Understanding and recognition of the right ventricular function and dysfunction: A numerical study

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Supplementary Information

METHODS

Hemodynamic model

To simulate the blood circulation, we used the lumped parameters methodology. It allows to represent the vascular compartments of the body, i.e., any vascular segment that it is necessary to describe, by pressure and flow rate, and the heart. This methodology is widely used to simulate the whole cardiovascular system since the Windkessel model proposed by Otto Frank in 1899 which approximates the hemodynamics of the systemic circulation[11–13]. Pressures and flows are obtained by computing the Navier-Stokes and mass conservation equations averaged over the domain[14]. The vascular compartments are described by lumped parameters able to represent the geometrical and physical features. Resistances (*R*) represent the resistance to flow due to blood viscosity, compliances (*C*) reproduce the elastic properties of the vessels, and the inductances (*L*) reflect the flow inertia. By the combination of these parameters, any section of the vascular system can be considered. Particularly, supplementary Fig. S1 represents an example of a compartment, described by

$$\begin{cases} C\frac{dP_j}{dt} = Q_j - Q_{j+1} \\ L\frac{dQ_{j+1}}{dt} = P_j - P_{j+1} - RQ_{j+1} \end{cases} \quad \text{(S1)}$$

where (P_j, Q_j) and (P_{j+1}, Q_{j+1}) are the upstream and downstream pressures and flow rates, respectively. In this work, the great vessels were reproduced considering the compliance and resistance effects, and the vascular bed was represented by the resistance effect (supplementary Fig. S2). This holds for both the systemic and pulmonary circulations. This choice allows to reproduce the elastic properties and small dissipative effects of the arteries and veins, and the dissipation effects that characterize the small vessels of the vascular bed. Finally, the heart valves were represented as an ideal diode associated to a resistance. They open and close instantaneously and they allow the blood to flow through only when there is a positive pressure gradient across them, forcing a unidirectional flow. The equation is

$$Q = \begin{cases} \frac{P_j - P_{j+1}}{R}, & if\ P_j - P_{j+1} \geq 0 \\ 0, & otherwise. \end{cases} \quad \text{(S2)}$$

with P_j and P_{j+1} the pressure upstream and downstream, respectively, *R* the valve resistance and *Q* the flow rate.

Note that, the present model does not account for chamber interaction via speta[59–61].

Time-varying elastance

To simulate the right ventricular dysfunction, the right time-varying elastances were modified. Supplementary Fig. S3 shows the right time-varying elastance for the systolic, diastolic, and combined dysfunctions, resulted from the change of the parameters of Eq. (1), as described in Section Dysfunctional case. In the systolic dysfunction (Fig. S3a), $E_{max_{RV}}$, the maximum contraction force, decreases linearly with p increasing, from 0.45 mmHg/mL in the healthy condition to the minimum value of $E_{min_{RV}}$ for the complete impairment ($E_{min_{RV}}$= 0.035 mmHg/mL). At the same time, the ejection time increases as well as the acceleration time, resulting in a delayed of the peak as the pathology worsens. On the contrary, in the diastolic dysfunction (Fig. S3b), $E_{max_{RV}}$ is rather constant and the systolic phase slightly varies with p, ranging between the 37% and the 40% of the heartbeat. However, an increase of ventricular stiffness and the decrease of the deceleration times are due to larger value of $E_{min_{RV}}$ and $m_{2_{RV}}$, respectively. Finally, in the combined dysfunction (Fig. S3c) the combination of the previous effects is visible.

Sensitivity analysis

A sensitivity analysis as in Mynard[18] was conducted to evaluate the sensitivity of the model. Input parameters were increased by 25%, one at a time, assessing the changes in the outputs. The sensitivity was computed considering the mean value of the outputs over one heartbeat as

$$S = \frac{mean(Y_1) - mean(Y)}{mean(Y)} \left(\frac{X}{X_1 - X} \right) \quad \text{(S6)}$$

where X and X_1 are the input at baseline and 25% increased value, respectively, and Y and Y_1 are the outputs with baseline and 25% increased inputs, respectively. Note that a positive value of S indicates that an increase in X determines an increase in Y, whereas, a negative value of S shows that an increase in X causes a decrease in Y[18]. Particularly, we evaluated 16 inputs and 20 outputs of the model. Table S2 reports the results. The inputs are ordered considering the global influence, i.e., as the sum of $|S|$ for all the outputs analyzed, showing the most influential on the left. The outputs are ordered based on the overall sensitivity, computed as the median value of $|S|$ for all the inputs, with the most sensitive at the top. Supplementary Fig. S4 shows the outputs listed on the horizontal axis and inputs listed on the vertical axis. Note that in the figure, the outputs are ordered with the most sensitive on the left, and the inputs are ordered with the most influential at the bottom. The most influential parameters are those related to the heart chamber contractility. These parameters are known from the physiology to affect pressures and flows, however, interestingly, the contractility of LV is less influential than that of the other heart chambers. This may be due to the extended research attention posed on LV compared to the other heart chambers, suggesting that the left ventricular parameters are better estimated. Thus, the higher sensitivity of RA, RV, and LA parameters suggests that more attention needs to be posed when calibrating these heart chambers to derive pertinent values and be able to simulate real cases. The most sensitive outputs are those related to the systemic arterial side and the volumes, that are directly linked to the heart chamber contractility. Moreover, only few output variables are sensitive to the variation of inputs, and this is clearly visible from Supplementary Fig. S4 that shows a cluster of larger data points in the left side. The least sensitive outputs signals are the right ventricular and pulmonary venous pressures, and this could be related to the reservoir functionality of the high-compliance pulmonary circulation.

FIGURES

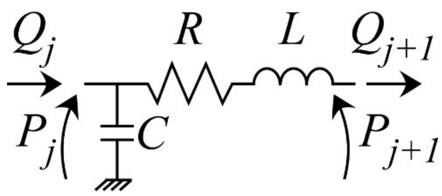

Fig. S1. Example of lumped parameter compartment. *R*, resistance, *C*, compliance, *L*, inductance, (P_j, Q_j) and (P_{j+1}, Q_{j+1}) the upstream and downstream pressures and flow rates, respectively.

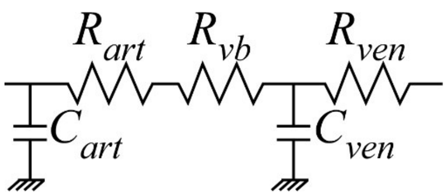

Fig. S2. Lumped parameter compartment used in the present work to represent the systemic and pulmonary circulations. The arterial and venous sides are composed by a resistance and a compliance (R_{art}, C_{art}) and (R_{ven}, C_{ven}), respectively, whereas the vascular bed is represented by a resistance (R_{vb}).

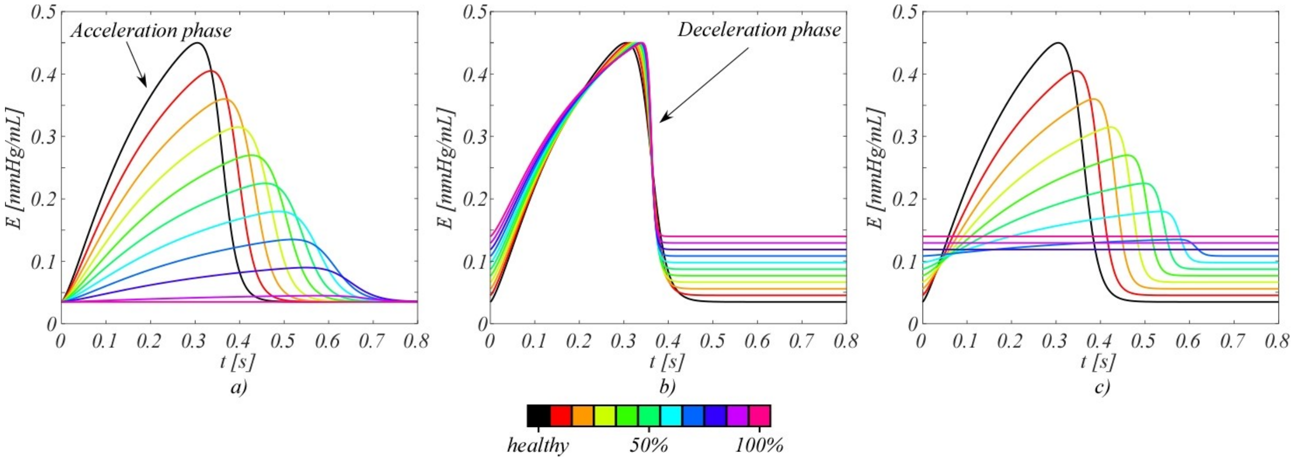

Fig. S3. Right ventricular activation function. *a)* systolic dysfunction, *b)* diastolic dysfunction, and *c)* combined systolic and diastolic dysfunction. Black line: healthy RV (*p=0%*); coloured lines: RV systolic impairment, *p*, from *10%* to *100%*.

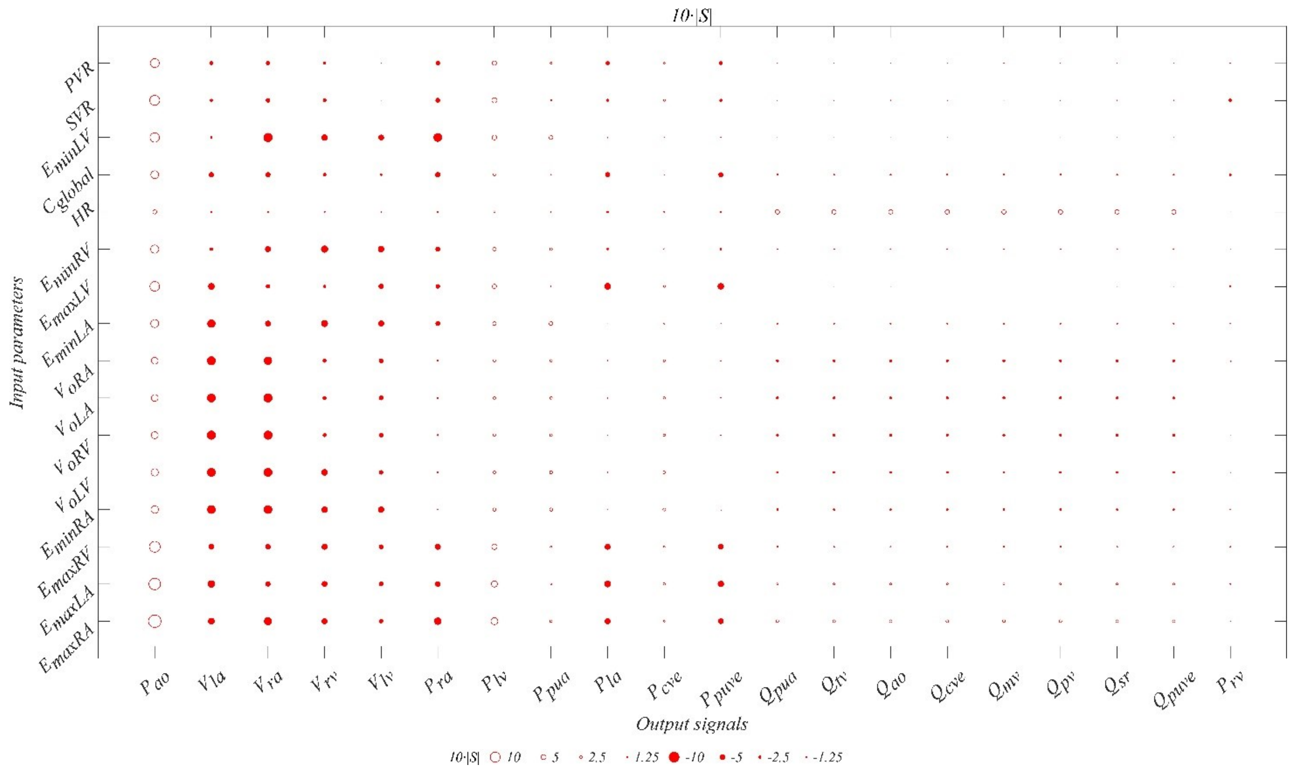

Fig. S4. Graphical representation of the sensitivity of the outputs to the 25% variation of the inputs. A larger symbol corresponds with higher sensitivity and filled/empty circles correspond to negative/positive *S*. Outputs are ordered according to the overall sensitivity (the most sensitive on the left) and inputs are ordered based on the global influence (the most influential at the bottom).

TABLES

Table S1. Heart parameters values.

	LV	**RV**	**LA**	**RA**
E_{max} $[mmHg/mL]$	2.8	0.45	0.13	0.09
E_{min} $[mmHg/mL]$	0.07	0.035	0.09	0.045
$V_{p=0}$ $[mL]$	20	30	3	7
τ_1 $[s]$	$0.269T$	$0.269T$	$0.110T$	$0.110T$
τ_2 $[s]$	$0.452T$	$0.452T$	$0.180T$	$0.180T$
m_1 $[-]$	1.32	1.32	1.99	1.99
m_2 $[-]$	21.9	21.9	11.2	11.2
t_{onset} $[s]$	0	0	$0.85T$	$0.85T$
R_{valve} $[mmHg \cdot s/mL]$	0.01	0.01	0.005	0.005

T is the heart period.

Table S2. Mean sensitivity (*S*) of output signals to the input parameters. The inputs are ordered based on the global influence (the most influential on the left), the outputs are ordered based on the overall sensitivity (the most sensitive at the top).

Output signals	**Input parameters**															
	$E_{max_{RA}}$	$E_{max_{LA}}$	$E_{max_{RV}}$	$E_{min_{RA}}$	$V_{0_{LV}}$	$V_{0_{RV}}$	$V_{0_{LA}}$	$V_{0_{RA}}$	$E_{min_{LA}}$	$E_{max_{LV}}$	$E_{min_{RV}}$	**HR**	**Cglobal**	$E_{min_{LV}}$	**SVR**	**PVR**
P_{ao}	1.251	1.154	1.077	0.750	0.724	0.685	0.681	0.672	0.798	0.963	0.817	0.408	0.778	0.939	0.995	0.892
V_{la}	-0.615	-0.679	-0.517	-0.796	-0.813	-0.838	-0.809	-0.815	-0.758	-0.600	-0.280	-0.170	-0.448	-0.180	-0.234	-0.327
V_{ra}	-0.737	-0.458	-0.493	-0.795	-0.811	-0.835	-0.837	-0.762	-0.521	-0.360	-0.532	-0.113	-0.447	-0.850	-0.389	-0.366
V_{rv}	-0.535	-0.521	-0.536	-0.575	-0.588	-0.324	-0.326	-0.331	-0.632	-0.254	-0.656	-0.120	-0.297	-0.569	-0.308	-0.228
V_{lv}	-0.355	-0.410	-0.409	-0.564	-0.382	-0.404	-0.406	-0.411	-0.533	-0.475	-0.583	-0.068	-0.179	-0.512	0.016	-0.061
P_{ra}	-0.674	-0.494	-0.532	-0.079	-0.101	-0.133	-0.136	-0.144	-0.415	-0.384	-0.428	-0.117	-0.479	-0.801	-0.417	-0.390
P_{lv}	0.692	0.604	0.541	0.315	0.291	0.256	0.252	0.244	0.360	0.438	0.367	0.187	0.239	0.481	0.521	0.425
P_{pua}	0.240	0.156	0.169	0.313	0.289	0.254	0.251	0.242	0.368	0.067	0.256	0.079	0.080	0.378	-0.121	0.200
P_{la}	-0.545	-0.613	-0.532	-0.026	-0.048	-0.081	-0.084	-0.091	0.022	-0.618	-0.185	-0.174	-0.460	-0.079	-0.240	-0.336
P_{cve}	0.153	0.214	0.159	0.277	0.254	0.219	0.215	0.207	0.106	0.194	0.107	0.109	0.061	-0.053	0.190	0.161
P_{puve}	-0.505	-0.574	-0.497	-0.009	-0.031	-0.064	-0.067	-0.075	0.040	-0.584	-0.163	-0.161	-0.433	-0.056	-0.234	-0.309
Q_{pua}	0.266	0.180	0.116	-0.172	-0.192	-0.224	-0.227	-0.234	-0.121	0.016	-0.104	0.431	-0.135	0.011	0.045	-0.042
Q_{tv}	0.265	0.180	0.116	-0.171	-0.192	-0.224	-0.227	-0.234	-0.122	0.016	-0.105	0.430	-0.135	0.009	0.043	-0.043
Q_{ao}	0.267	0.180	0.117	-0.171	-0.192	-0.223	-0.226	-0.234	-0.120	0.017	-0.104	0.431	-0.134	0.011	0.045	-0.042
Q_{cve}	0.267	0.180	0.117	-0.171	-0.192	-0.223	-0.227	-0.234	-0.120	0.017	-0.103	0.431	-0.134	0.011	0.045	-0.042
Q_{mv}	0.266	0.180	0.116	-0.170	-0.191	-0.223	-0.226	-0.233	-0.120	0.016	-0.103	0.430	-0.135	0.011	0.044	-0.043
Q_{pv}	0.267	0.181	0.117	-0.171	-0.192	-0.223	-0.226	-0.234	-0.120	0.017	-0.103	0.431	-0.134	0.011	0.045	-0.042
Q_{sr}	0.266	0.180	0.117	-0.171	-0.192	-0.224	-0.227	-0.234	-0.120	0.016	-0.104	0.431	-0.134	0.011	0.045	-0.042
Q_{puve}	0.267	0.181	0.118	-0.170	-0.191	-0.223	-0.226	-0.233	-0.119	0.017	-0.103	0.431	-0.133	0.012	0.045	-0.041
P_{rv}	-0.024	-0.080	-0.092	0.065	0.042	0.009	0.006	-0.002	0.075	-0.159	0.011	-0.024	-0.195	-0.007	-0.268	-0.089

P_{ao}, aortic (arterial vessel) pressure, V_{la}, LA volume, V_{ra}, RA volume, V_{rv}, RV volume, V_{lv}, LV volume, P_{ra}, RA pressure, P_{lv}, LV pressure, P_{pua}, PuA pressure, P_{la}, LA pressure, P_{cve}, CVe pressure, P_{puve}, PuVe pressure, Q_{pua}, PuA flow, Q_{tv}, tricuspid valve flow, Q_{ao}, aortic valve flow, Q_{cve}, CVe flow, Q_{mv}, mitral valve flow, Q_{pv}, pulmonary valve flow, Q_{sr}, systemic vascular bed flow, Q_{puve}, PuVe flow, and P_{rv}, RV pressure.