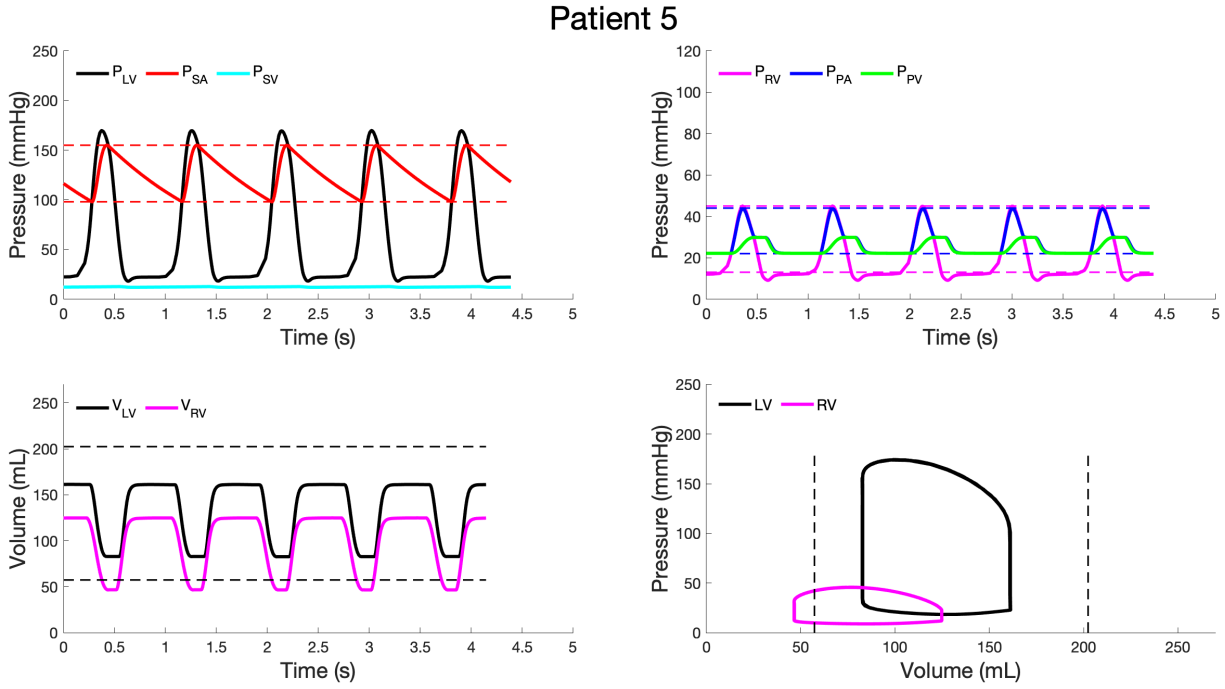

Fig. S9. Simulation fits to data for Patient 5 where dashed lines indicate the clinical measures and solid lines represent simulated cardiovascular function. CO is also matched during parameter optimization. For RHC: measured CO_{RHC} is 5.43 L/min and simulation CO is 5.44 L/min. For TTE: measured $CO_{MOD/T}$ is 10.44 L/min, measured CO_{LVOT} is 4.50 L/min and simulation CO is 5.67 L/min

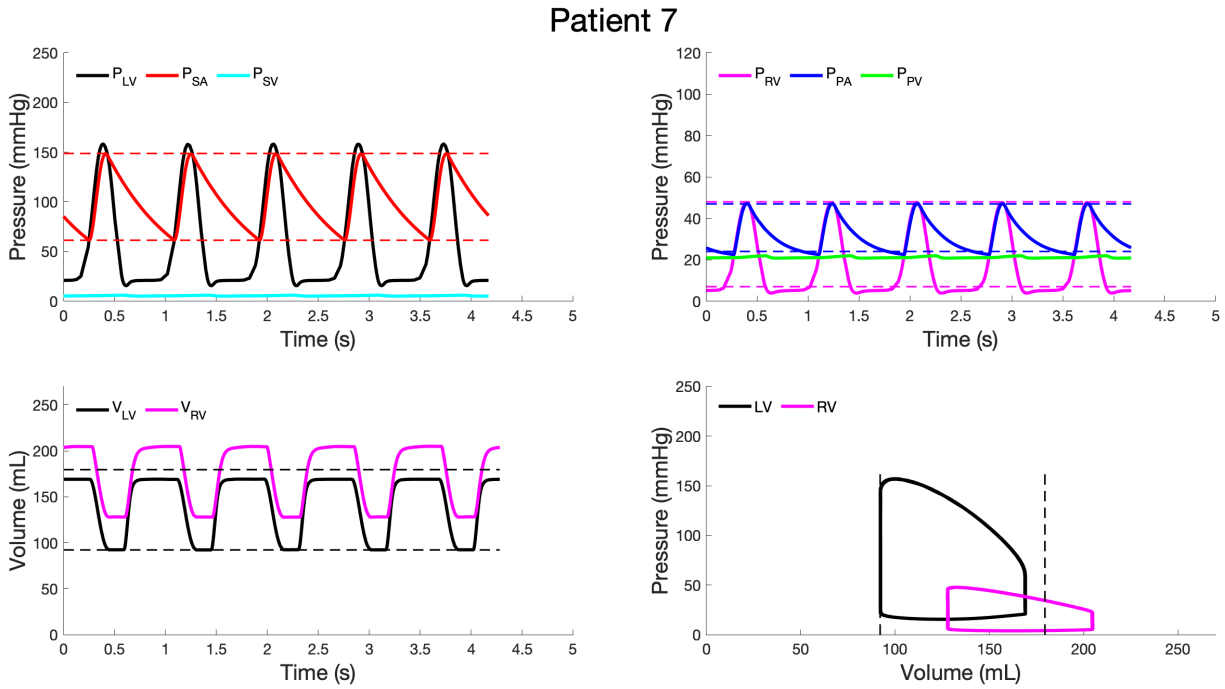

Fig. S10. Simulation fits to data for Patient 7 where dashed lines indicate the clinical measures and solid lines represent simulated cardiovascular function. CO is also matched during parameter optimization. For RHC: measured CO_{RHC} is 5.47 L/min and simulation CO is 5.47 L/min. For TTE: measured $CO_{MOD/T}$ is 6.11 L/min, measured CO_{LVOT} is 5.45 L/min and simulation CO is 5.39 L/min

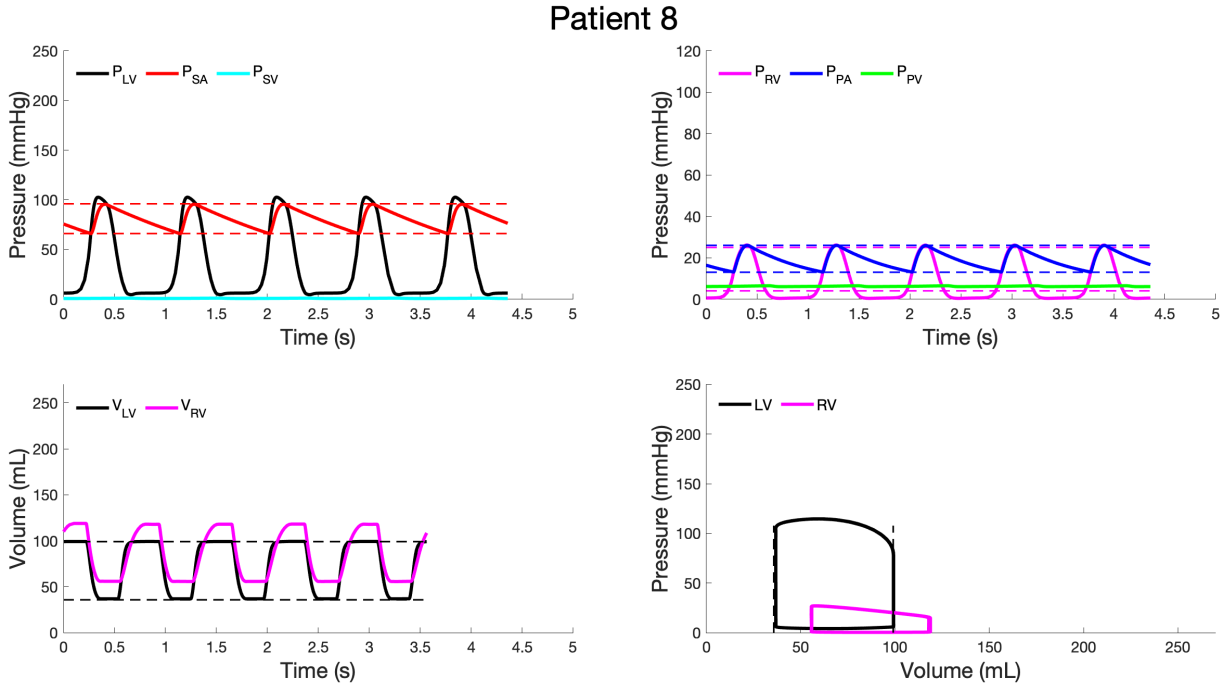

Fig. S11. Simulation fits to data for Patient 8 where dashed lines indicate the clinical measures and solid lines represent simulated cardiovascular function. CO is also matched during parameter optimization. For RHC: measured CO_{RHC} is 5.63 L/min and simulation CO is 4.59 L/min. For TTE: measured $CO_{MOD/T}$ is 5.32 L/min, measured CO_{LVOT} is 3.06 L/min and simulation CO is 5.25 L/min

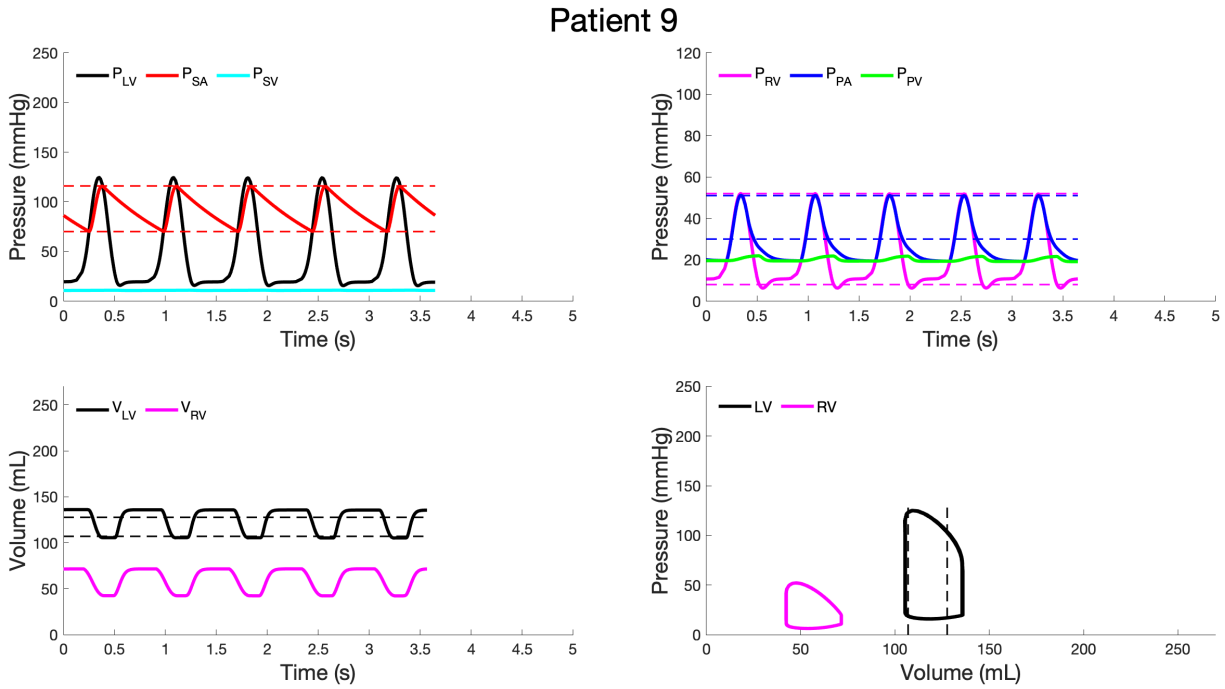

Fig. S12. Simulation fits to data for Patient 9 where dashed lines indicate the clinical measures and solid lines represent simulated cardiovascular function. CO is also matched during parameter optimization. For RHC: measured CO_{RHC} is 2.95 L/min and simulation CO is 2.57 L/min. For TTE: measured $CO_{MOD/T}$ is 1.74 L/min, measured CO_{LVOT} is 8.09 L/min and simulation CO is 2.60 L/min

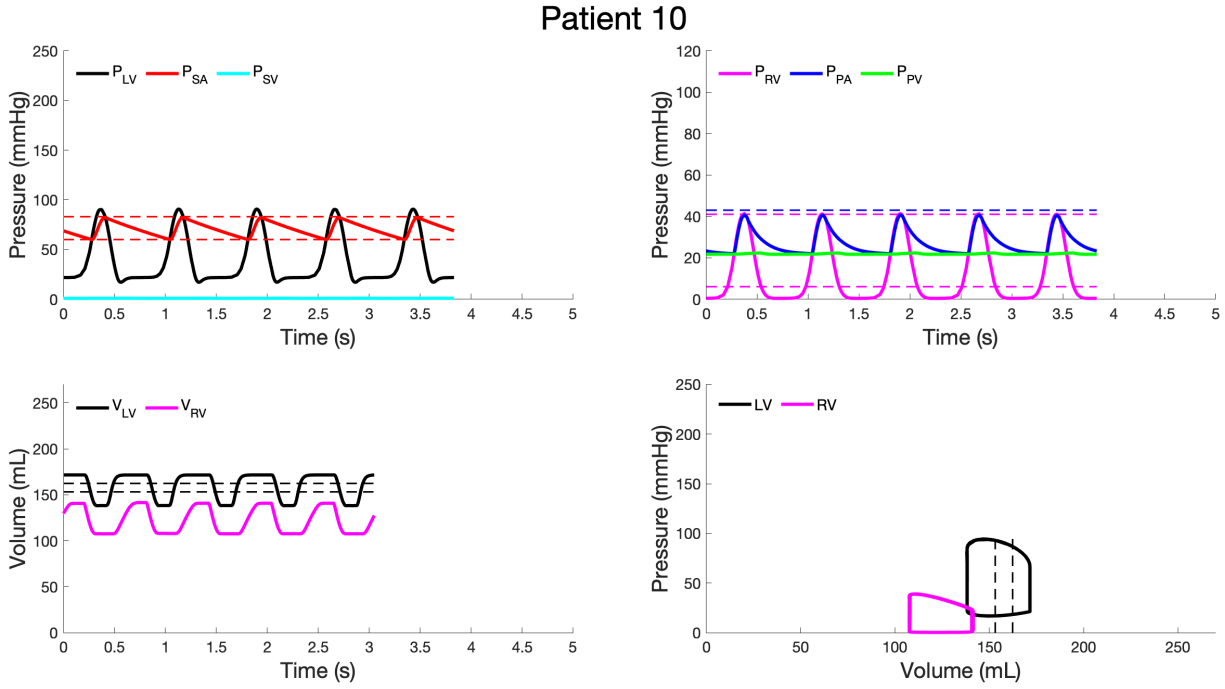

Fig. S13. Simulation fits to data for Patient 10 where dashed lines indicate the clinical measures and solid lines represent simulated cardiovascular function. CO is also matched during parameter optimization. For RHC: measured CO_{RHC} is 3.43 L/min and simulation CO is 3.08 L/min. For TTE: measured $CO_{MOD/T}$ is 0.90 L/min, measured CO_{LVOT} is 3.25 L/min and simulation CO is 3.28 L/min

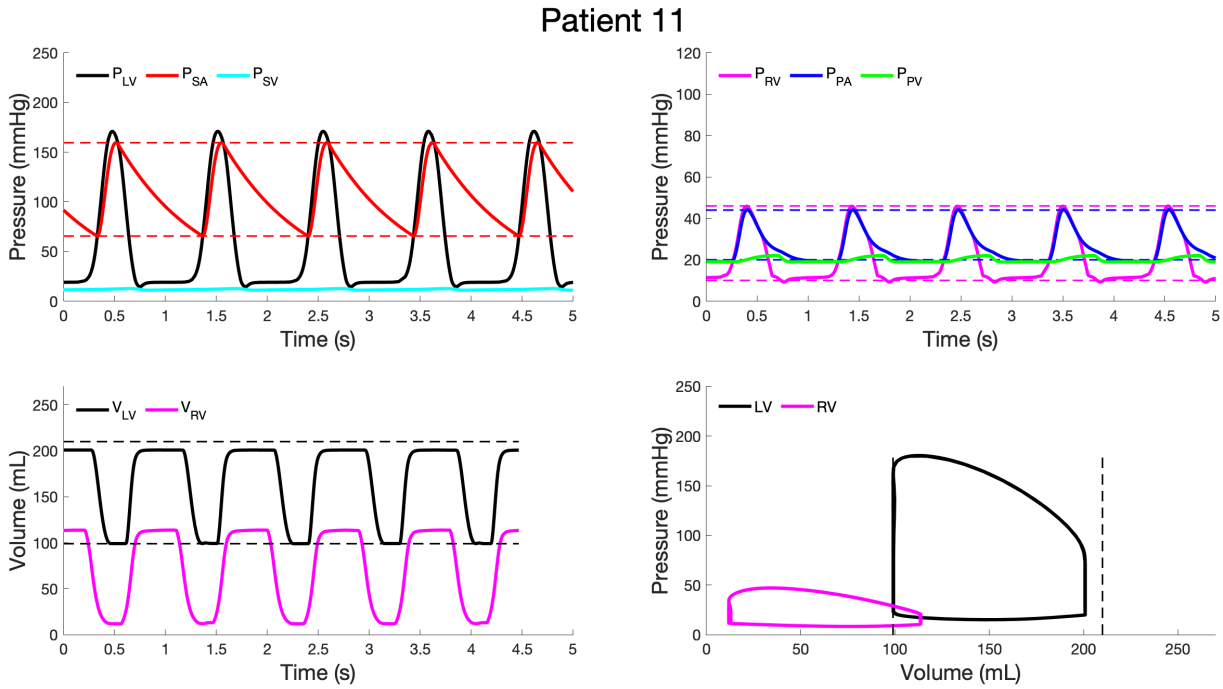

Fig. S14. Simulation fits to data for Patient 11 where dashed lines indicate the clinical measures and solid lines represent simulated cardiovascular function. CO is also matched during parameter optimization. For RHC: measured CO_{RHC} is 6.10 L/min and simulation CO is 6.10 L/min. For TTE: measured $CO_{MOD/T}$ is 7.44 L/min, measured CO_{LVOT} is 5.00 L/min and simulation CO is 6.83 L/min

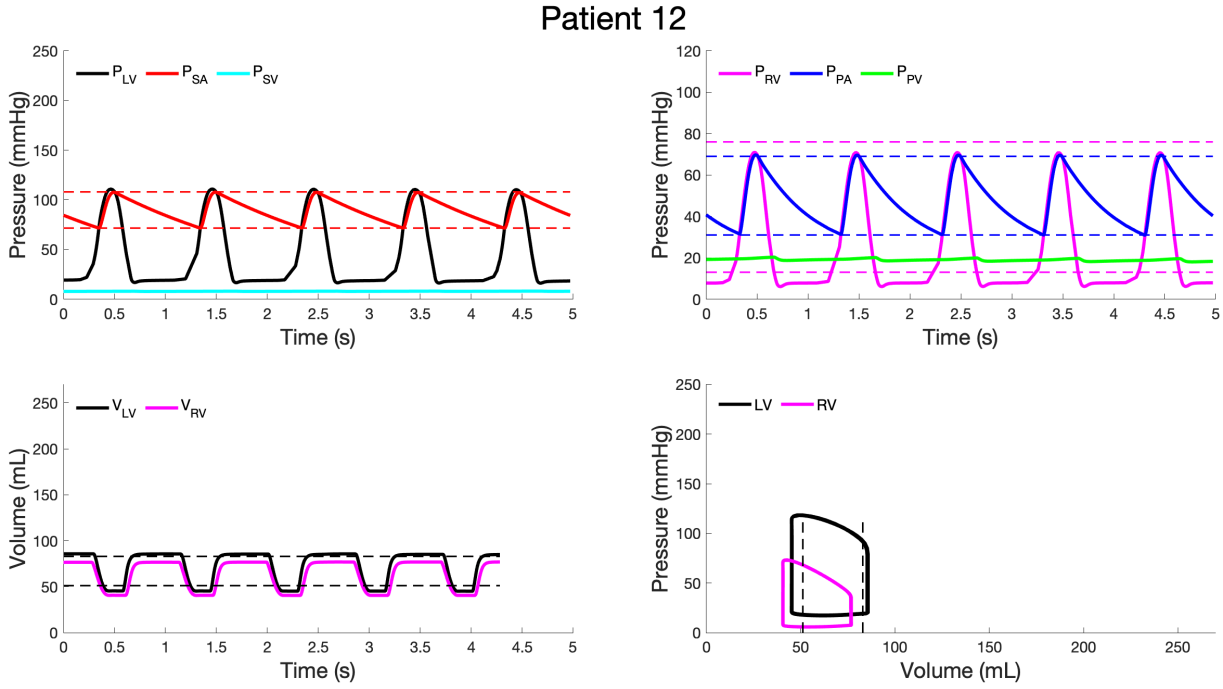

Fig. S15. Simulation fits to data for Patient 12 where dashed lines indicate the clinical measures and solid lines represent simulated cardiovascular function. CO is also matched during parameter optimization. For RHC: measured CO_{RHC} is 5.80 L/min and simulation CO is 2.58 L/min. For TTE: measured $CO_{MOD/T}$ is 2.23 L/min, measured CO_{LVOT} is 4.60 L/min and simulation CO is 2.85 L/min

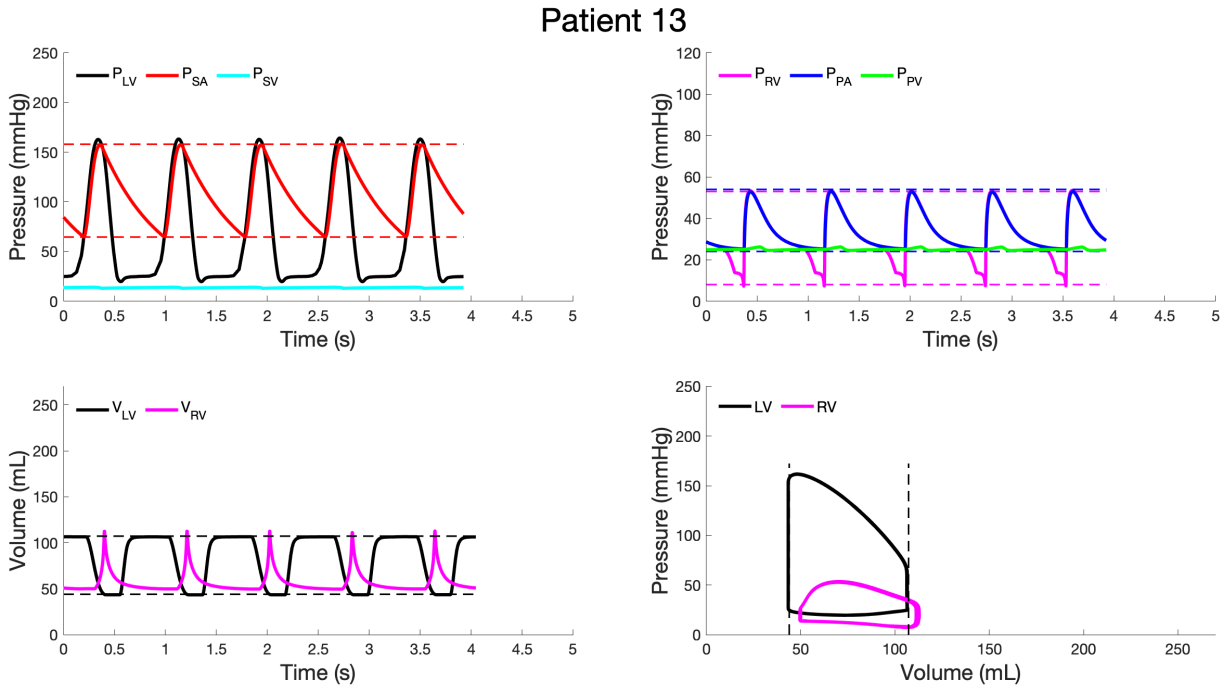

Fig. S16. Simulation fits to data for Patient 13 where dashed lines indicate the clinical measures and solid lines represent simulated cardiovascular function. CO is also matched during parameter optimization. For RHC: measured CO_{RHC} is 6.84 L/min and simulation CO is 4.83 L/min. For TTE: measured $CO_{MOD/T}$ is 4.68 L/min and simulation CO is 4.67 L/min

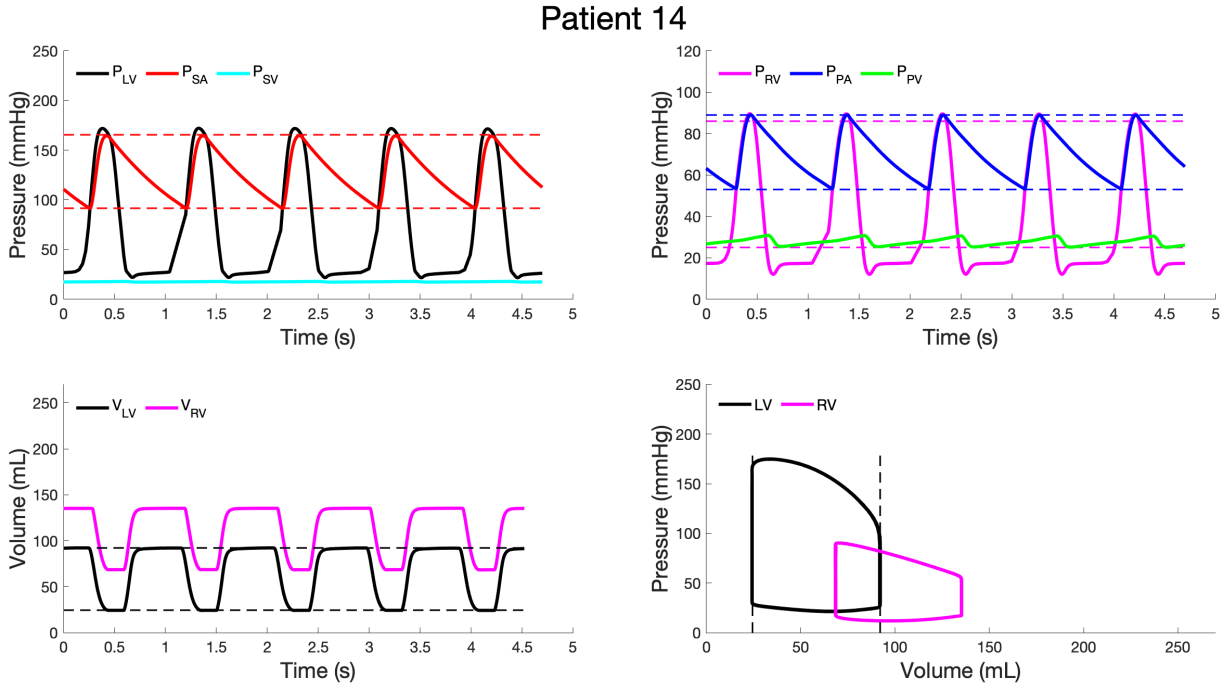

Fig. S17. Simulation fits to data for Patient 14 where dashed lines indicate the clinical measures and solid lines represent simulated cardiovascular function. CO is also matched during parameter optimization. For RHC: measured CO_{RHC} is 5.70 L/min and simulation CO is 4.36 L/min. For TTE: measured $CO_{MOD/T}$ is 4.47 L/min and simulation CO is 4.49 L/min

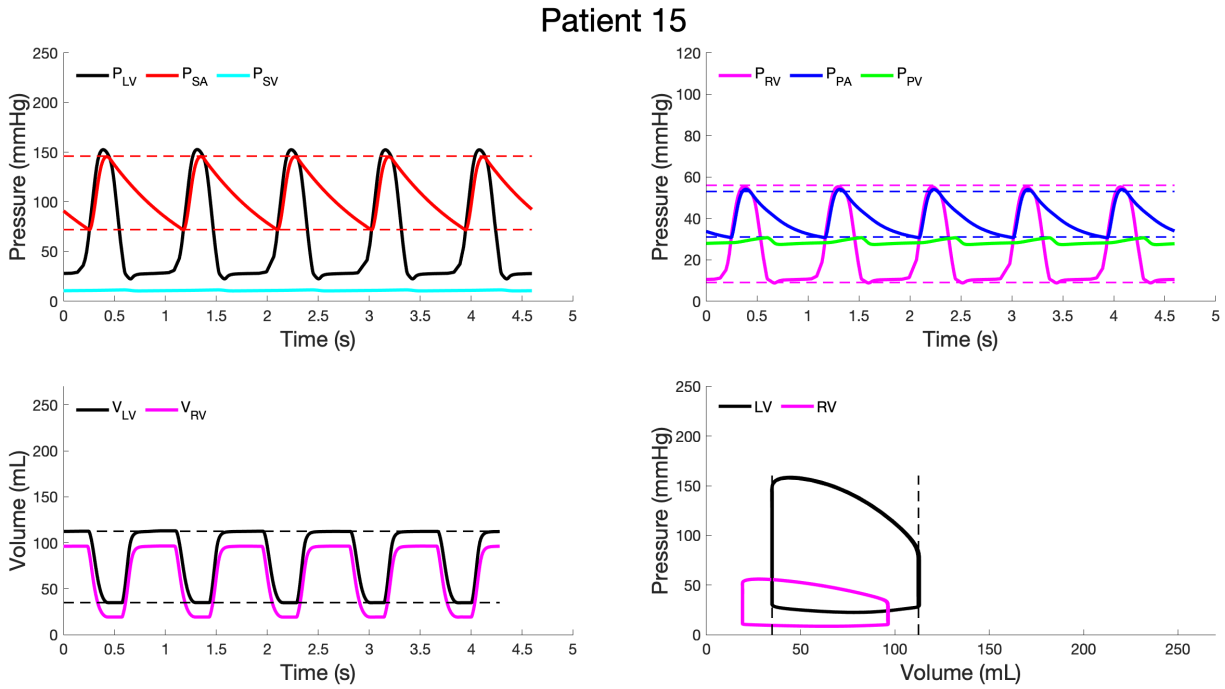

Fig. S18. Simulation fits to data for Patient 15 where dashed lines indicate the clinical measures and solid lines represent simulated cardiovascular function. CO is also matched during parameter optimization. For RHC: measured CO_{RHC} is 6.10 L/min and simulation CO is 5.12 L/min. For TTE: measured $CO_{MOD/T}$ is 5.43 L/min and simulation CO is 5.48 L/min

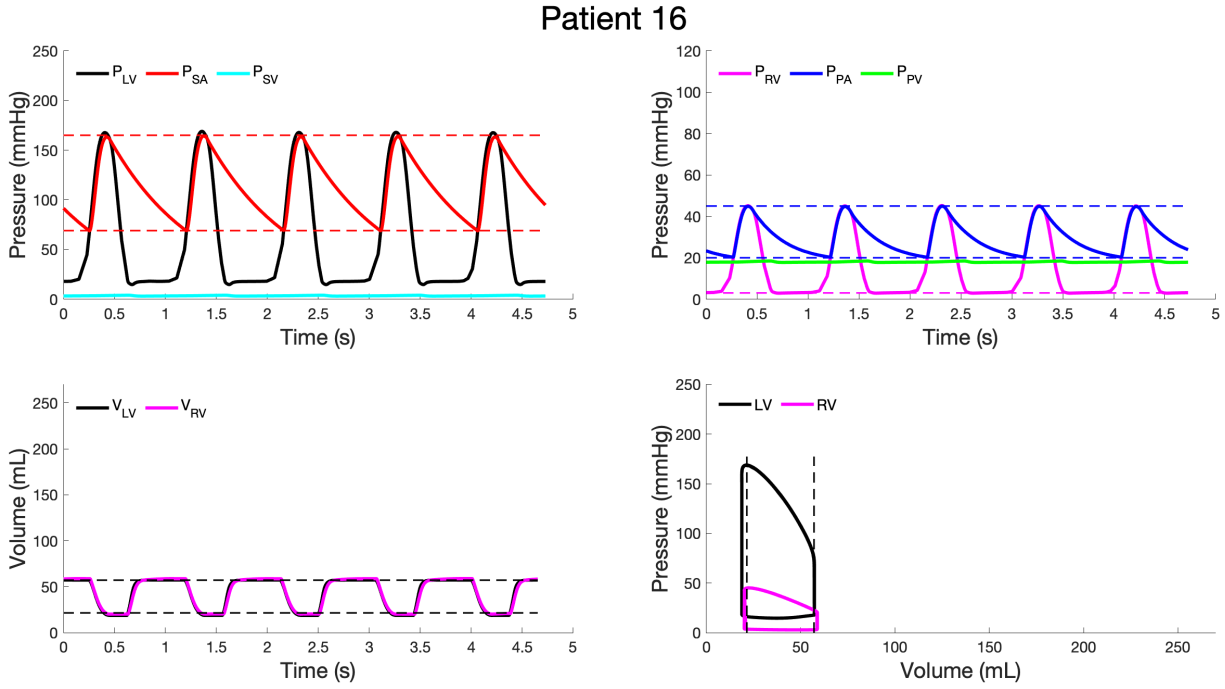

Fig. S19. Simulation fits to data for Patient 16 where dashed lines indicate the clinical measures and solid lines represent simulated cardiovascular function. CO is also matched during parameter optimization. For RHC: measured CO_{RHC} is 4.40 L/min and simulation CO is 2.47 L/min. For TTE: measured $CO_{MOD/T}$ is 2.28 L/min, measured CO_{LVOT} is 3.90 L/min and simulation CO is 2.47 L/min

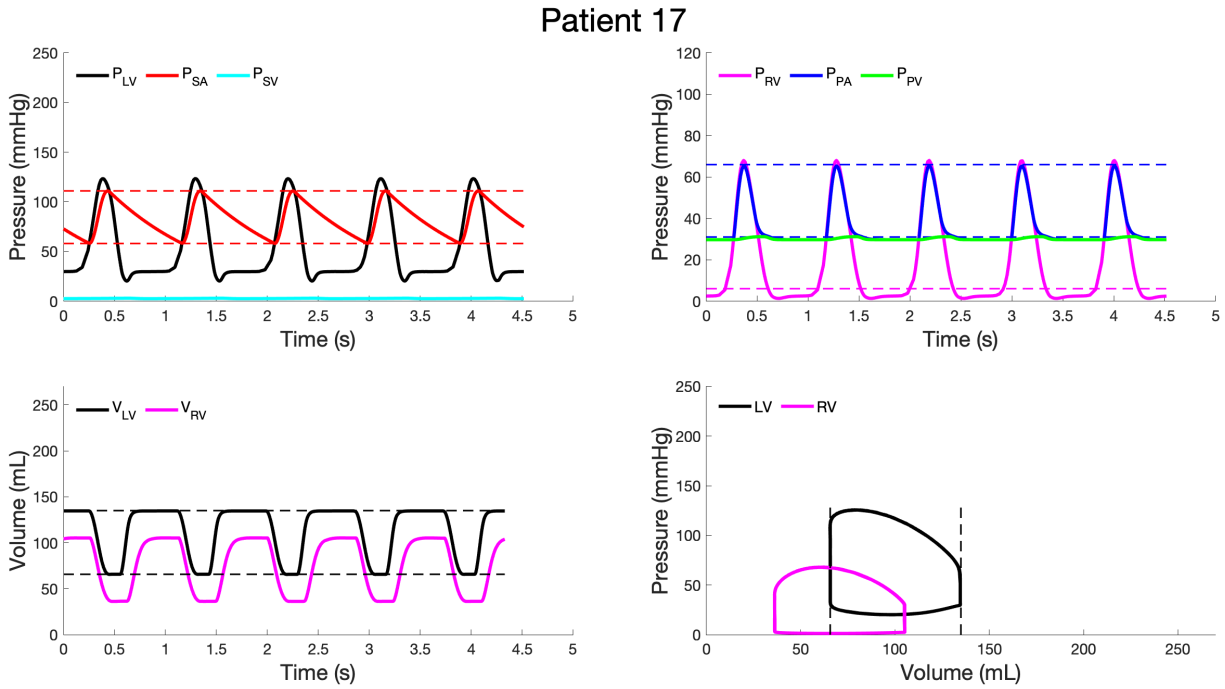

Fig. S20. Simulation fits to data for Patient 17 where dashed lines indicate the clinical measures and solid lines represent simulated cardiovascular function. CO is also matched during parameter optimization. For RHC: measured CO_{RHC} is 3.50 L/min and simulation CO is 4.63 L/min. For TTE: measured $CO_{MOD/T}$ is 4.78 L/min and simulation CO is 4.77 L/min

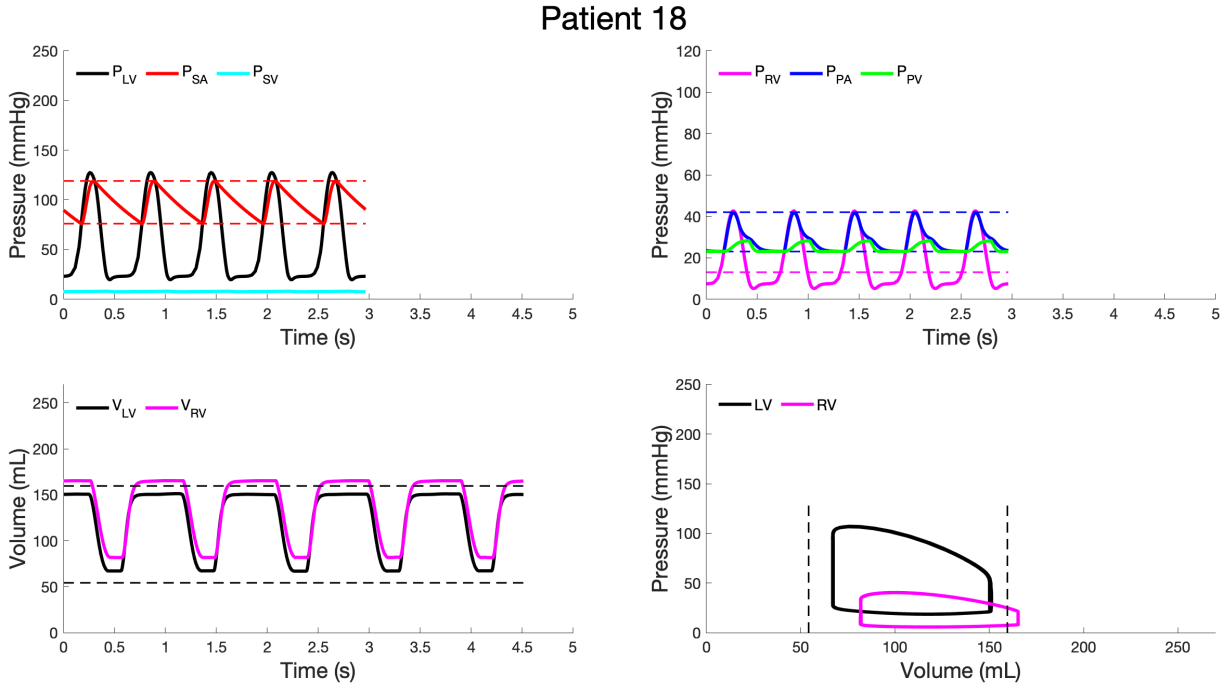

Fig. S21. Simulation fits to data for Patient 18 where dashed lines indicate the clinical measures and solid lines represent simulated cardiovascular function. CO is also matched during parameter optimization. For RHC: measured CO_{RHC} is 7.43 L/min and simulation CO is 7.43 L/min. For TTE: measured $CO_{MOD/T}$ is 6.95 L/min, measured CO_{LVOT} is 4.30 L/min and simulation CO is 5.56 L/min

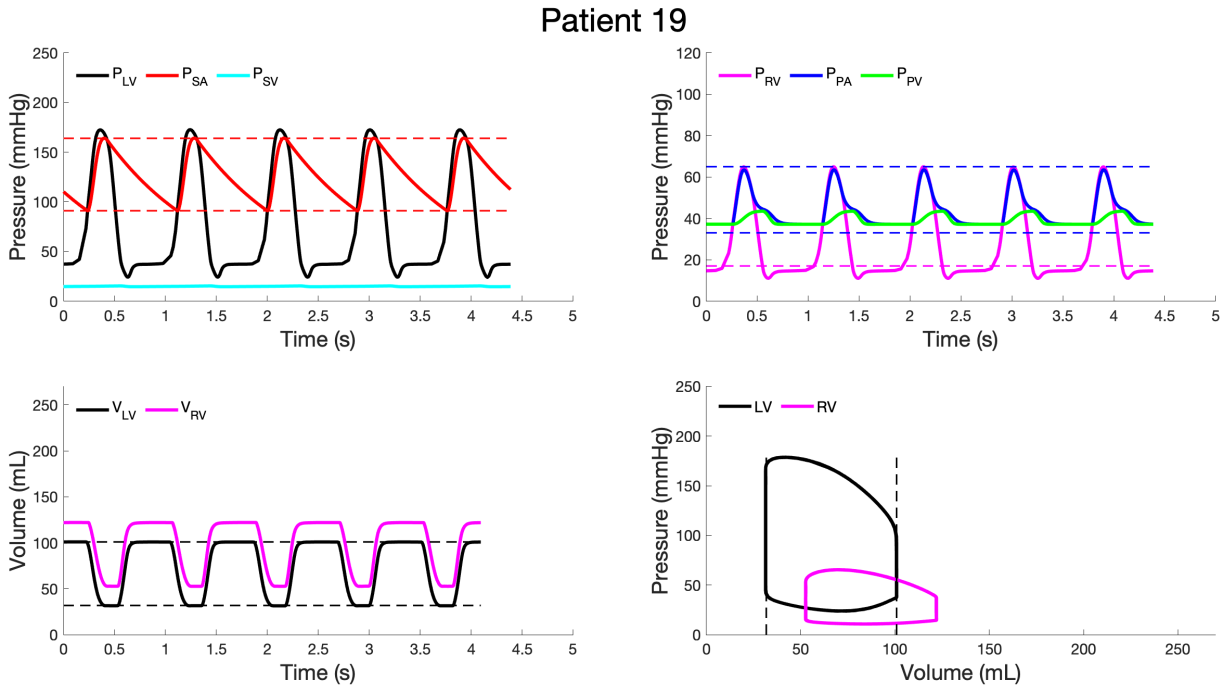

Fig. S22. Simulation fits to data for Patient 19 where dashed lines indicate the clinical measures and solid lines represent simulated cardiovascular function. CO is also matched during parameter optimization. For RHC: measured CO_{RHC} is 5.67 L/min and simulation CO is 4.79 L/min. For TTE: measured $CO_{MOD/T}$ is 5.04 L/min, measured CO_{LVOT} is 3.20 L/min and simulation CO is 5.08 L/min

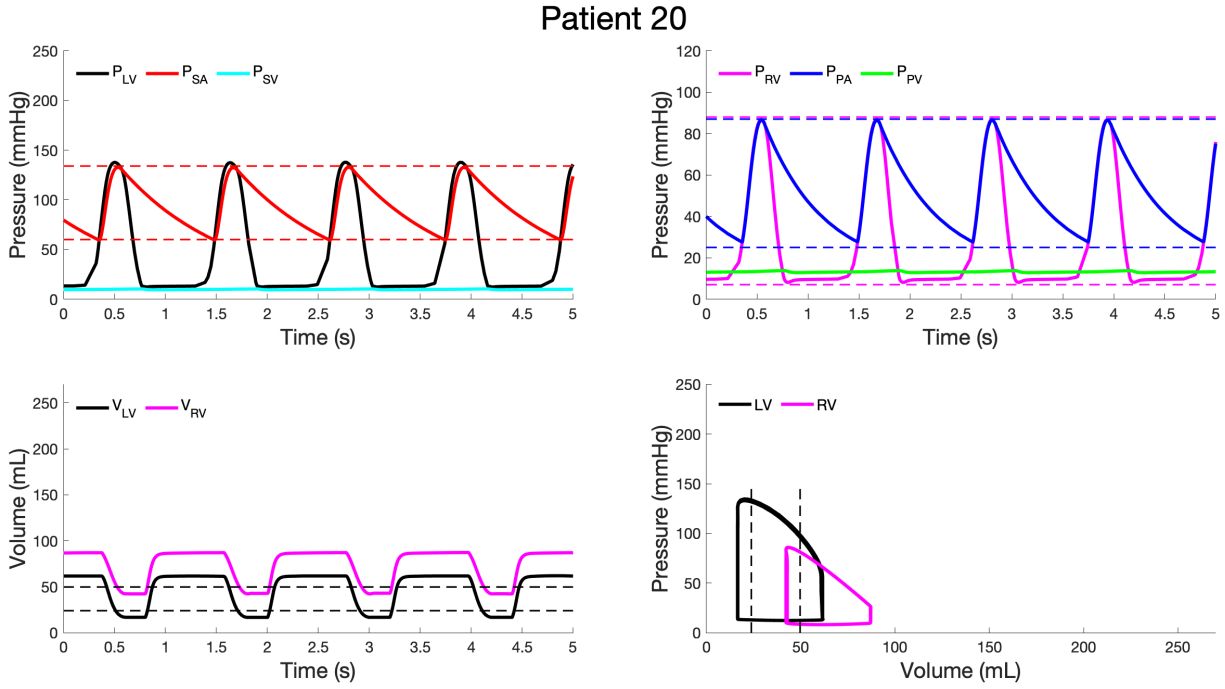

Fig. S23. Simulation fits to data for Patient 20 where dashed lines indicate the clinical measures and solid lines represent simulated cardiovascular function. CO is also matched during parameter optimization. For RHC: measured CO_{RHC} is 3.50 L/min and simulation CO is 2.37 L/min. For TTE: measured $CO_{MOD/T}$ is 1.29 L/min, measured CO_{LVOT} is 3.40 L/min and simulation CO is 2.27 L/min

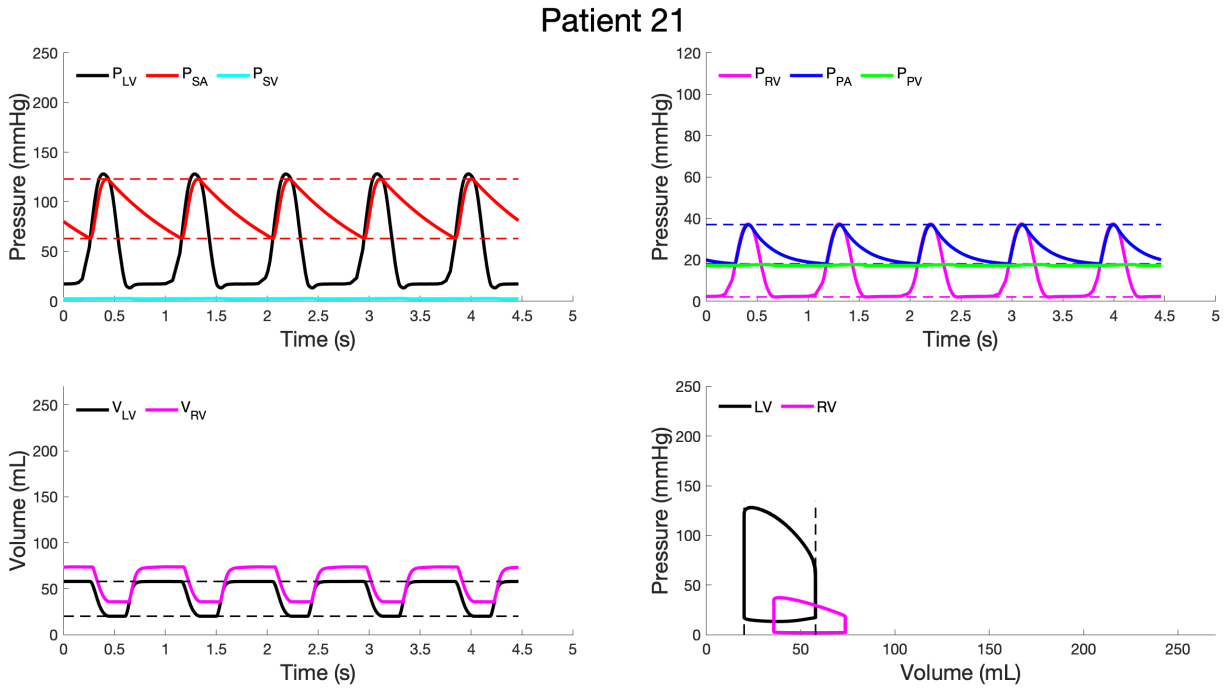

Fig. S24. Simulation fits to data for Patient 21 where dashed lines indicate the clinical measures and solid lines represent simulated cardiovascular function. CO is also matched during parameter optimization. For RHC: measured CO_{RHC} is 3.37 L/min and simulation CO is 2.54 L/min. For TTE: measured $CO_{MOD/T}$ is 2.54 L/min, measured CO_{LVOT} is 4.60 L/min and simulation CO is 2.54 L/min

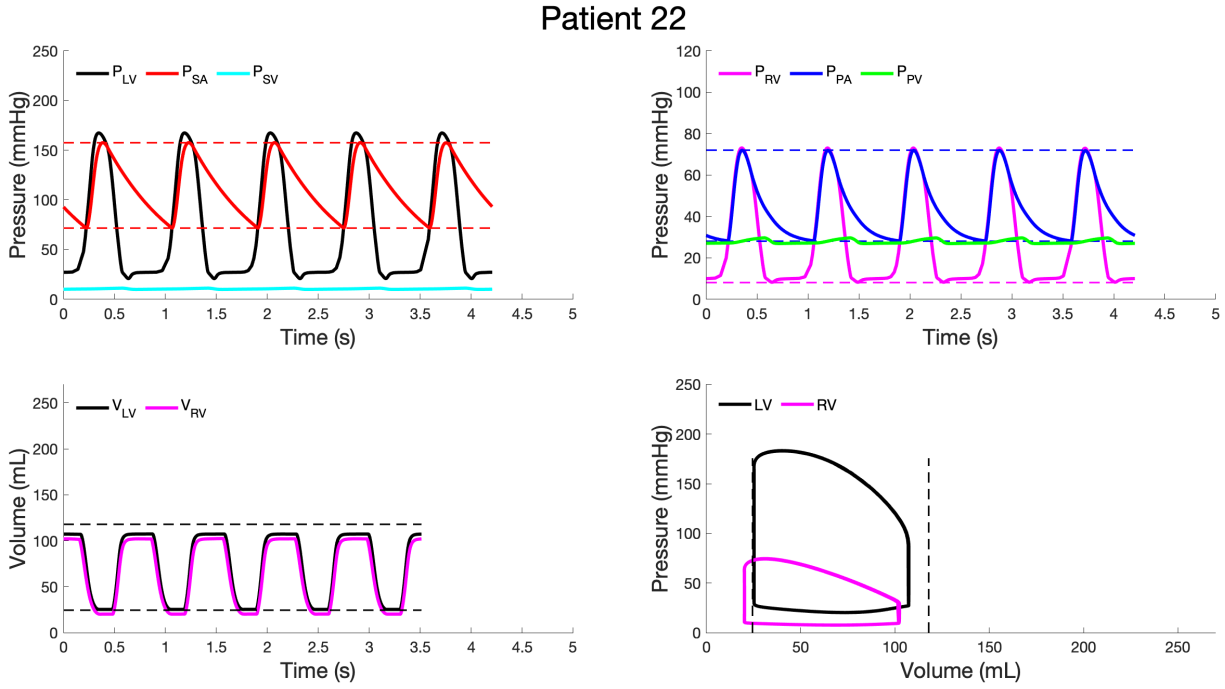

Fig. S25. Simulation fits to data for Patient 22 where dashed lines indicate the clinical measures and solid lines represent simulated cardiovascular function. CO is also matched during parameter optimization. For RHC: measured CO_{RHC} is 5.63 L/min and simulation CO is 5.98 L/min. For TTE: measured $CO_{MOD/T}$ is 7.94 L/min, measured CO_{LVOT} is 5.10 L/min and simulation CO is 6.98 L/min

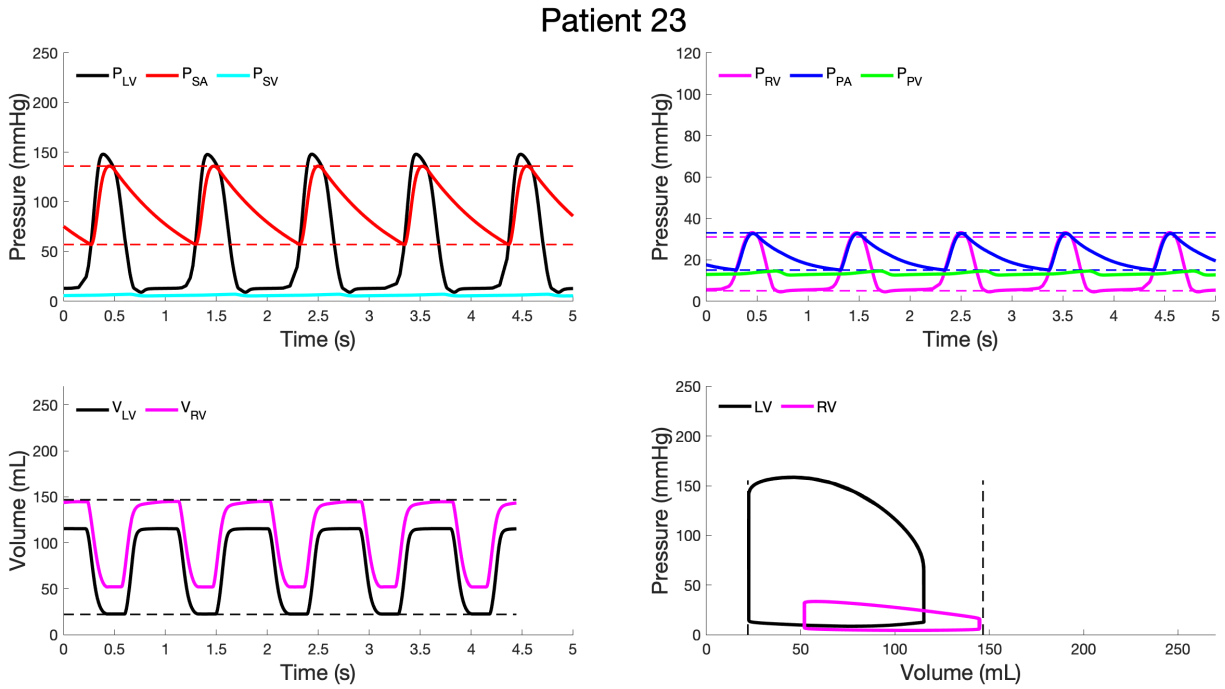

Fig. S26. Simulation fits to data for Patient 23 where dashed lines indicate the clinical measures and solid lines represent simulated cardiovascular function. CO is also matched during parameter optimization. For RHC: measured CO_{RHC} is 4.50 L/min and simulation CO is 5.55 L/min. For TTE: measured $CO_{MOD/T}$ is 8.35 L/min, measured CO_{LVOT} is 4.95 L/min and simulation CO is 6.23 L/min

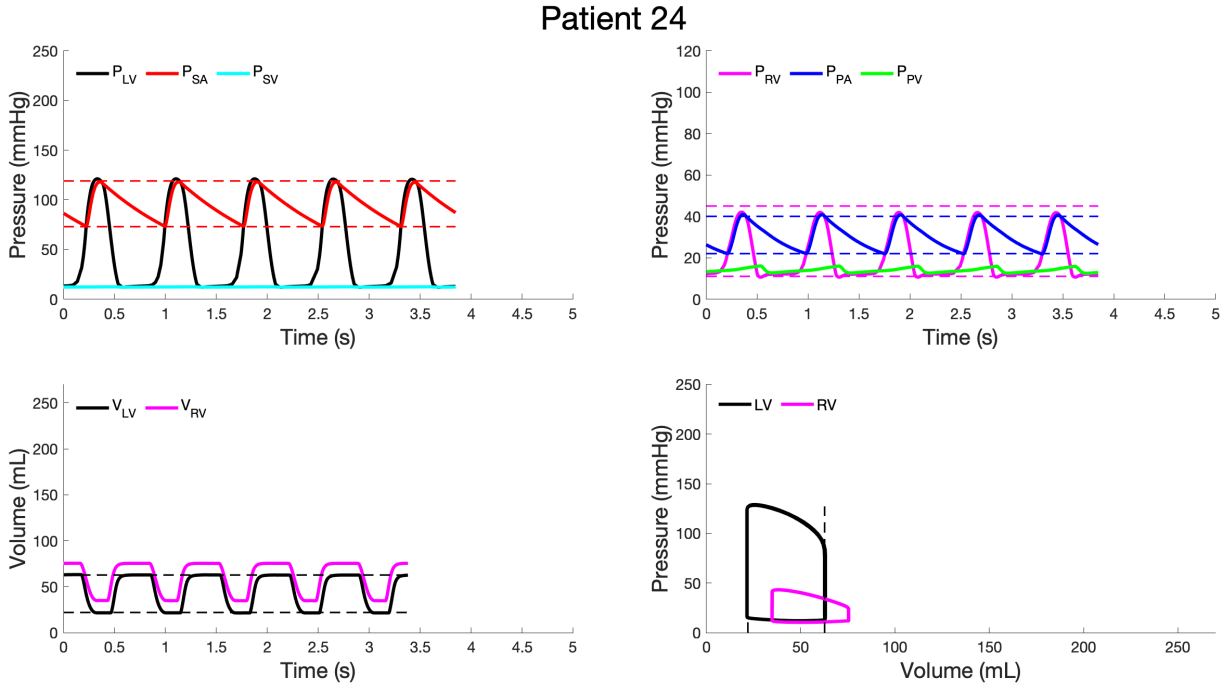

Fig. S27. Simulation fits to data for Patient 24 where dashed lines indicate the clinical measures and solid lines represent simulated cardiovascular function. CO is also matched during parameter optimization. For RHC: measured CO_{RHC} is 6.23 L/min and simulation CO is 3.32 L/min. For TTE: measured $CO_{MOD/T}$ is 3.58 L/min, measured CO_{LVOT} is 6.05 L/min and simulation CO is 3.67 L/min

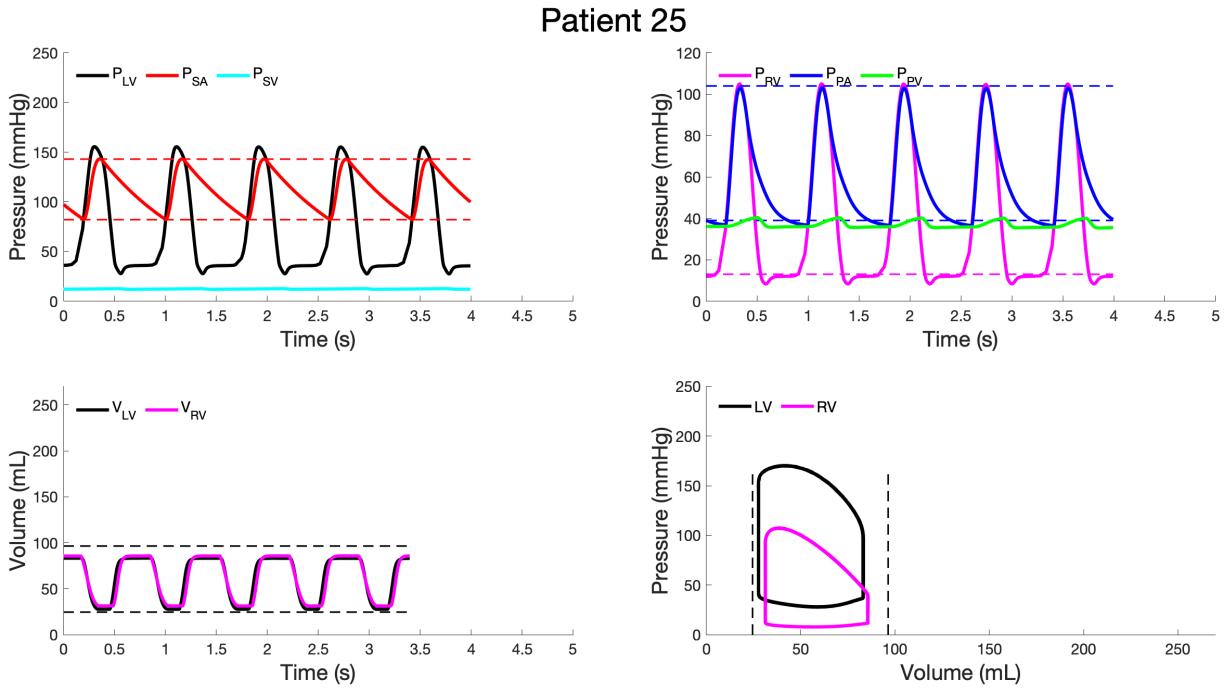

Fig. S28. Simulation fits to data for Patient 25 where dashed lines indicate the clinical measures and solid lines represent simulated cardiovascular function. CO is also matched during parameter optimization. For RHC: measured CO_{RHC} is 3.67 L/min and simulation CO is 4.28 L/min. For TTE: measured $CO_{MOD/T}$ is 6.32 L/min, measured CO_{LVOT} is 4.24 L/min and simulation CO is 4.90 L/min

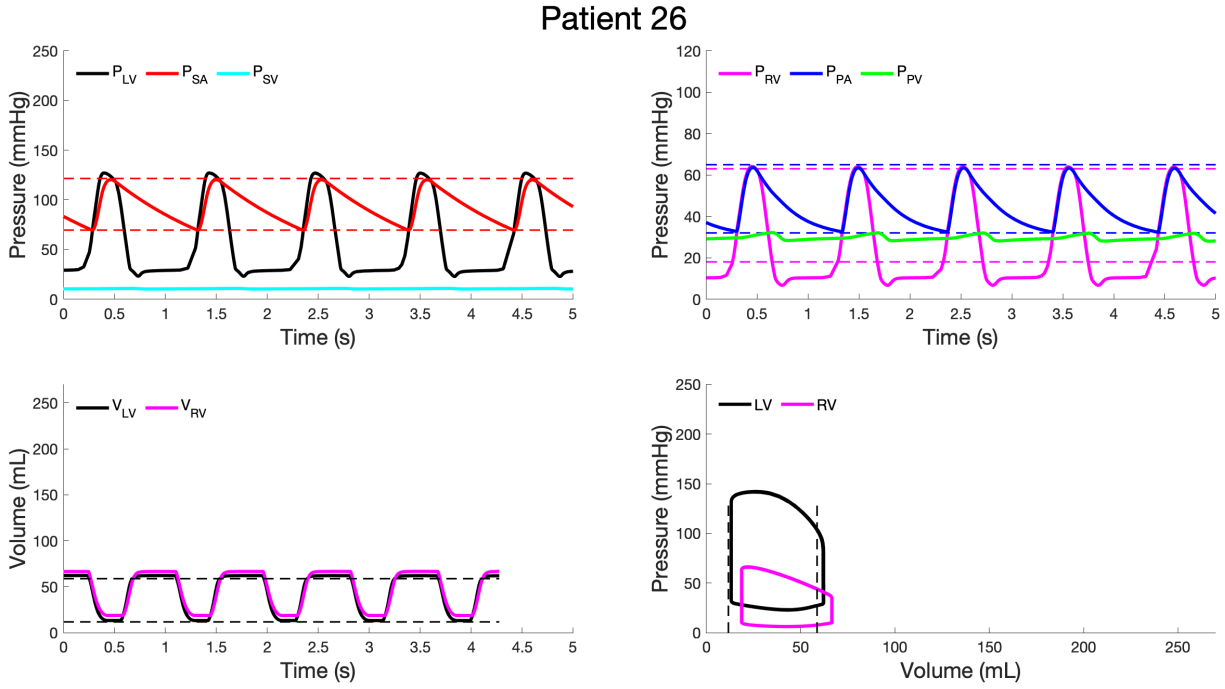

Fig. S29. Simulation fits to data for Patient 26 where dashed lines indicate the clinical measures and solid lines represent simulated cardiovascular function. CO is also matched during parameter optimization. For RHC: measured CO_{RHC} is 3.47 L/min and simulation CO is 2.91 L/min. For TTE: measured $CO_{MOD/T}$ is 3.29 L/min, measured CO_{LVOT} is 4.22 L/min and simulation CO is 3.43 L/min

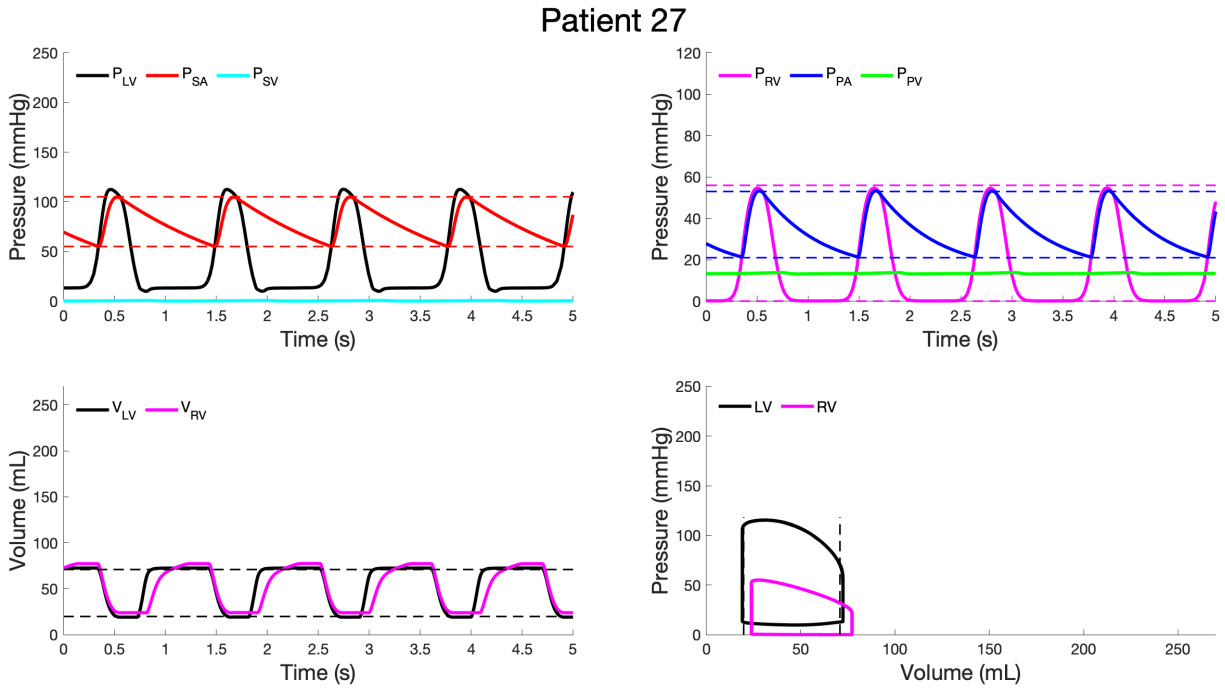

Fig. S30. Simulation fits to data for Patient 27 where dashed lines indicate the clinical measures and solid lines represent simulated cardiovascular function. CO is also matched during parameter optimization. For RHC: measured CO_{RHC} is 2.90 L/min and simulation CO is 2.84 L/min. For TTE: measured $CO_{MOD/T}$ is 2.81 L/min, measured CO_{LVOT} is 3.59 L/min and simulation CO is 2.94 L/min

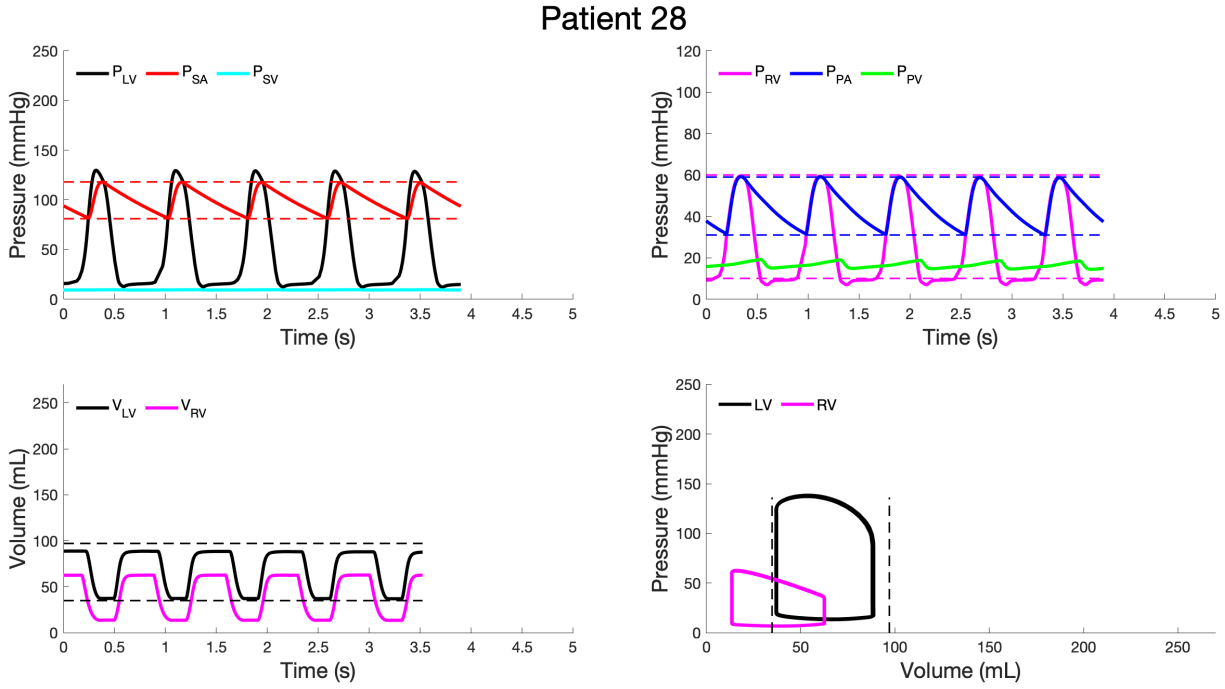

Fig. S31. Simulation fits to data for Patient 28 where dashed lines indicate the clinical measures and solid lines represent simulated cardiovascular function. CO is also matched during parameter optimization. For RHC: measured CO_{RHC} is 4.03 L/min and simulation CO is 4.05 L/min. For TTE: measured $CO_{MOD/T}$ is 5.28 L/min, measured CO_{LVOT} is 5.34 L/min and simulation CO is 4.41 L/min

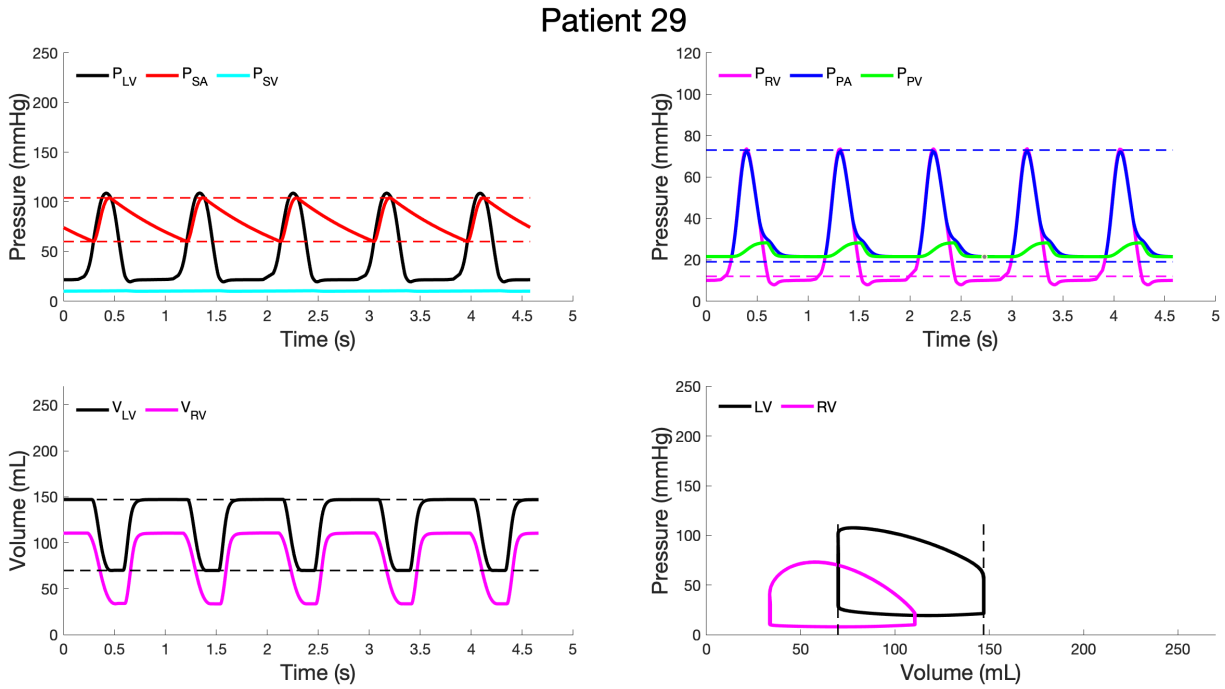

Fig. S32. Simulation fits to data for Patient 29 where dashed lines indicate the clinical measures and solid lines represent simulated cardiovascular function. CO is also matched during parameter optimization. For RHC: measured CO_{RHC} is 7.27 L/min and simulation CO is 5.04 L/min. For TTE: measured $CO_{MOD/T}$ is 4.94 L/min and simulation CO is 4.95 L/min

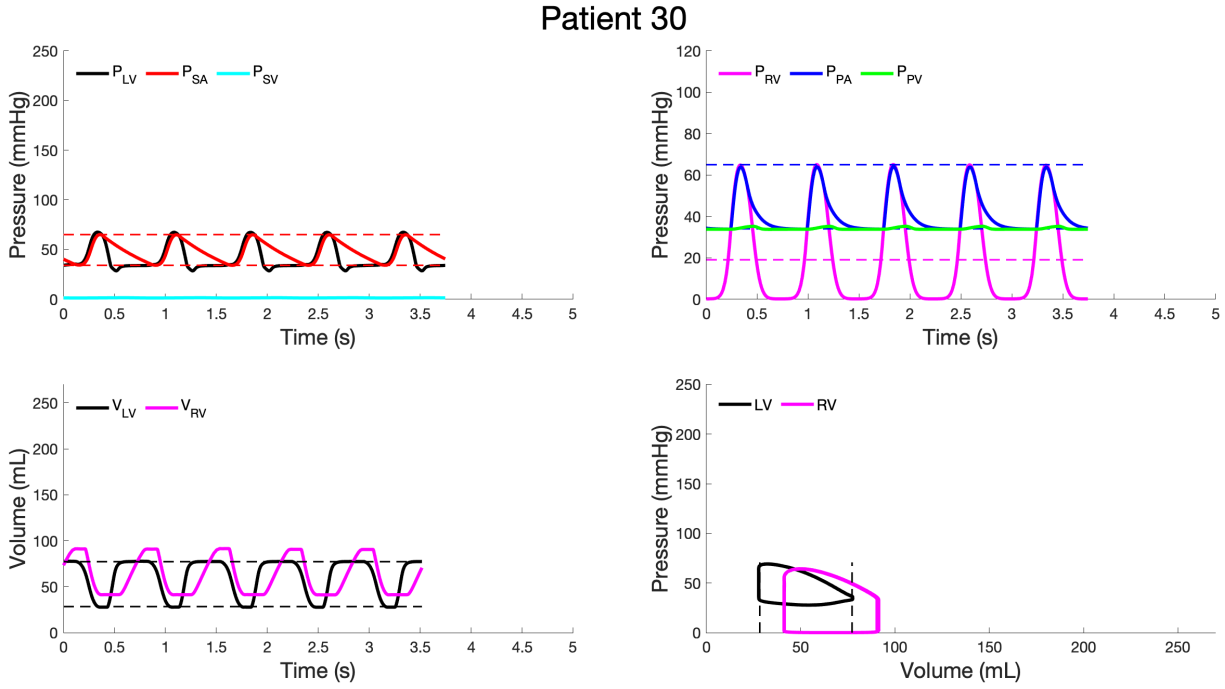

Fig. S33. Simulation fits to data for Patient 30 where dashed lines indicate the clinical measures and solid lines represent simulated cardiovascular function. CO is also matched during parameter optimization. For RHC: measured CO_{RHC} is 5.25 L/min and simulation CO is 4.08 L/min. For TTE: measured $CO_{MOD/T}$ is 4.16 L/min, measured CO_{LVOT} is 4.27 L/min and simulation CO is 4.25 L/min

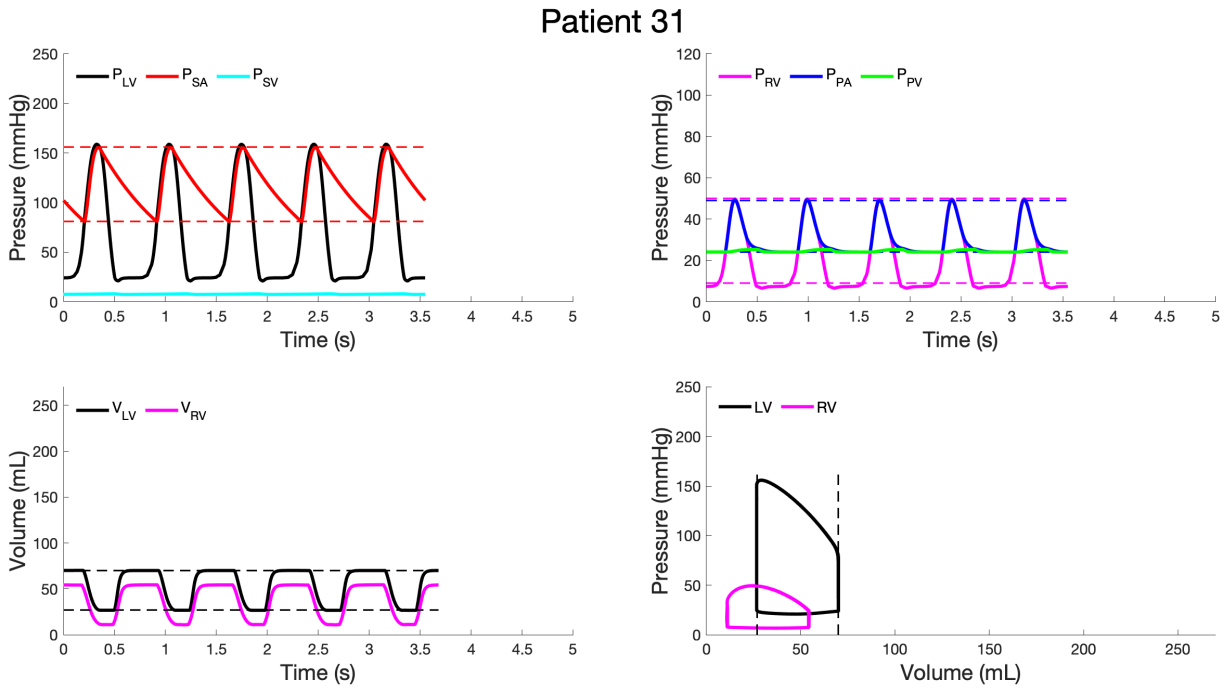

Fig. S34. Simulation fits to data for Patient 31 where dashed lines indicate the clinical measures and solid lines represent simulated cardiovascular function. CO is also matched during parameter optimization. For RHC: measured CO_{RHC} is 7.53 L/min and simulation CO is 3.63 L/min. For TTE: measured $CO_{MOD/T}$ is 3.48 L/min, measured CO_{LVOT} is 6.73 L/min and simulation CO is 3.52 L/min