Heart Surgery Forum 2024; 27(8): E914–E923
doi: 10.59958/hsf.7697

Article

A Study on Ejection Fraction in Patients with Mitral and Aortic Regurgitation Based on Cardiovascular Models

Xuehua Xing[1], Gang Li[2], Zhaoming He[3,*]

[1]Research Center of Fluid Machinery Engineering Technology, Jiangsu University, 212013 Zhenjiang, Jiangsu, China
[2]Pediatric Cardiology Department of Beijing Anzhen Hospital Affiliated to Capital Medical University, 100000 Beijing, China
[3]Department of Mechanical Engineering, Texas Tech University, Lubbock, TX 79409, USA
*Correspondence: zhaoming.he@ttu.edu; hezhaoming2@163.com (Zhaoming He)

Submitted: 21 May 2024 Revised: 19 June 2024 Accepted: 5 July 2024 Published: 18 August 2024

Abstract

Background: Whether it is healthy or patients with mitral and aortic regurgitation, clinicians cannot measure the regurgitation of the valve when using two-dimensional echocardiography to measure ejection fraction. Whether the mitral valve and aortic valve are in a healthy state or in a reflux state, there is a reflux volume. The actual stroke output will be less than the stroke output measured by echocardiography, making the calculated ejection fraction higher. **Methods**: This article proposes for the first time the concept of net ejection fraction (NEF) as the percentage of net stroke output to left ventricular end diastolic volume. The net stroke output is the integral of aortic valve flow during one cardiac cycle at the same time. Using a systemic arterial circulation model, investigate the relationship between ejection fraction and net ejection fraction through numerical simulation methods. **Results**: The final results showed a strong linear correlation between mitral regurgitation volume (VR_{mi}), aortic regurgitation volume (VR_{ao}), and the difference between ejection fraction and net ejection fraction (DEF). The net ejection fraction of the moderate mitral regurgitation group decreased by an average of 26.3% $\pm$ 9.95% compared to the ejection fraction measured by echocardiography. The severe mitral regurgitation group showed a decrease of 31.9% $\pm$ 9.3%. Moderate descent of aortic valve by 25.8% $\pm$ 11.1%. Severe aortic valve descent of 30.9% $\pm$ 10.3%. **Conclusions**: Clinical doctors can evaluate the left ventricular systolic function of patients based on the ejection fraction measured by echocardiography combined with valve regurgitation. The net ejection fraction avoids overestimation of left ventricular systolic function and has high reliability. It can accurately reflect the left ventricular systolic function of patients with mitral and aortic regurgitation, and has certain guiding significance for clinical doctors to grasp the patient's condition.

Keywords

ejection fraction; net ejection fraction; stroke volume; net stroke volume; cardiovascular model

Introduction

The indexes for evaluating cardiac pumping function include ejection fraction (EF) and stroke volume (SV). EF refers to the percentage of SV to left ventricular end-diastolic volume, which is one of the important indications for judging the type of heart failure [1,2]. It has important clinical significance for rapid and accurate assessment of left ventricular systolic function, early diagnosis, treatment decision-making, prognosis and efficacy evaluation of cardiovascular diseases. Left ventricular SV: refers to a cardiac left ventricular ejection to the aorta blood, is the difference between ventricular end-diastolic volume minus ventricular end-systolic volume [1].

The modified Simpson method is most commonly used in clinical practice to calculate the ejection fraction by calculating the left ventricular volume measured by two-dimensional echocardiography [3]. When using echocardiography to measure left ventricular volume, the maximum ventricular volume (V_{min}) corresponds to ventricular end-diastolic volume, and the minimum ventricular volume (V_{max}) corresponds to end-systolic volume [4]. The calculation formula of EF is Eqn. 1.

$$EF = \frac{(V_{\max} - V_{\min})}{V_{\max}} \times 100\% \tag{1}$$

In 1999, Leyh *et al*. [5] in their study of valve motion found that valve closure is a transient process with more or less small amounts of regurgitation. In 2011, Xu *et al*. [6] proposed the left ventricular ejection fraction (LVEF) measured by conventional ultrasound technology was less reliable for evaluating left ventricular systolic function in patients with moderate or severe mitral insufficiency. They proposed a correction formula, and the corrected LVEF has high reliability. In 2013, Li Dongling and Fan Xixin [7] discussed the reliability and accuracy of ultrasonic measurement of LVEF in patients with moderate or severe mitral insufficiency. They found that ultrasound detection of LVEF in patients with moderate or severe mitral regurgitation could not truly reflect the patient's left ventricular systolic function. The LVEF value obtained after removing

Table 1. Comparison relationship between hemodynamic parameters and electrical parameters.

Blood flow parameters	Blood flow resistance	Inertia	Compliance	Pressure	Flow
Circuit parameters	electric resistance	inductance	capacitance	voltage	current

the mitral regurgitation volume (VR_{mi}) can accurately reflect the patient's left ventricular systolic function. In 2020, Salame *et al*. [8] pointed out the limitations of echocardiography in evaluating left ventricular systolic function in mitral and aortic regurgitation. In 2024, Michael Dandel [9] proposed it is time to think about further optimization of the echocardiographic assessment of left ventricular responses to mitral regurgitation. Due to the limitations of the device and the shortness of the valve closing time, the volume of the valve closing is difficult to measure. The closing volume provide great help for valve replacement or repair in clinical practice. It is a very important characteristic parameter that cannot be ignored. When using ultrasound technology to measure SV, it is assumed that both the mitral valve and the aortic valve are closed instantaneously, no reflux. Therefore, the SV calculated by the left ventricular volume measured by the Simpson method will be higher, which will lead to the calculated EF will also be higher. However, there are few studies on the EF measured by two-dimensional echocardiography. Based on the study of ejection fraction in the cardiovascular model, the closing volume and leakage volume of the valve can be accurately calculated.

For patients with mitral regurgitation, especially moderate or severe, there is ineffective output per beat due to the fact that some of the blood in their heart flows back into the left atrium during systole. So the actual volume of blood flow ejected from the left ventricle into the aorta is smaller than what is measured clinically, which results in a calculated ejection fraction that is larger than the actual ejection fraction or a lower output per beat than the theoretically calculated value [10–12]. In the case of aortic regurgitation, the aorta returns blood to the left ventricle during diastole and the actual output per beat is also reduced. If both aortic and mitral regurgitation occurs, this actual output per beat will be even lower.

Therefore, in this paper, the concept of net ejection fraction (NEF) is proposed for the first time. EF is the ratio of SV to ventricular maximum volume. Different from the calculation of EF, the NEF is the ratio of net stroke volume (NSV) to maximum ventricular volume. It is explained above that the SV contains part of the reverse flow. However, unlike the SV, NSV is the amount of blood that enters the artery through the side bottom of the active arterial valve without reflux during a cardiac cycle.

The relationship between ejection fraction and NEF measured by echocardiography under different degrees of mitral regurgitation and aortic regurgitation was found by numerical simulation, so that clinicians and biomedical engineering researchers can accurately grasp the left ventricular function of patients with mitral regurgitation and aortic regurgitation.

Materials and Methods

In this paper, numerical simulation is used to investigate the relationship between EF and NEF because both ventricular volume and valvular regurgitation can be accurately simulated. A model of the systemic aortic circulation is used. In the field of cardiovascular circulatory system modeling, it is common to use electro-hydraulic comparisons to model the equivalent circuit of the cardiovascular system [13–16], and the comparison relationships are shown in Table 1. Using Matlab to solve the column state equations for the aggregate parameter model of the peripheral circulatory system, we can compute V_{max}, V_{min}, SV, and NSV, and compute the aortic valve, the mitral valve normal and the EF and NEF for different degrees of regurgitation. Eqn. 2 is the calculation formula of NEF.

$$NEF = NSV/V_{\max} \times 100\% \tag{2}$$

Computational Modeling of the Systemic Arterial Circulatory System

The modeling of the ventricle was done on the basis of a pressure-volume curve describing the contraction of the ventricle. The ventricle was modeled with the time-varying elasticity function proposed by Suga *et al*. [17]. Taking the modeling of the left ventricle as an example, E(t) is the time-varying elasticity coefficient defined as the ratio of pressure to volume of the left ventricle at a given moment, and its mathematical expression is given in Eqns. 3,4,5.

$$E(t) = \frac{LVP(t)}{V(t) - V_0} \tag{3}$$

$$E(t) = (E_{\max} - E_{\min}) E_n(t_n) + E_{\min} \tag{4}$$

$$E_n(t_n) = 1.55 \left(\frac{\left(\frac{t_n}{0.7}\right)^{1.9}}{1 + \left(\frac{t_n}{0.7}\right)} \right) \left(\frac{1}{1 + \left(\frac{t_n}{1.17}\right)^{21.9}} \right) \tag{5}$$

Where LVP (t) is the left ventricular pressure, V_0 is the theoretical volume of the left ventricle at zero pressure. $E_n(t_n)$ is the normalized inverse capacitance value, and the calculation scheme is derived from the study of Suga *et al*.

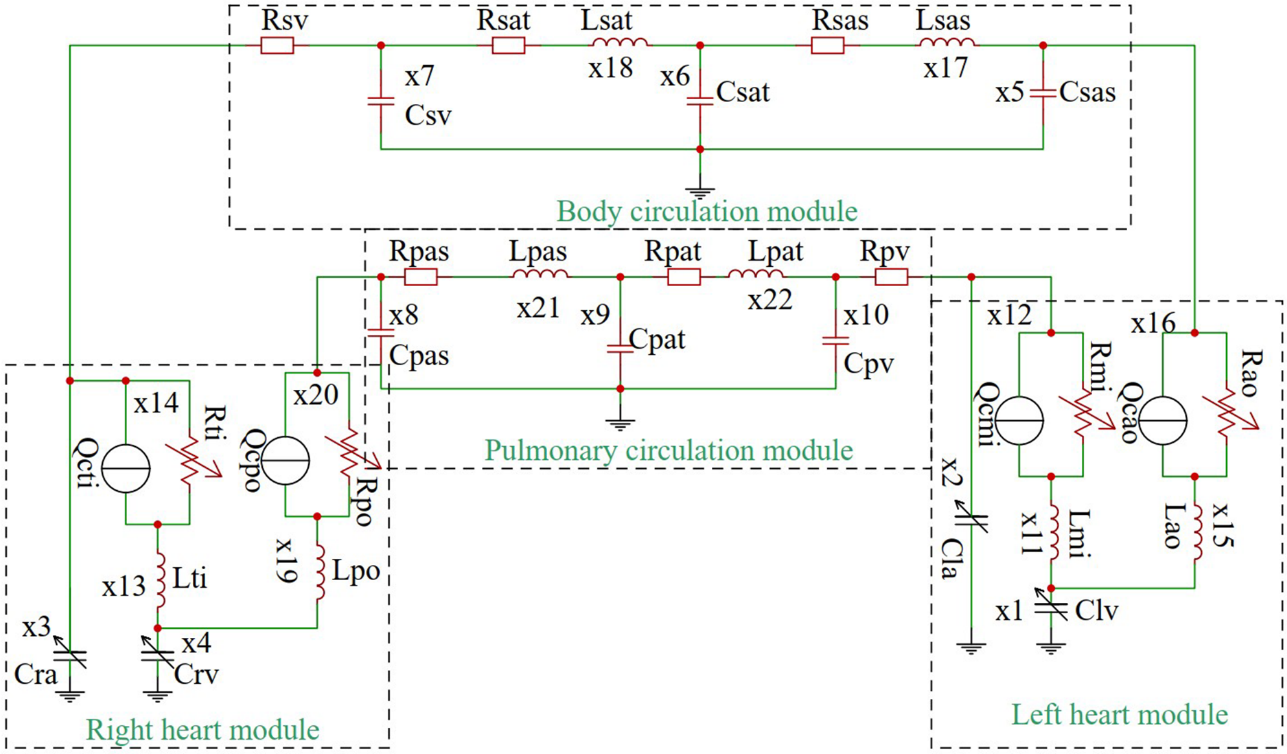

Fig. 1. Equivalent circuit diagram of the peripheral circulation system. Clv, Left ventricular volume-pressure ratio; Crv, Right ventricular volume-pressure ratio; Cla, Left atrial volume-pressure ratio; Cra, Right atrial volume-pressure ratio.

[17]. $t_n = t/T_{max}$, $T_{max} = 0.2 + 0.15 \times tc$, $tc = 60/HR$, tc represents the duration of one cardiac cycle, HR is the heart rate, and in this paper HR = 72 bpm. E_{max} and E_{min} represent the ratio of ventricular pressure to volume at the end of systole and end of diastole, respectively.

In this study, the left and right hearts were modeled using the atrial mathematical model developed by Korakianitis and Shi [18]. Its mathematical model is shown in Eqn. 6 below:

$$E(t) = \begin{cases} 0 & 0 \le t \le T_{pb} \\ 1 - \cos\left(\left(t - T_{pb}\right)/T_{pw} \cdot 2\pi\right) & T_{pb} \le t < T_{pb} + T_{pw} \\ 0 & T_{pb} + T_{pw} \le t \le t_c \end{cases} \tag{6}$$

Where $T_{pb} = 0.85 \times tc$, is the beginning of the P wave in the electrocardiogram (ECG). $T_{pw} = 0.09 \times tc$, is the duration of the P wave.

Fig. 1 shows the coupled circuit model of heart, systemic circulation and pulmonary circulation based on the theory of hemodynamics. The vascular elasticity of the large artery and the middle artery is good, and it has a certain buffering effect on the blood. The RLC combination is used for the modeling of these two vessels. In small arteries, arterioles and capillaries, the elasticity of vascular wall is relatively small, and friction loss is the main factor, so they are equivalent to pure resistance elements. Compared with the artery, the vein wall is thin and soft, with large inner diameter and small elasticity, like a blood container. The venous blood flow is relatively stable, so the inertial effect is often ignored. The value of the elastic coefficient of the cardiac chamber, the initial value setting, the component parameters and the effective orifice area under the steady state of the valve are shown in Tables 2,3,4,5. The equation of state is given in Table 6. The specific step of numerical simulation is to iteratively solve the state equation after inputting the mathematical model of each model.

Heart Valve Model

In the study of Yoganathan *et al*. [19], the blood circulation flow was divided into forward flow volume, closed volume and leakage volume, as shown in Fig. 2. The positive flow volume is the flow volume from the atrium to the ventricle or from the ventricle to the aorta from the time of valve opening to the time of valve closing. The closing volume refers to the reverse flow volume through the valve during valve closing. According to ISO5840, in the pulsating flow experiment, the closing volume can be obtained by integral calculation. In the experimental device of Hao Wang *et al*. [20], the closing volume is the displacement of the piston during the valve closing. After the valve is closed, the blood flow volume flowing through the valve is caused by leakage. This part of the volume is called the leakage volume, which can also be calculated by integral calculation. The degree of valvular regurgitation is graded as shown in Table 7.

Table 2. Values of elasticity coefficient.

Meaning	Parameter	Value/(mmHg/mL)
Left ventricular pressure-volume ratio	Elv_{max}	3.00
	Elv_{min}	0.10
Left atrial pressure-volume ratio	Ela_{max}	1.00
	Ela_{min}	0.10
Right ventricular pressure-volume ratio	Erv_{max}	0.50
	Erv_{min}	0.05
Right atrial pressure-volume ratio	Era_{max}	0.30
	Era_{min}	0.12

Table 3. Meaning and initial value setting of variables.

Variable	Physiological meaning	Initial value	Variable	Physiological meaning	Initial value
x1	Left ventricular pressure	8.2000 mmHg	x12	Mitral valve leaflet opening arc angle	1.5533 rad
x2	Left atrial pressure	7.6000 mmHg	x13	Tricuspid valve flow	52.0000 mL/s
x3	Right atrial pressure	6.0000 mmHg	x14	Tricuspid valve leaflet opening arc angle	1.5533 rad
x4	Right ventricular pressure	5.0000 mmHg	x15	Aortic valve flow	52.0000 mL/s
x5	Aortic pressure	80.0000 mmHg	x16	Aortic valve leaflet opening arc angle	1.5533 rad
x6	Arterial system pressure	67.0000 mmHg	x17	Aortic flow	0.0000 mL/s
x7	Venous pressure	5.0000 mmHg	x18	Arterial system flow	0.0000 mL/s
x8	Pulmonary artery pressure	15.0000 mmHg	x19	Pulmonary valve flow	52.0000 mL/s
x9	Pulmonary artery system pressure	10.0000 mmHg	x20	Pulmonary valve leaflet opening arc angle	1.5533 rad
x10	Pulmonary vein pressure	7.0000 mmHg	x21	Pulmonary artery flow	0.0000 mL/s
x11	Left ventricular pressure	52.0000 mL/s	x22	Pulmonary artery system flow	0.0000 mL/s

Table 4. Cardiovascular model parameters.

Resistance	mmHg·s/Hg	Compliance	mL/mmHg	Inertance	mmHg·s²/mL
Rsas	0.085000	Csas	0.150000	Lmi	0.000980
Rsat	0.800000	Csat	5.000000	Lao	0.000600
Rsv	0.035000	Csv	16.000000	Lti	0.001100
Rpas	0.015000	Cpas	0.800000	Lpo	0.000320
Rpat	0.0800000	Cpat	5.000000	Lsas	0.000060
Rpv	0.002000	Cpv	13.500000	Lsat	0.001700
				Lpas	0.000052
				Lpat	0.001700

Table 5. Effective orifice area of valve in steady state.

Valve	Orifice area in fully open state/cm^2	Orifice area in closed state/cm^2
Mitral valve	7	0.015
Aortic valve	5	0.008
Tricuspid valve	7	0.015
Pulmonary valve	5	0.008

In this paper, the valve model with controllable closing volume proposed by Zhaoming He *et al.* [13] is used, as shown in Fig. 3. Qc represents the amount of blood squeezed out by the valve leaflets during exercise, L simulates the inertia of blood flow and the delay of mitral valve closure, and the resistance of the valve to blood flow during exercise is reflected by the variable resistance R.

After the valve is opened, the valve model divides the blood flowing through the valve into two parts. One part is caused by the cross-valve pressure difference on both sides of the valve. This part of the blood flow volume is Q_o, and the other part of the blood flows through the valve due to the crowding effect of the valve leaf during the movement, which is Qc. The valve model divides the movement of the valve into four processes: opening state-closing process-closing state-opening process. “AR” represents the ratio of the orifice area opened in real time to the maximum orifice area, and its expression is Eqn. 7. Where k and λ determine

Table 6. Equations of State.

Equations of state	Equations of state
$Clv\frac{dx_1}{dt}+x_1\frac{dClv}{dt}=x_1-x_5$	$Cpv\frac{dx_{10}}{dt}=x_{22}-\frac{x_{10}-x_2}{Rpv}$
$Cla\frac{dx_2}{dt}+x_2\frac{dCla}{dt}=\frac{x_{10}-x_2}{Rpv}-x_{11}$	$Lmi\frac{dx_{11}}{dt}=x_2-x_1-(x_{11}-Qcmi)\cdot Rmi$
$Crv\frac{dx_3}{dt}+x_3\frac{dCrv}{dt}=x_{13}-x_{19}$	$Lti\frac{dx_{13}}{dt}=x_4-x_3-(x_{13}-Qcti)\cdot Rti$
$Cra\frac{dx_4}{dt}+x_4\frac{dCra}{dt}=\frac{x_7-x_4}{Rsv}-x_{13}$	$Lti\frac{dx_{13}}{dt}=x_4-x_3-(x_{13}-Qcti)\cdot Rti$
$Csas\frac{dx_5}{dt}=x_{15}-x_{17}$	$Lsas\frac{dx_{17}}{dt}=x_5-x_6-Rsas\cdot x_{17}$
$Csat\frac{dx_6}{dt}=x_{17}-x_{18}$	$Lsat\frac{dx_{18}}{dt}=x_6-x_7-Rsat\cdot x_{18}$
$Csv\frac{dx_7}{dt}=x_{18}-\frac{x_7-x_4}{Rsv}$	$Lpo\frac{dx_{19}}{dt}=x_3-x_8-(x_{19}-Qcpo)\cdot Rpo$
$Cpas\frac{dx_8}{dt}=x_{19}-x_{21}$	$Lpas\frac{dx_{21}}{dt}=x_8-x_9-Rpas\cdot x_{21}$
$Cpas\frac{dx_9}{dt}=x_{21}-x_{22}$	$Lpat\frac{dx_{22}}{dt}=x_9-x_{10}-Rpat\cdot x_{22}$

Table 7. Range of regurgitation volume levels for mitral and aortic valves.

Regurgitation degree	Normal	Mild	Moderate	Severe
Mitral valve	7–14 mL	15–20 mL	20–30 mL	30–40 mL
Aortic valve	2–7 mL	7–10 mL	10–20 mL	20–30 mL

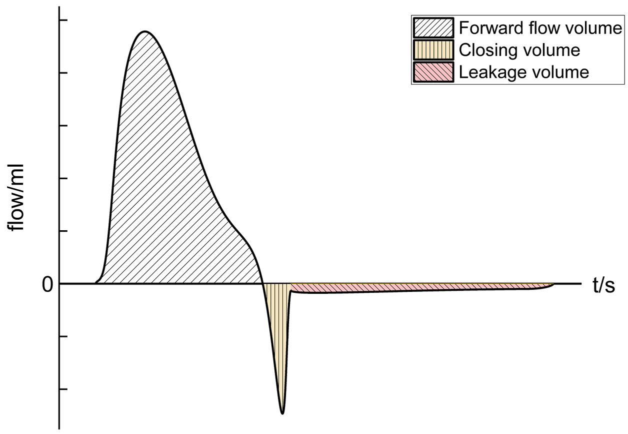

Fig. 2. Classification of flow cycles.

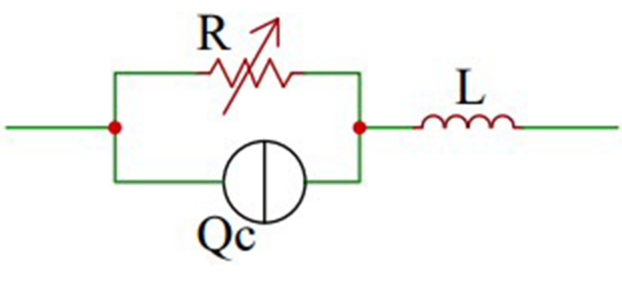

Fig. 3. Valve model with controllable closure volume. R represents the resistance of the valve to blood flow during movement. Qc represents the amount of blood squeezed out by the leaflet during its movement. L represents the inertia of blood flow and the delay in valve closure.

the closing characteristics of the valve, and their values affect the valve closing volume. Under the condition that the maximum and minimum orifice area of the valve is fixed and the closing time is fixed, the corresponding closing volume can be obtained by giving different λ values, and then the data are fitted to obtain the closing volume. The expression of closing time, k, λ, so that the closing volume can be controlled.

$$AR=\begin{cases}1 & \text{opening state}\\ e^{k\cdot(t-t_1)^{\lambda}} & \text{closing process}\\ (r-L\cos\theta_{\min})\,/\,(r-L\cos\theta_{\max}) & \text{closing state}\\ (r-L\cos\theta)/\,(r-L\cos\theta_{\max}) & \text{opening process}\end{cases} \tag{7}$$

The formula for calculating the blood flow volume through the orifice of the valve caused by the transvalvular pressure difference on both sides of the valve is Eqn. 8, where CQ is Eqn. 9, and ρ is the blood density. The calculation of time-varying resistance is shown in Eqn. 10.

$$Q_o=CQ\cdot AR\cdot\sqrt{TP} \tag{8}$$

$$CQ=\frac{51.6}{\sqrt{\rho}}EOA_{\max} \tag{9}$$

$$R=\frac{TP}{Q_0}=\frac{|Q_0|}{(CQ\cdot AR)^2} \tag{10}$$

The formula for calculating the blood flow of the valve leaflet motion is Eqn.11, where L is the length of the valve leaflet, r is the radius of the valve ring, and θ is the angle between the valve leaflet and the plane of the valve ring.

$$Qc=\pi L^2\cos^2\theta\left(r-\frac{2}{3}L\cos\theta\right)\frac{d\theta}{dt} \tag{11}$$

Table 8. Simulated data.

VR_{ao}/mL	VR_{mi}/mL	NSV/mL	V_{max}/mL	V_{min}/mL	SV/mL	EF	NEF	DEF
3.98	12.30	64.52	120.83	40.92	79.91	66.14%	53.39%	12.74%
4.08	18.72	63.34	124.62	40.09	84.53	67.83%	50.83%	17.01%
3.90	21.57	62.88	126.14	39.73	86.41	68.51%	49.85%	18.65%
3.83	31.50	60.65	132.46	38.71	93.74	70.77%	45.79%	24.98%
8.77	11.78	63.16	123.32	40.66	82.67	67.03%	51.21%	15.82%
8.51	18.62	61.87	127.29	39.84	87.45	68.70%	48.60%	20.10%
8.21	22.26	61.12	129.46	39.48	89.98	69.50%	47.21%	22.29%
8.91	31.83	59.25	135.52	38.40	97.12	71.66%	43.72%	27.94%
14.62	11.49	62.21	126.72	40.44	86.28	68.09%	49.10%	18.99%
14.93	18.80	60.76	131.30	39.53	91.78	69.90%	46.27%	23.62%
14.93	20.77	60.45	132.40	39.29	93.12	70.33%	45.66%	24.67%
14.14	31.50	58.85	137.83	37.97	99.87	72.46%	42.70%	29.76%
25.40	12.74	59.78	134.55	39.92	94.63	70.33%	44.43%	25.91%
24.83	18.93	58.89	137.65	39.20	98.44	71.52%	42.78%	28.74%
25.80	21.77	58.29	139.79	38.83	100.96	72.22%	41.70%	30.52%
25.99	30.59	56.47	145.38	37.92	107.46	73.91%	38.85%	35.07%

Note: VR_{ao}, aortic regurgitation volume; VR_{mi}, mitral regurgitation volume; NSV, net stroke volume; V_{max}, the minimum ventricular volume; V_{min}, the maximum ventricular volume; SV, stroke volume; EF, ejection fraction; NEF, net ejection fraction; DEF, the difference between EF and NEF.

Table 9. Correlation analysis of DEF on aortic valve and mitral regurgitation volume.

The degree of valvular regurgitation	Normal	Mild	Moderate	Severe
Pearson correlation coefficient of mitral regurgitation	0.98946	0.99156	0.97175	0.96558
p-value	9.38×10^{-54}	4.86×10^{-46}	1.73×10^{-59}	2.98×10^{-53}
Pearson correlation coefficient of aortic valve regurgitation	0.99480	0.99679	0.99723	0.99782
p-value	2.59×10^{-19}	5.64×10^{-19}	6.47×10^{-15}	6.20×10^{-18}

There are two ways to adjust the valve regurgitation volume and regurgitation fraction: one is to adjust the size of the valve closing volume, and the other is to adjust the regurgitation fraction of the valve by adjusting the minimum orifice area of the valve, so as to achieve different degrees of regurgitation.

Results

Table 8 shows some simulation data. From the table, it can be seen that the EF measured by ultrasound is severely overestimated in cases of moderate to severe regurgitation of the valve. It can be seen that in the case of a certain degree of aortic regurgitation, as the degree of mitral regurgitation increases, the SV gradually increases, the positive flow volume of the mitral valve increases, the V_{max} increases, the NSV decreases, the EF increases, and the NEF decreases. The increase of aortic regurgitation volume (VR_{ao}) directly leads to the decrease of NSV. During diastole, the V_{max} increased due to aortic regurgitation. As the left ventricular volume increases, it will lead to an increase in left ventricular pressure, and the positive flow volume that flows through the aortic valve during the systolic period, that is, the stroke volume, will increase.

As with aortic regurgitation, due to mitral regurgitation, blood will flow back to the left atrium during systole, resulting in increased blood flow to the left ventricle through the mitral valve during diastole and V_{max} increases, too. However, in the case of mitral regurgitation, the amount of blood ejected from the left ventricle to the aorta is reduced due to partial blood reflux to the left atrium during systole. Therefore, as the reflux fraction increases, the net ejection fraction NEF results will gradually decrease.

Fig. 4A–D are the scatters of DEF on VR_{mi} when the VR_{ao} is 4.0 ± 0.5 mL, 8.5 ± 0.5 mL, 14.5 ± 0.5 mL and 25 ± 0.5 mL, respectively. Fig. 4E–H is the scatters of DEF about VR_{ao} when the VR_{mi} is 115.0 ± 0.5 mL, 16.5 ± 0.5 mL, 23.5 ± 0.5 mL, 34 ± 0.5 mL.

The correlation analysis of VR_{ao}, VR_{mi} and DEF obtained by simulation is carried out respectively, and the Pearson correlation coefficient is close to 1, as shown in Table 9. The closer the Pearson correlation coefficient is to 1, the stronger the positive correlation between VR_{ao}, VR_{mi} and DEF. The probability of correlation (p value) was less than 0.01. If this p value is very small, the probability of no correlation between the two variables is very small. Thus, VR_{ao} and VR_{mi} are strongly correlated with the linear relationship of DEF. Therefore, the difference between the

Table 10. DEF value range under different degrees of mitral regurgitation and aortic regurgitation.

Degree of aortic regurgitation	Degree of mitral regurgitation	DEF	Degree of aortic regurgitation	Degree of mitral regurgitation	DEF
Normal	Normal	8.14%–15.82%	Mild	Normal	12.02%–17.86%
	Mild	12.56%–19.61%		Mild	16.08%–21.34%
	Moderate	16.35%–25.92%		Moderate	19.56%–27.14%
	Severe	22.66%–32.23%		Severe	25.36%–32.94%
Moderate	Normal	14.78%–23.06%	Severe	Normal	20.65%–28.37%
	Mild	18.51%–26.27%		Mild	24.09%–31.33%
	Moderate	21.72%–31.61%		Moderate	27.05%–36.25%
	Severe	27.06%–36.95%		Severe	31.97%–41.17%

volume of mitral regurgitation and the difference between the EF and the NEF, DEF, under different degrees of aortic regurgitation was fitted, and the value range of DEF under different degrees of mitral and aortic regurgitation was calculated, as shown in Table 10.

Discussion

The EF of patients with mitral and aortic regurgitation measured by echocardiography will be higher, and in fact NEF is lower than EF measured by echocardiography. The reason for this is that the part of the blood in the systolic ventricle that flows back to the atrium through the mitral valve and the part of the blood that returns to the left ventricle from the aorta in the diastolic period are calculated in the SV. In the absence of mitral regurgitation, the systolic left ventricle shoots blood into the aorta, then into various tissues and organs of the human body. But a little return to the left atrium, which is negligible. However, if there is mitral regurgitation, a part of the blood that cannot be ignored will return to the left atrium through the mitral valve. Therefore, for patients with mitral regurgitation and aortic regurgitation, ultrasound examination of cardiac systolic function is normal, which may not be accurate. For patients with aortic regurgitation, the SV calculated by subtracting the end-systolic volume from the left ventricular end-diastolic volume contains the part of the blood that the aorta returns to the left ventricle during the diastolic period, and the actual stroke volume will be overestimated.

As shown in Fig. 5, regardless of whether the valve is in healthy or reflux conditions, the left ventricular volume is at its maximum when the mitral valve begins to close. At the moment when the aortic valve begins to close, the ventricular volume is minimized. Mitral and aortic regurgitation affects clinician-measured left ventricle end-diastolic volume, V_{max}. The clinically measured left ventricle maximum volume and SV increase with the degree of mitral or aortic regurgitation, as does the clinically measured EF. However, NEF and NSV decrease with increasing regurgitation degree. DEF increases with the severity of valve regurgitation.

This study showed that EF measured by echocardiography in normal aortic valve and moderate mitral regurgitation group decreased by 26.3% ± 9.95% on average compared with NEF. Severe mitral regurgitation group decreased by 31.9% ± 9.3%. The value measured by the correction formula proposed by Xu *et al.* [6] decreased by 10.4 ± 2.5% on average compared with the moderate regurgitation group measured by conventional methods. Severe mitral regurgitation group decreased by 13.7 ± 3.2%. Correction formula: ELVEF = $(V_{max} - V_{min} - VR_{mi})/V_{max} \times 100\%$. Mitral regurgitation volume was calculated by distal flow convergence method. The reason for the difference is that the VR_{mi} mitral regurgitation volume in the correction formula is quantitatively calculated by the distal blood flow convergence method, while the mitral regurgitation volume in this study is obtained by the flow curve integral. The correction formula defaults that the aortic valve has no regurgitation, and the default is NSV = $V_{max} - V_{min} - VR_{mi}$, without considering the volume of aortic regurgitation. In fact, whether it is valve health or reflux, there is reflux. Bamidele T. Otemuyiwa *et al.*' s study [21] on the effect of mitral valve prolapse on cardiac magnetic resonance imaging (MRI) quantitative mitral regurgitation and ejection fraction showed that EF = 58.6% ± 6.3% when the left ventricular end-diastolic volume did not include the prolapse volume, and EF = 51.7% ± 5.7% when the left ventricular end-diastolic volume included the prolapse volume. Although they measured NSV with MRI, SV was still used to calculate ejection fraction. The NEF in this paper is calculated by NSV and ventricular end-diastolic volume.

In the calculation of EF, aortic regurgitation and mitral regurgitation have slightly different meanings. Mitral regurgitation leads to a direct reduction in the amount of blood ejected from the aortic valve, which is less than the difference between the maximum volume and the minimum volume of the ventricle. The regurgitation of the aortic valve leads to an indirect decrease in the amount of blood ejected, because the blood does eject from the aortic valve, but it leaks back during the diastolic period, which indirectly leads to a decrease in NSV. If NSV cannot meet the metabolic needs of the body, inadequate perfusion of blood to tissue organs will occur, leading to congestive heart fail-

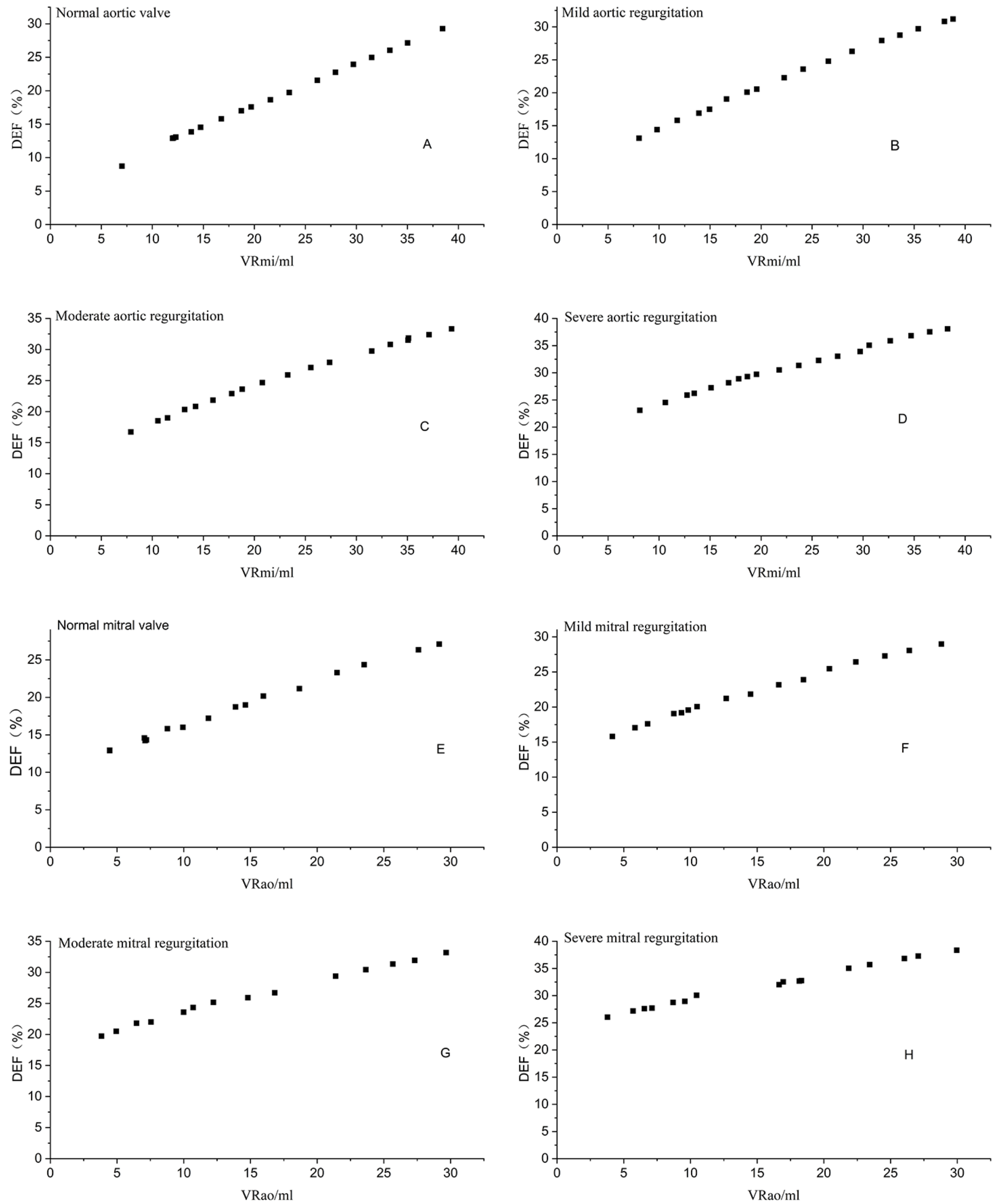

Fig. 4. Scatters plot of DEF with respect to different valve regurgitation volumes. (A) Scatter plot of DEF on VR_{mi} under normal aortic valve. (B) Scatter plot of DEF on VR_{mi} under mild aortic regurgitation. (C) Scatter plot of DEF on VR_{mi} under moderate aortic regurgitation. (D) Scatter plot of DEF on VR_{mi} under severe regurgitation valve. (E) Scatter plot of DEF on VR_{ao} under normal mitral valve. (F) Scatter plot of DEF on VR_{ao} under mild mitra regurgitation. (G) Scatter plot of DEF on VR_{ao} under moderate mitra regurgitation. (H) Scatter plot of DEF on VR_{ao} under severe mitra regurgitation. (Note: DEF is the difference between EF and NEF; VR_{mi} is the volume of mitral regurgitation; VR_{ao} is the volume of aortic regurgitation).

ure or even death. Therefore, it is particularly important to grasp the left ventricular systolic function of patients.

Left ventricular systolic function is a major prognostic factor for heart disease. Therefore, a reliable assessment of left ventricular function is essential. Ejection fraction

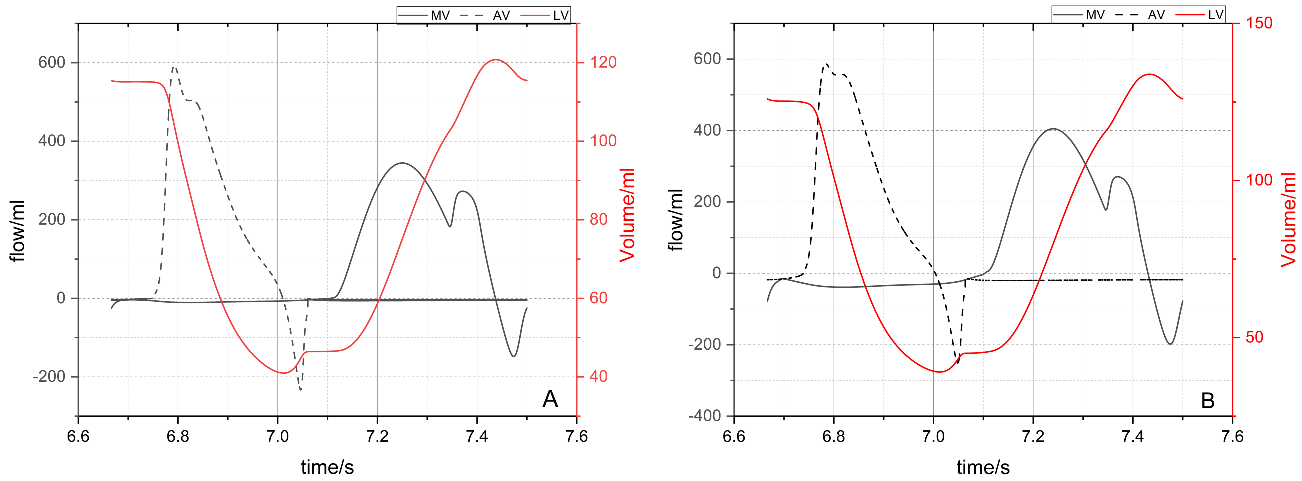

Fig. 5. Mitral valve, aortic valve flow curve and left ventricular volume curve. (A) Mitral valve, aortic valve flow curve and left ventricular volume curve in healthy valve state. (B) The flow curve and left ventricular volume curve of mitral and aortic regurgitation. Note: MV, mitral valve; AV, aortic valve; LV, left ventricular volume.

is an important index to evaluate ventricular systolic function. The accuracy and reliability of ejection fraction affect the assessment of left ventricular systolic function. Especially in patients with mitral and aortic regurgitation, the evaluation of EF by echocardiography is not completely accurate. EF is an important index for clinical evaluation of heart failure, and it is also an important evaluation index before valve repair and valve replacement. For patients with severe valvular regurgitation, valve repair surgery or valve replacement is required to improve. The left ventricular systolic function of patients with moderate or severe mitral insufficiency is significantly overestimated, which leads to the low coincidence rate between the results measured by conventional ultrasound and the clinical symptoms, signs and other auxiliary examination results of patients with mitral insufficiency, and even causes clinicians to misjudge the patient 's condition. NEF can solve this problem well. Compared with EF, NEF is more accurate, and NEF can more accurately reflect left ventricular function. In addition, NEF can also be used as an indicator to assess the risk of death in patients. The lower the NEF, the worse the cardiac function, the more severe the left ventricular function injury, the less the blood perfusion of tissues and organs, and the higher the risk of death. Doctors can estimate NEF based on the EF and degree of valve regurgitation measured by ultrasound, or calculate NEF by measuring NSV, which is the net flow volume of the aortic valve.

Limitations

In this study, regardless of the degree of mitral and aortic regurgitation, it was performed under the assumption that there was no heart failure. However, there are many patients with moderate and severe mitral and aortic regurgitation who suffer from varying degrees of heart failure. In addition, due to the difficulty in collecting data for MRI measurement of net ejection fraction and the need for a large number of samples, this study did not use NEF obtained from MRI-based measurements for verification. In the next stage of our study, we will consider the differences between EF and NEF under different degrees of mitral and aortic regurgitation in patients with different degrees of heart failure and collect a large number of samples for verification.

Conclusions

In this paper, the concepts of net stroke volume and net ejection fraction were proposed for the first time. Based on the established systemic circulation model, the ejection fraction, SV, VR_{mi}, VR_{ao}, net ejection fraction and net stroke volume were calculated according to the established circulatory system model. The results showed that EF measured by echocardiography decreased by 26.3% ± 9.95% compared with NEF in the moderate mitral regurgitation group. The severe mitral regurgitation decreased by 31.9% ± 9.3%, aortic valve decreased moderately by 25.8% ± 11.1% and aortic valve severity decreased by 30.9% ± 10.3%. Doctors can estimate NEF based on the EF and degree of valve regurgitation measured by ultrasound, or calculate NEF by measuring NSV, which is the net flow volume of the aortic valve. NEF avoids the overestimation of left ventricular systolic function and has high reliability. NEF can be used to evaluate heart failure and is also an important evaluation indicator before valve repair and valve replacement surgery. It can accurately reflect the left ventricular systolic function of patients with mitral and aortic regurgitation, and has certain guiding significance for clinicians to grasp the patient's condition.

Availability of Data and Materials

The data supporting the findings of this study are available from the corresponding author upon reasonable request. The materials used in this study are available upon request from the corresponding author.

Author Contributions

XX: Responsible for literature retrieval, simulation operation, data analysis, literature review, reading and revising the final manuscript. GL: Responsible for designing experimental methods, obtaining data, analyzing data and providing guidance. ZH: Responsible for proposing solutions to challenging problems, providing guidance, reading and modifying the final script to ensure the integrity of the experiment and the correctness of the data. All authors read and approved the final manuscript. All three authors contributed to the revision of the manuscript. All three authors have a sufficient expectation of the work, assume public responsibility for the appropriate part of the content, and agree to be responsible for all aspects of the work to ensure issues relating to the accuracy or completeness of the work.

Ethics Approval and Consent to Participate

Not applicable.

Acknowledgment

Not applicable.

Funding

This research received no external funding.

Conflict of Interest

The authors declare no conflict of interest.

References

[1] Greaves SC. Assessment of left ventricular systolic function in research and in clinical practice. Heart (British Cardiac Society). 2000; 83: 493–494.

[2] Fan Y, Pui-Wai Lee A. Valvular Disease and Heart Failure with Preserved Ejection Fraction. Heart Failure Clinics. 2021; 17: 387–395.

[3] Suri RM, Schaff HV, Dearani JA, Sundt TM, Daly RC, Mullany CJ, *et al*. Recovery of left ventricular function after surgical correction of mitral regurgitation caused by leaflet prolapse. The Journal of Thoracic and Cardiovascular Surgery. 2009; 137: 1071–1076.

[4] Mitchell C, Rahko PS, Blauwet LA, Canaday B, Finstuen JA, Foster MC, *et al*. Guidelines for Performing a Comprehensive Transthoracic Echocardiographic Examination in Adults: Recommendations from the American Society of Echocardiography. Journal of the American Society of Echocardiography: Official Publication of the American Society of Echocardiography. 2019; 32: 1–64.

[5] Leyh RG, Schmidtke C, Sievers HH, Yacoub MH. Opening and closing characteristics of the aortic valve after different types of valve-preserving surgery. Circulation. 1999; 100: 2153–2160.

[6] Xu Z, Liu Q, Su XJ. Reliability analysis of ultrasonic measurement of left ventricular ejection fraction in patients with moderate to severe mitral regurgitation. Shenzhen Journal of Integrated Traditional Chinese and Western Medicine. 2011; 21: 46–48. (In Chinese)

[7] Li DL, Fang XX. The reliability of LVEF measured by ultrasound in patients with moderate or severe mitral regurgitation. Chinese and Foreign Medical Research. 2013; 11: 64–65. (In Chinese)

[8] Salame G, Northcutt N, Soni NJ. Focused Cardiac Ultrasonography for Left Ventricular Systolic Function. The New England Journal of Medicine. 2020; 382: 976–977.

[9] Dandel M. It is time to think about further optimization of the echocardiographic assessment of left ventricular responses to mitral regurgitation. International Journal of Cardiology. 2024; 401: 131841.

[10] Kataria R, Khalil A, Coglianese E, Crowley J, Silverman MG, Shelton K, *et al*. Effect of Impella 5.5 on Preexisting Functional Mitral Regurgitation in Patients with Heart Failure-Related Cardiogenic Shock. Structural Heart: the Journal of the Heart Team. 2022; 6: 100072.

[11] Bartko PE, Hülsmann M, Hung J, Pavo N, Levine RA, Pibarot P, *et al*. Secondary valve regurgitation in patients with heart failure with preserved ejection fraction, heart failure with mid-range ejection fraction, and heart failure with reduced ejection fraction. European Heart Journal. 2020; 41: 2799–2810.

[12] Corporan D, Onohara D, Amedi A, Saadeh M, Guyton RA, Kumar S, *et al*. Hemodynamic and transcriptomic studies suggest early left ventricular dysfunction in a preclinical model of severe mitral regurgitation. The Journal of Thoracic and Cardiovascular Surgery. 2021; 161: 961–976.e22.

[13] He ZM, Liu YF, Jing T, Zhang GJ, Liu HY, Wang H. Heart valve model with controllable closing volume. Journal of Drainage and Irrigation Machinery Engineering. 2019; 37: 1–6,37. (In Chinese)

[14] Shim EB, Sah JY, Youn CH. Mathematical modeling of cardiovascular system dynamics using a lumped parameter method. The Japanese Journal of Physiology. 2004; 54: 545–553.

[15] Frolov SV, Sindeev SV, Lischouk VA, Gazizova DS, Liepsch D, Balasso A. A Lumped Parameter Model of Cardiovascular System with Pulsating Heart for Diagnostic Studies. Journal of Mechanics in Medicine and Biology. 2017; 17: 21.

[16] Shimizu S, Une D, Kawada T, Hayama Y, Kamiya A, Shishido T, *et al*. Lumped parameter model for hemodynamic simulation of congenital heart diseases. The Journal of Physiological Sciences: JPS. 2018; 68: 103–111.

[17] Suga H, Sagawa K, Shoukas AA. Load independence of the instantaneous pressure-volume ratio of the canine left ventricle and effects of epinephrine and heart rate on the ratio. Circulation Research. 1973; 32: 314–322.

[18] Korakianitis T, Shi Y. Numerical simulation of cardiovascular dynamics with healthy and diseased heart valves. Journal of Biomechanics. 2006; 39: 1964–1982.

[19] Yoganathan AP, He Z, Casey Jones S. Fluid mechanics of heart valves. Annual Review of Biomedical Engineering. 2004; 6: 331–362.

[20] Wang H, Cui Z, Zhou Z, He Z. A Single-opening&closing Valve Tester for Direct Measurement of Closing Volume of the Heart Valve. Cardiovascular Engineering and Technology. 2022; 13: 80–89.

[21] Otemuyiwa BT, Lee EM, Sella E, Madamanchi C, Balasubramanian S, Ma T, *et al*. Effects of Mitral Valve Prolapse on Quantification of Mitral Regurgitation and Ejection Fraction Using Cardiac MRI. Radiology. Cardiothoracic Imaging. 2023; 5: e220069.