Analog Circuit Platform for Simulating Typical Pulmonary Hypertensions from Point of Hemodynamics

Hong Tang\*, Ziyin Dai, Miao Wang, Binbin Guo

School of Biomedical Engineering, Dalian University of Technology, Dalian city, China

Correspondence: tanghong@dlut.edu.cn; Tel.: +86-411-8470-6009Ext 3013

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**Abstract**

**Background:** Pulmonary hypertension (PH) behaves unusual hemodynamic states characterized by abnormal high blood pressure in pulmonary artery. It is interesting to understand the hemodynamic development of typical PHs.

**Results:** This study sets up an analog circuit platform of human circulation system to simulate hemodynamic abnormalities of PH caused by different etiologies and pathogenesis. Four typical causes are considered. They are distal pulmonary artery stenosis (DPAS), left ventricular diastolic dysfunction (LVDD), ventricular septal defect (VSD), and mitral stenosis (MS). The authors propose a simulation method for each cause and regulation rules for chambers, vessels to adapt the abnormal hemodynamic conditions. The occurrence and development of each PH are simulated over time in the platform. The blood pressure, blood flow, pressure-volume relation for chambers, vessels are numerically calculated in each PH progress. It is shown that the simulation results for the PHs are close to clinical investigations.

**Conclusions:** The performances prove that the platform is qualified and effective for computer simulation of PHs. It could be a quite powerful tool to understand the hemodynamic mechanism of PH caused by various etiologies and pathogenesis.

**Keywords:** Pulmonary hypertension, Human circulation system, Distal pulmonary artery stenosis, Left ventricular diastolic dysfunction, Ventricular septal defect, Mitral stenosis, Hemodynamic modelling

1. Background

Pulmonary Hypertension (PH) is a general term to describe groups of clinical syndromes characterized by high pressure in the lungs caused by different etiologies and pathogenesis. The World Health Organization (WHO) defines five groups of PH based on different causes. They are referred to as PH WHO groups [1]. The first group is pulmonary arterial hypertension (PAH), which is caused as the arteries in the lungs become narrowed, thickened or stiff. The second group is PH due to left heart disease. In this group, there are problems in the manner how the heart squeezes or relaxes, or problems with the valves on the left side of the heart. The third group is PH due to lung disease. The fourth group is PH due to chronic blood clots in the lungs. The fifth group is PH due to unknown causes. PH lacks distinctive clinical manifestations in the early stage. No matter which group one patient is in, PH is a serious disease. If PH is not treated timely, it could progress to right heart failure and even death [2]. Since any group of PH can be reflected by the abnormal hemodynamics in the right heart and lungs, it is necessary to understand the hemodynamic changes therein. At present, right heart catheterization that directly measure blood pressure in the right heart and lung is the ‘gold standard’ operation for diagnosis and assessment of PH [3].

Computer simulation is possibly a cheap and convenient way to understand the causes and development of abnormal hemodynamics in systemic and pulmonary circulation system. Various models have been proposed for circulation hemodynamic simulation. A circuit model was built for heart failure, which found a decrease in left ventricular blood pressure, cardiac output, and a significant change in the pressure-volume (P-V) loop of left ventricle (LV) [4-6]. Korurek et al modeled severe aortic valve stenosis by increasing the value of the resistance to the aortic valve in the analog circuit model [7], a remarkable increase in LV systolic blood pressure and aortic pressure mean gradient, and decrease in aortic systolic blood pressure were consequently observed. In addition, mitral stenosis [8], mitral regurgitation and aortic regurgitation [9], caused the abnormal hemodynamics in the cardiovascular system, were also studied by computer model. In [10], two causes that lead to left ventricular diastolic dysfunction were discussed. Impaired left ventricular active relaxation (IR-type) was modeled by changing the activation function of LV. Increased passive stiffness (R-type) was modeled by increasing diastolic stiffness of LV wall and septum. The simulation results showed that abnormal LV diastolic performance alone can result in decreased LV and right ventricular (RV) systolic performance [10]. Besides, Korurek et al simulated Eisenmenger syndrome with ventricular septal defect [11]. It was found that there was a remarkable increase in the pulmonary artery pressure and RV pressure, but decrease in LV pressure, aortic pressure, aortic flow and pulmonary compliance.

In this study, the authors set up an analog circuit as a platform for simulating four typical PHs, including PH caused by distal pulmonary artery stenosis (DPAS), left ventricular diastolic dysfunction (LVDD), ventricular septal defect (VSD) and mitral stenosis (MS). The simulations show the occurrence and development of the typical PHs. These simulations are helpful for physicians to understand the causes to lead PHs. They have potential applications in early detection of typical PHs by screening abnormal hemodynamics in human circulation system.

2. An Analog Circuit Platform for Normal Human Circulation System

Previous studies have clearly disclosed that there is general equivalence between blood flow in circulation system and current flow in analog circuit [12-15]. The blood pressure and blood flow are equivalent to voltage and charge flow. The resistance of blood flow is equivalent to electronic resistance. The inertia of blood flow can be modeled by inductance. Inflow and outflow blood to vessel are similar to charging and discharging to linear or nonlinear capacitance. Blood pumping of a heart chamber can be simulated by a nonlinear voltage source with respect to volume and time. Valves in heart and vessels are like diodes. Therefore, an improved model for human circulation system circuit is proposed in this paper and taken as a platform to simulate four typical PHs, see **Fig. 1**. The P-V relation of a vein or artery is generally modeled by three-element segment: resistance, compliance and inductance. The initial values of the elements in the model are given in Appendix A.



**Fig. 1** Analog circuit platform for normal human circulation system. R: resistances; C: compliances; L: inductances; D: valves; LV: left ventricle; LA: left atrium; RV: right ventricle; RA: right atrium. Full name for the abbreviations used in subscripts: Dm-mitral valve; Da-aortic valve; Dt-tricuspid valve; Dp-pulmonary valve; haa-head and arm artery; lna-left neck artery; lca-left clavicular artery; aop-proximal aorta; rula-right upper limb artery; rica-right internal carotid artery; lica-left internal carotid artery; lula-left upper limb artery; sap-proximal systemic artery; rsv-right subclavian vein; rijv-right internal jugular vein; lijv-left internal jugular vein; lsv-left subclavian vein; sv-systemic veins; vc-vena cava; lpap-left proximal pulmonary artery; rpap-right proximal pulmonary artery; lpad-left distal pulmonary artery; rpad-right distal pulmonary artery; lpv-left pulmonary veins; rpv-right pulmonary veins; c-viscoelastic resistance. D1, D2, D3, D4, D51, D52, D53, D54, D6, D7, D8, D9, D10, D11, and D12 are diodes for valves.

2.1 Ventricular Model

The ventricular model in this paper is based on the work of Chung et al [13]. Each ventricle is characterized as a time-varying elastic function that is controlled by end-systolic P-V relation (ESPVR), end-diastolic P-V relation (EDPVR) and a time-varying activation function. From a physiological point of view, great sympathetic tone increases myocardial elastance and shortens ventricular systole. Therefore, A rising in the sympathetic efferent discharge frequency,  increases maximum elastance [14]. For example, the blood pressure in the left ventricle,, is a function of volume , time  and ,

, (1)

, (2a)

, (2b)

where  represents ESPVR and  represents EDPVR.  is a constant volume.  is the end-systolic elastance.  is the volume intercept of EDPVR,  is the pressure intercept and  is an empirical constant. In addition, a rising in  also shortens the ventricular systolic period, Lu and Clark et al [14] modified the ventricular activation function that is a function of , and the activation function  consists of four Gaussian functions,

, (3)

where  and  are functions of ,

, (4a)

, (4b)

 and  are the minimum values of the functions  and .  and  are scaling factors. Those parameters are shown in **Table 1**.

**Table 1** Parameters for control of ventricle contractility

|  |  |  |  |
| --- | --- | --- | --- |
| Ventricle Contractility | | | |
|  |  |  |  |
| 0 | 0.7 | 3 | 0.5 |

2.2 Atrial Model

The atrial model uses the same principle as the ventricular model, however the ESPVR of atrial model is not affected by . For example, the blood pressure in the left atrium,, thus is a function of volume , time ,

, (5a)

, (5b)

. (5c)

The activation function  is fitted by one Gaussian function,

. (6)

The right ventricular model and the right atrial model are like that of left ventricle and left atrium. The parameters for the models are shown in **Table 2** and **Table 3**. Therefore, the blood pressure of the four chambers , , ,  can be modeled with respect to volume and time.

**Table 2** Parameters of the ventricular and atrial model [15]

|  |  |  |  |
| --- | --- | --- | --- |
| Parameters | Values | Parameters | Values |
| mmHg/ml | 4.3 | mmHg/ml | 0.8 |
| mmHg/ml | 0.3 | mmHg/ml | 0.3 |
| mmHg | 1.7 | mmHg | 0.67 |
| mmHg | 0.5 | mmHg | 0.5 |
| ml | 25 | ml | 25 |
| ml | 20 | ml | 20 |
| ml | 40 | ml | 40 |
| ml | 20 | ml | 20 |
| ml-1 | 0.015 | ml-1 | 0.015 |
| ml-1 | 0.025 | ml-1 | 0.025 |

**Table 3** Parameters of the activation functions [15]

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Parameters | / | / | | | |
|  |  |  |  |  |
| (Left, Right) | 0.9 | 0.3 | 0.35 | 0.5 | 0.55 |
| (Left, Right) | 0.038 | 0.045 | 0.035 | 0.037 | 0.036 |
| (Left) | 0.145 | 0.275 | 0.33 | 0.375 | 0.4 |
| (Right) | 0.125 | 0.288 | 0.343 | 0.388 | 0.413 |

2.3 Nonlinear P-V Relations for Specified Vessels

The P-V relations of systemic veins, superior and inferior vena cava, and proximal systemic artery are non-linear, and the compliance of these vessels varies with pressure and volume. The nonlinear vascular model proposed by Lu and Clark et al [14], in which the compliances are expressed by P-V relation, meanwhile the vascular resistance of the superior, inferior vena cava and proximal systemic artery are nonlinear functions of blood volume.

***Systemic veins***The systemic veins stiffen as blood volume increases. The P-V relation is modeled as,

, (7)

where  and  are the pressure and volume of systemic veins, respectively.  is a scale, and  is the maximum volume of systemic veins.

***Vena cava*** The P-V relation of the vena cava is a stepwise function,

 , (8)

where  and  are the pressure and volume of vena cava.  and  are the unstressed and minimum volume, respectively. The P-V relation is able to simulate the human venous system by adjusting the parameters of , ,  and . The resistance of the vena cava is,

, (9)

where  is a scaling factor, and  is an offset parameter,  denotes the maximum volume.

***Proximal systemic artery***. The compliance and resistance of proximal systemic artery are related to vasoconstriction, which is controlled by normalized sympathetic efferent frequency, . Hence, the P-V relation for proximal systemic artery is represented by both fully activated and passive states,

, (10a)

, (10b)

, (10c)

where  and  are the pressures of proximal systemic artery in the fully activated and passive pressures, respectively.  is the volume, and  is the minimum volume. ,  and  are scaling factors.  is a volume parameter and  is constant. The resistance of the proximal systemic artery is,

, (11)

where  is a scaling factor, and  is the maximal volume. The all parameters of model are shown in **Table 4**.

**Table 4** Parameters for nonlinear P-V relations of specified vessels [15]

|  |  |  |  |
| --- | --- | --- | --- |
| Parameters | Values | Parameters | Values |
| **Systemic Veins** |  | ml | 350 |
| mmHg | 40 | ml | 50 |
| ml | 3500 | **Proximal Systemic Artery** | |
| **Vena Cava** | | ml | 50 |
| mmHg | 0 | mmHg | 1000 |
| mmHg | -5 | mmHg | 0.03 |
| mmHg | 0.15 | mmHg/ml2 | 0.2 |
| mmHg | 0.4 | mmHg·s·ml-1 | 0.04 |
| mmHg·s·ml-1 | 0.001 | ml | 210 |
| mmHg·s·ml-1 | 0.025 | ml | 250 |
| ml | 130 | ml-1 | 0.1 |

2.4 Heart Rate Controls of the Model

The heart rate is controlled by vagal and sympathetic neural activity that is described as a three-dimensional response by Sunagawa [16]. The human heart rate response is further improved by Lu and Clark [14],

, (12)

where  are constants that shown in **Table 5**,  and  are represented as normalized sympathetic and vagal frequencies, respectively.

**Table 5** Parameters for control of heart rate

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Heart Rate | | | | | |
|  |  |  |  |  |  |
| 35 | 140 | 40 | 32 | 10 | 20 |

2.5 Solution to the Blood Circulation Model

The relations between compliance , inductance , blood flow  and blood pressure  in the circuit system are,

, (13a)

. (13b)

By using the relation between pressure and volume for the compliance, , **(13)** can be written as,

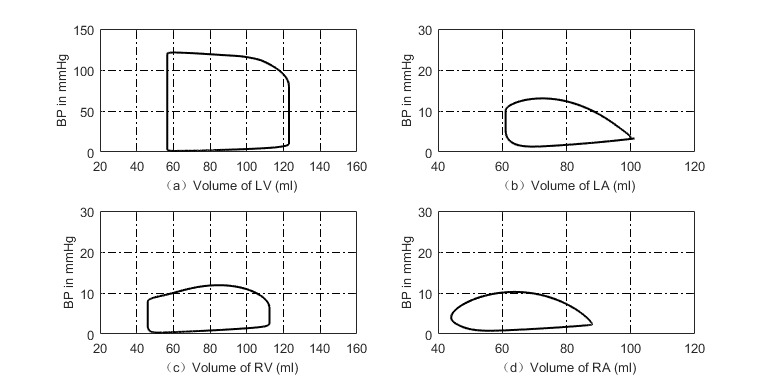
, (14a)

. (14b)

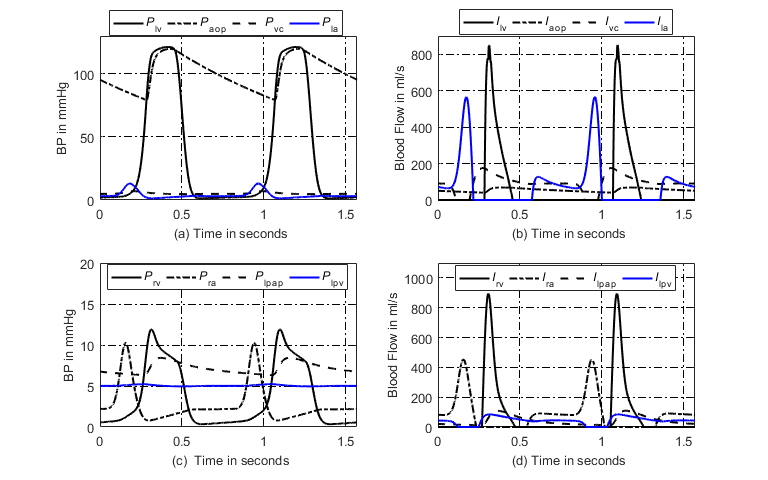
Therefore, the platform shown in **Fig. 1** can be transformed into a group of differential equations. The blood pressure and flow at any node of the platform can be numerically calculated.

2.6 Simulated Normal Hemodynamics

The simulated P-V loops of four heart chambers for normal hemodynamics are shown in **Fig. 2(a)-(d).** The blood pressures, blood flows at typical systemic and pulmonary node are shown in **Fig. 3(a)-(d)**. It can be seen that the analog circuit platform works like a normal human circulation system. The left ventricle pumps blood into aortic artery with systolic pressure 121 mmHg. The aortic artery receives blood and pushes blood forward where the pressure varies from 80 to 120 mmHg. The instantaneous flow at the outlet of left ventricle is seen in **Fig. 3(b)**. At the end of systemic circulation, the pressure in systemic vein is down to almost zero and has little variation. The pulmonary related pressures and flows at representative nodes and branches are illustrated in **Fig. 2(c)**, **Fig. 2(d)**, **Fig. 3(c)** and **Fig. 3(d)**. They all show that the simulated circulation system works in a normal state.



**Fig. 2** P-V loops of four heart chambers for normal state. (a) P-V loop of left ventricle; (b) P-V loop of left atrium; (c) P-V loop of right ventricle; (d) P-V loop of right atrium.



**Fig. 3** Simulated hemodynamics of two cardiac cycles. (a) Key systemic blood pressures; (b) Corresponding blood flows of (a); (c) Key pulmonary blood pressures; (d) Corresponding pulmonary blood flows of (c).

3. Simulations for Typical Pulmonary Hypertensions

3.1. PH Due to Distal Pulmonary Artery Stenosis (DPAS)

There are common pathological basis for the occurrence and development of different etiologies of PH, including vasoconstriction, pulmonary vascular remodeling and in situ thrombosis [17,18]. If pulmonary arteries are healthy and flexible, blood runs easily through the vessels. The synergistic effects cause an increase in pulmonary vascular resistance (PVR) and lead to PH. The increase in pulmonary artery pressure caused by pulmonary vasoconstriction is reversible in the early stage of PH. With the development of stenosis, the intima and medial membrane thickens, resulting in thickening of the vessel wall, narrowing of the lumen, remodeling of angiogenesis, and showing irreversible changes in vascular structure. Thick and stiff artery walls limit blood flow and increase the resistance. As the artery narrows further, blood flow in restricted. Pulmonary vascular remodeling is the main pathological change of PH. The change of vascular radius before and after vascular remodeling are shown in **Fig. 4**.



**Fig. 4** Schematic example of normal vessels and after vascular structure remodeling. (a) Healthy pulmonary artery; (b) Thick and stiff pulmonary artery.

1) Model of Nonlinear P-V Relation for Distal Pulmonary Arteries Due to Stenosis

Based on the well-known Poiseuilli’s law, the flow of liquid  is proportional to the pressure difference at both ends of the pipe and the fourth order of the pipe radius, and inversely proportional to the length of the pipe, .

, (15)

where  is the radius of the pile,  is the pressure difference,  is the pipe length, and  is liquid viscosity. The blood flow resistance  is similar to the charge flow in a conductor, which is not directly measurable.  is proportional to , and inversely proportional to  are known by using Ohm’s law,

, (16)

thus the blood flow resistance, , is inversely proportional to the fourth power of 

. (17)

Assume  and  are constants. In order to simulate the development of distal pulmonary arteries narrowing over time, the radius decreases as a function of time is

, (18)

where  is the initial radius and  is used for change rate. This study simulates the stenosis of the distal left, right pulmonary arteries ,  by this way. So, the relation between,  and  can be written as,

, (19a)

, (19b)

where  and  are initial values of  and  which are given in **Table 6**.

**Table 6** Initial values of pulmonary vascular resistance in the pulmonary circulation

|  |  |  |  |
| --- | --- | --- | --- |
| Parameter | Value | Parameter | Value |
|  | 0.02 mmHg·s·ml-1 |  | 0.02 mmHg·s·ml-1 |
|  | 0.02 mmHg·s·ml-1 |  | 0.03 mmHg·s·ml-1 |
|  | 0.045 mmHg·s·ml-1 |  | 0.045 mmHg·s·ml-1 |

The previous study [19] has shown that the resistance  and compliance  are inversely related. The product of  and  is called the , which has the constant time. Therefore,

. (20)

Lankhaar et al [20] proposed that patients with PH (chronic thromboembolic pulmonary hypertension, CTEPH and idiopathic pulmonary arterial hypertension, IPAH) and without PH (NONPH) had the same -time, and the  value for NONPH, CTEPH and IPAH groups are ,  and , respectively. Hence, the compliance of distal left and right pulmonary arteries  and  are

, (21a)

. (21b)

In this paper  is set as a typical value s. The blood pressure  in the distal left and right pulmonary arteries. Hence, the P-V relations of the distal right, left pulmonary arteries implied by **(19a)-(19b)**, **(21a)-(21b)** areobtained by integration as

, (22a)

. (22b)

2) Nonlinear P-V Relation for Proximal Pulmonary Arteries

With the development of PH, the pressures in proximal left, right pulmonary arteries gradually increase to abnormal high state. The P-V relation becomes nonlinear to adapt the abnormality. On the basis of works proposed by Salazar et al [21] and Hardy et al [22], within physiological limits, the blood vessel is considered as a container for blood, increasing pressure within vessel causes an increasing vessel stiffness.  tends zero as pressure  increases, and the volume  approaches the maximum volume . Therefore,

, (23)

where  is constant, and  is the maximum value of the vessel volume. The pressure implied by **(23)** can be obtained by integration,

, (24)

 is an arbitrary point on the P-V curve. If , therefore,

. (25)

where . The nonlinear P-V relation is applied to the proximal left and right pulmonary arteries,

, (26a)

, (26b)

where  and  are the maximum volume of proximal left, right pulmonary arteries,

 and  are constants, the values of these parameters are given in section 4. 1.

3) Compensation for Right Ventricular Contractibility

Right ventricular systolic function is a comprehensive reflection of right ventricular contractility, afterload and preload. With the progress of distal pulmonary arteries stenosis, PVR, afterload, mean pulmonary artery pressure (mPAP) could gradually increase. In this case, right ventricular hypertrophy can be reformed by increasing the thickness and contractility of one ventricular wall in order to adapt to the continuous increase of mPAP. The compensation of right ventricle in this paper is achieved by increasing right ventricular end-systolic elastance, .

The previous work [23] showed  has an upward trend with the aggravation of the disease, which increased rapidly in the early stage of PH, slowly in the middle and late stage. The maximum right ventricular elastance  is , and mPAP=1/3\*sPAP+2/3\*dPAP, where sPAP and dPAP are the systolic and diastolic blood pressure in the proximal pulmonary arteries. In this paper,  is modeled to increase following a piecewise function over time,

, , (27a)

, . (27b)

The piecewise function has a breakpoint as the mPAP reaches 50 mmHg, and  is the time as,  and  are parameters to control the change rate. The simulation results for the occurring and development of PH caused by DPAS are shown in section 4. 1.

3.2. PH Caused by Left Ventricular Diastolic Dysfunction (LVDD)

LVDD is one of most common cause to lead PH. The decrease of left ventricular myocardial compliance and filling disorder result in excessive left ventricular end-diastolic pressure, increased left atrial filling pressure. Because of this dysfunction, the left heart is unable to keep up with blood returning from the lungs. Pressure in the lungs raises. Pulmonary hypertension and congestion occur consequently [24]. The previous study showed that, the contractile function of the myocardium has no change and the ESPVR is the same as a normal heart in the LVDD, but the P-V relation during diastole shifts upwards as shown in **Fig. 5**, meanwhile the ejection fraction (EF) is normal or slightly decreased [25].



**Fig. 5** Schematic diagram of P-V relation for normal and left ventricular diastolic dysfunction. Dashed line indicates EDPVR in the left ventricular diastolic dysfunction.

In LVDD development, impaired left ventricular relaxation and increased passive stiffness is the principal functional derangement [26]. Because of increasing in left ventricular end-diastolic pressure, there is an increase in left atrial and pulmonary venous pressure. Hence, pulmonary artery pressure increases consequently. As shown in previous study, left atrial structure and function were altered by increased LA stiffening and greater LA pressure [27,28], meanwhile left atrial remodeling occurred in patients with LVDD and LA volume expressed the severity of diastolic dysfunction [29,30]. The P-V loop of LA is out of normal relation and shifts to a trend characterized by two loops. This relation differs greatly to that of a normal Left atrium, see in **Fig. 6**. In addition, the compliance of pulmonary arteries has also changed due to the accumulation of blood in the pulmonary circulation. In the early stage of this PH, there may be no significant change in PVR. However, as the disease progresses, it eventually damages the pulmonary blood vessels, resulting in an increase in PVR [31].



**Fig. 6** Schematic diagram of P-V relation of left atrium in PH caused by LVDD.

This PH is closely related to the right heart. The concept of integration of right ventricle and pulmonary circulation has been proposed by researchers previously [32]. In normal physiological conditions, the right ventricle is connected to the low pressure, low resistance, and high compliance pulmonary circulation, and the right ventricle is sensitive to increased pressure load. In the early stage of PH, the right ventricle will compensate for the increase of pulmonary artery pressure. With the development of the disease, in order to adapt to the continuous increase of afterload and maintain the ability of ejection, right ventricle compensatory hypertrophy until right heart failure occurs finally. Previous researchers have attempted to compensate for right ventricular [21, 33]. In this paper, the compensation of right ventricle is achieved by increasing right ventricular end -systolic elastance, .

1) Model of EDPVR for Left Ventricle

The P-V loop of left ventricle is the most direct manifestation of hemodynamic abnormalities. As shown in **Fig. 5**, the EDPVR shifts upwards in the LVDD [34], which is an exponential function controlled by . and . In order to simulate the pathogenesis of LVDD, it is necessary to increase the values of  and  with respect to time to rise the left ventricle diastolic pressure,

, (28)

, (29)

where  and  are coefficients,  and  are initial values of  and .

2) Model of P-V Relation for Pulmonary Vessels

In the development of LVDD, the authors assume that the compliance of the blood vessels in the pulmonary circulation varies within a reasonable range. The P-V relation of proximal and distal pulmonary arteries and pulmonary veins are given in **(25)**. The end-diastolic pressure is increased due to LVDD, causing obstruction of left atrial and pulmonary veins. Therefore, blood is deposited in the left atrium and pulmonary circulatory system, which in turn affects vessel elasticity in the pulmonary circulation. In the process of increasing blood accumulation, the parameters  for proximal right and left pulmonary arteries, distal right and left pulmonary arteries, right and left pulmonary veins increase over time and vary within a reasonable range, which are given as,

, (30a)

, (30b)

, (30c)

, (30d)

, (30e)

, (30f)

where ,  and  are coefficients to control change rate, , , ,   and  are constants. The P-V relations for pulmonary vessels become,

, (31a)

, (31b)

, (31c)

, (31d)

, (31e)

, (31f)

where ,  , ,  and  are the maximum volumes of corresponding vessels. The values of these parameters are given in section 4. 2.

3) Model of Pulmonary Vascular Resistances

For PH caused by LVDD, with the development of the disease, eventually irreversible damage to the pulmonary vessels results in increased PVR. However PVR increases little in the early stage of PH. Therefore, in this study the authors consider the resistance of blood vessels in the pulmonary circulation increase as follows when ,

, (32a)

, (32b)

, (32c)

, (32d)

, (32e)

, (32f)

where  is the time as , and , ,  and  are initial values of , ,  and , which are given in **Table 6**,  is a scale coefficient.

4) Model for Right Ventricular Compensation

With the development of this type of PH, the right ventricle in the LVDD model overcomes the increase of afterload by increasing myocardial contractility  which is given as follows,

, (33)

where  is an parameter to control change rate,  is initial value of .

5) Models for P-V Loop and Activation Function of Left Atrium

In the cardiovascular system, the left atrium acts as an elastic reservoir, passive conduit and active booster to regulate left ventricular filling. Left atrium dysfunction and remodeling are common in patients with heart failure (HF). Increasing evidence showed that left atrial dysfunction is a positive cause of symptoms and disease progression [35]. In order to overcome the increase of left atrial pressure and volume caused by LVDD, the previous studies on left atrial dysfunction disclosed that the P-V loop of the left atrium has changed [30, 31], as shown in **Fig. 7**. The systolic and diastolic blood pressures of LA are increased to adapt to the rise of left ventricular end-diastolic pressure and pulmonary vein pressure. Therefore, the parameters of ,  and  in the left atrial model increase over time,

, (34)

, (35)

, (36)

where ,  and  are parameters to control change rate, ,  and  are initial values of ,  and .



**Fig. 7** Relation between blood pressure and volume for left atrium. (a) For normal hemodynamics, (b) For abnormal hemodynamics due to LVDD.

For a normal heart, the pressure and volume of left atrium in one cardiac cycle are shown in **Fig. 7(a)**. The activation function of the left atrium can be well modeled by one Gaussian function, see in **Fig. 8**. During the process from normal to this PH, left ventricular filling pressure continues to increase. The left atrium needs to increase continuously systolic blood pressure to push blood to the left ventricle. However, as the disease progresses, persistent long-term left ventricular end-diastolic pressure increases, this will cause block blood flow back to the left ventricle. Blood silts in the left atrium, leading to an increase in left atrial volume and diastolic blood pressure. Increased pressure retrogrades conduction to the pulmonary veins. Pressures in pulmonary veins and pulmonary artery increase in turn. The pathophysiology of PH due to left ventricular diastolic dysfunction is shown in **Fig. 9**. The varying pressure and volume of left atrium in one cardiac cycle are shown in **Fig. 7(b)**. Compared with the normal hemodynamic state, there are two peaks in the left atrial pressure, and the systolic and diastolic blood pressures are increased. Therefore, the authors propose a new left atrial activation function, see in **Fig. 8**, and the modified activation function is expressed by the sum of nine Gaussian functions,

. (37)

As the disease progresses, the first peak amplitude has no change, but it becomes wide. The left atrial pressure increases during diastole, thus the authors assume the amplitude of Gaussian curves could vary in time with the following rules,

, (38a)

, (38b)

, (38c)

, (38d)

, (38e)

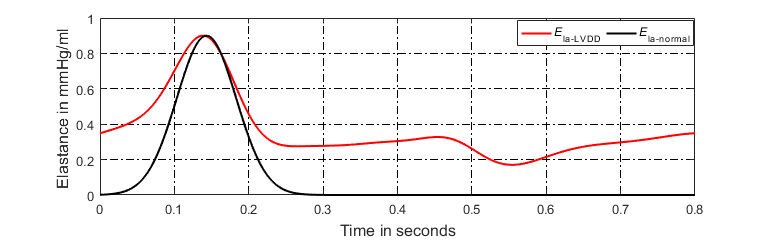
, (38f)

, (38g)

, (38h)

, (38i)

where , , , , , , ,  and  are coefficients. The simulation results for the occurring and development of PH caused by LVDD are shown in section 4. 2.



**Fig. 8** Regulation of left atrial activation function to adapt PH due to LVDD.



**Fig. 9** Pathophysiology of PH caused by LVDD.

3.3. PH Caused by Ventricular Septal Defect (VSD)

Congenital heart disease is one of the major causes of PH, and patients with VSD is the most common congenital cardiac disorder, characterized by an abnormal opening in the ventricular septum, which allows blood to shunt between the left and right ventricles [11,36,37], see in **Fig. 10**. Because the blood pressure of the left ventricle is much larger than the right ventricle, most of them originally are left-to-right shunting. The left-to-right shunting of congenital ventricular septal defect leads to an increase in pulmonary blood flow and pulmonary artery pressure, which in turn affects pulmonary vascular endothelial function, resulting in increased PVR, making to left-to-right shunting originally that develops bidirectional or right-to-left shunting, or appears cyanosis [38], that is, Eisenmenger syndrome (ES). ES is the terminal stage of PH in congenital heart disease, and about 50% of patients with VSD will eventually develop into ES.

PH caused by VSD also affects the function of right ventricle. The right ventricle needs to overcome the continuous increase of pulmonary artery pressure. As time goes on, the right ventricle will eventually decompensate, leading to right heart failure. Previous studies showed that in the early stage of PH caused by VSD, PVR can be normal, only the pulmonary artery pressure increase. However, with the development of the disease, PVR will still increase, causing pulmonary vascular lesions to an irreversible stage [39,40].



**Fig. 10** Illustration of blood flow for a normal heart and a heart with VSD. (a) Blood flow in normal heart; (b) Blood flow in heart with VSD.

1) Model of Shunting Resistance

VSD is characterized by an abnormal opening in the septum between the ventricles. The authors model the open shunting as a branch using a resistor  in the analog circuit, see **Fig. 11**. As the degree of VSD increases, the defect area  also increases gradually, meanwhile  decreases. According to Poiseuilli’s law and **(16)**, the blood flow resistance, , is inverse proportional to four-order of radius

. (39)

 is radius of ventricular septal defect. Assuming that the defect area is a regular circle, thus . Thus the blood flow resistance  is inversely proportional to the square of the defect area ,

. (40)

In a normal heart, there is no blood flow through the septum.  is equivalent to an infinite resistance. In modelling VSD,  continues to decrease as the defect area increases over time,

. (41)

Where  is the initial value of , and  is a coefficient. Clinical investigation released that the maximum defect area is possibly greater than 2 square centimeters.



**Fig. 11** Analog circuit model for PH caused by VSD.

2) Model of Pulmonary Vascular Resistances

Long-term left-to-right shunting VSD leads to increased blood flow in the pulmonary circulation, and abnormal pulmonary vascular endothelial function, resulting in increased PVR. In the early stage of this PH, PVR is normal. With the development of the disease, the resistances of vessels are increased over time when . Increasing trend of resistances are applied to proximal right and left pulmonary arteries, distal right and left pulmonary arteries, right and left pulmonary veins,

, (42a)

, (42b)

, (42c)

, (42d)

, (42e)

, (42f)

where  is the time when , ,  and  are coefficients.

3）Model of Activation Function for Left Atrium

In the development of VSD, a part of blood in the left ventricle flows into the right ventricle, directly involved in pulmonary circulation, leading to a large amount of blood entering the left atrium, resulting in abnormal enlargement of left atrial volume and increased pressure. In a normal heart, the left atrial activation function does not adapt to abnormal changes in pressure and volume of left atrium. Therefore, the authors propose a model of left atrial activation function to adapt the abnormal hemodynomics, see in **Fig. 12**, which is expressed by the sum of three Gaussian curves,

. (43)

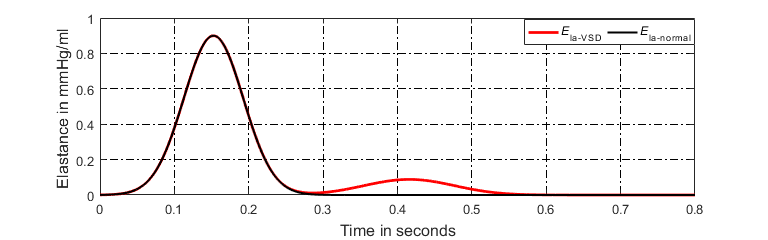
As the disease progresses, both the systolic and diastolic blood pressures of left atrium increase. The proposed left atrial activation function has two peaks. The first peak is determined by the first Gaussian curve controlled by three constants ,  and . So, the first peak doesn’t vary in the disease development, as seen in **Fig. 12**. However, the amplitude of the second peak, reflected by the second and the third Gaussian curve, increases over time,

, (44a)

, (44b)

, (44c)

where ,  and  are coefficients.



**Fig. 12** Regulation of left atrial activation function to adapt PH caused by VSD.

The P-V relations of proximal, distal pulmonary arteries and pulmonary veins are given in **(31a)**-**(31f)**, and the compensation of left atrium and right ventricle are given by **(33)-(34)**. The simulation results for the occurring and development of PH caused by VSD are shown in section 4. 3.

3.4. PH Caused by Mitral Stenosis (MS)

The mitral valve ensures the unidirectional flow of blood from left atrium to left ventricle. Pathological changes such as ischemic necrosis and trauma can cause abnormalities in the structure and function of the mitral valve, leading to MS. Under normal conditions, blood flow from left atrium to left ventricle does not cause any obstacles. When the mitral stenosis occurs, the hemodynamics will obviously change [41,42]. The blood flow from left atrium to left ventricle encounters an obstacle, resulting in an increase in left atrial pressure, which in turn causes an increase in pressure in the pulmonary veins and pulmonary arteries, leading to PH. In addition, the right ventricle is in a long-term increase in post-load pressure, eventually resulting in right heart failure [43].

Due to limited blood flow from left atrium to left ventricle, the left ventricular end-diastolic volume and pressure are reduced, and left ventricular end-systolic volume and stroke volume are also decreased. The P-V relation of left ventricle in these conditions is shown in **Fig. 13**.



**Fig. 13** P-V relation of left ventricle caused by MS.

1) Model of Mitral Resistance

In the analog circuit platform, the mitral valve simulated by a resistor  and a diode . From a physiological point of view, the blood flow resistance of mitral valve increases gradually from opening to closing. Increasing degree of MS also contributes to the continuous increasing in . The increasing resistance  over time is modeled as,

, (45)

where  is initial value of , =0.015 mmHg·s·ml-1. And  is a parameter to control change rate.

2) Model of Pulmonary Vascular Resistances

In the early stage of PH caused by MS, PVR is normal. When , PVR begins to increase. The increasing resistances are involved in pulmonary vessels, such as proximal right and left pulmonary arteries, distal right and left pulmonary arteries, right and left pulmonary veins,

, (46a)

, (46b)

, (46c)

, (46d)

, (46e)

. (46f)

Where  is a coefficient to adjust change rate.

3) Left Atrial Compensation for Contractibility

MS is one of the left ventricular valve diseases. Pathological mechanisms may lead to elevated pressure in the left atrium. Therefore, the left atrium increase contractibility to overcome elevated pressure through its own regulation,

, (47)

, (48)

. (49)

Where ,  and  are coefficients, ,  and  are initial values of ,  and .

4）Model of Activation Function for Left Atrium

The pathophysiology of this PH is shown in **Fig. 14**. In the development of MS, the resistance of blood flowing from the left atrium to the left ventricle gradually increases. Blood stasis in the left atrium results in an increased volume and pressure in the left atrium. The increased pressure reverses to the pulmonary veins, leading to an increase in pulmonary venous pressure, which in turn leads to an increase in pulmonary artery pressure. According to previous studies, P-V loop in left atrium changed in the progress of PH [44]. Therefore, the authors propose modified activation function for the left atrium, see in **Fig. 15**, and it is expressed by the sum of Gaussian functions and a linear function,

, (50)

where  is a linear coefficient. As the disease progresses, the magnitude of the first peak of the activation function has no change, but it becomes wide over time. The magnitude of the second peak gradually increases over time. The parameters to control the activation function could be written as

, (51a)

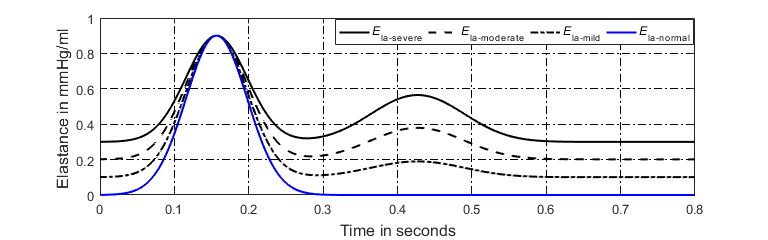
, (51b)

, (51c)

where  and  are coefficients.  is a constant to control the magnitude of the first peak.



**Fig. 14** Pathophysiology of PH due to MS.



**Fig. 15** Regulation of left atrial activation function to adapt PH caused by MS.

The P-V relations of proximal, distal pulmonary arteries and pulmonary veins are given in **(31a)**-**(31f)**, and right ventricular compensation is given by **(33)**. The simulation results for the occurring and development of PH caused by MS are shown in section 4. 4.

4. Computer Simulation Results

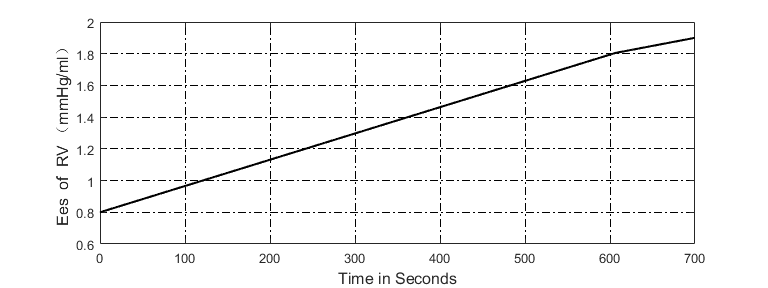
In this study, the simulation time is set as 700s, and the cardiac cycle is set as 0.7845s (heart rate is about 76.5 beat per minute). The time step size in numerical solution is 0.0005s. The total blood volume in the circulation system is set as 4711 ml. Sympathetic frequencies (,,) and vagal frequency  are all set as 0.5. The initial values for blood volume of each capacitor, current of each inductor in the platform are all given in Appendix A, as well as the values of capacitances, inductances and resistances. The authors assume that the time-varying parameters is constant within a cardiac cycle and has an increment or reduction between adjacent cycles.

4. 1 Simulation Results of PH Caused by Distal Pulmonary Artery Stenosis

The P-V relations of proximal left and right pulmonary arteries are given by **(26a)- (26b)**, and the values of , ,  and  are shown in **Table 7**. The equation **(27)** gives that  increases linearly over time. It is nature that the PH disease develops in a continuous way. Hence, it is reasonable to assume that the time-varying  keeps constant within a cardiac cycle and has an increment between cycles. The change process in  over simulation time is shown in **Fig. 16**. . The coefficients  and  are given in **Table 7**.

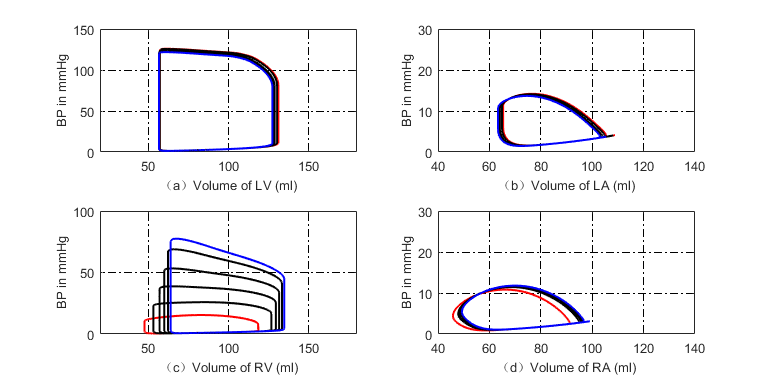
**Table 7** Parameters in the simulation of DPAS

|  |  |  |  |
| --- | --- | --- | --- |
| Parameter | Value | Parameter | Value |
|  | 20 mmHg |  | 100 ml |
|  | 20 mmHg |  | 100 ml |
|  | 0.0013 |  | 0.0008 |
|  | 1 |  | 0.043743 |



**Fig. 16** Time-varying  used in this simulation.

In the simulation of DPAS, the pathological mechanism is to increase the resistances of distal pulmonary arteries over time. The P-V relations of proximal, distal pulmonary arteries are changed, and the right ventricle compensation is added to simulate the development from health to PH. The obtained P-V relations of the four heart chambers and the output of blood pressures of vessels in the pulmonary circulation are shown in the in **Fig. 17(a)-(d)** and **Fig. 18**. Compared these with the normal hemodynamic conditions, it can be found that the systolic blood pressure of right ventricle continues to increase to 78 mmHg. Thus, the increased pulmonary artery pressure is high enough to push the flow of blood in the pulmonary circulation forward. As shown in **Fig. 18**, an increase in the resistance of the distal pulmonary artery directly leads to an increase in the blood pressure of distal pulmonary artery. The blood pressure rising in  can overcome the increase in  to make the flow of blood in the artery to go forward.



**Fig. 17** P-V loops of four chambers for PH caused by DPAS. The red loops are normal. The black ones are for developing PH and the blue ones show the late PH stage. (a) P-V loops of left ventricle; (b) P-V loops of left atrium; (c) P-V loops of right ventricle; (d) P-V loops of right atrium.



**Fig. 18** Development of the key pulmonary blood pressures for PH caused by DPAS.

4. 2 Simulation Results of PH Caused by Left Ventricular Diastolic Dysfunction

The P-V relations of proximal, distal pulmonary arteries and pulmonary veins are given in **(31a)-(31f)**. The values of , , , , , , , , ,,  and  are shown in **Table 8**. The values of adjustable parameters in the PH model due to LVDD are given in **Table 9**. The modified activation function of left atrium consists of nine Gaussian functions by **(37)-(38i)**, and initial values of parameters in the left atrial activation function are given in **Table 10** and **Table 11**.

**Table 8** Values of parameters  and  in the model of LVDD

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Parameter | Value | Parameter | Value | Parameter | Value |
|  | 20 mmHg |  | 20 mmHg |  | 15 mmHg |
|  | 100 ml |  | 100 ml |  | 150 ml |
|  | 15 mmHg |  | 5 mmHg |  | 5 mmHg |
|  | 150 ml |  | 180 ml |  | 180 ml |

**Table 9** Values of adjustable parameters inthe model of LVDD

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| Parameter | Value | Parameter | Value | Parameter | Value | Parameter | Value |
|  | 0.004 |  | 0.00001 |  | 0.035 |  | 0.035 |
|  | 0.035 |  | 0.00022 |  | 0.0012 |  | 0.0004 |
|  | 0.0008 |  | 0.000002333 |  |  |  |  |

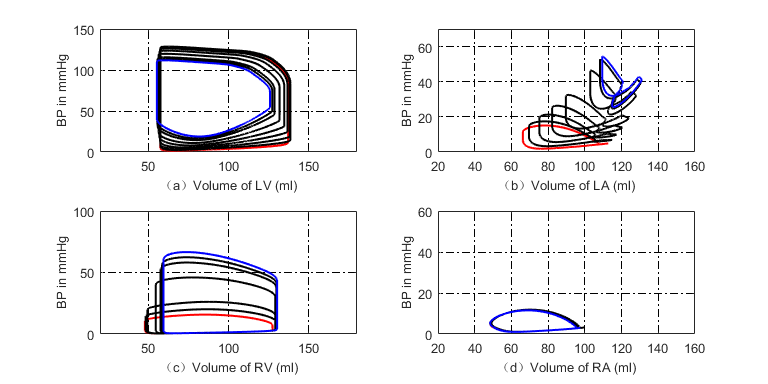
**Table 10** Values of parameters inthe left atrial activation function

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Parameter | Value | Parameter | Value | Parameter | Value |
|  | 0.0004488 |  | 0.000168 |  | 0.000375 |
|  | 0.0002 |  | 0.0002 |  | 0.000168 |
|  | 0.000291 |  | 0.000265 |  | 0.0004887 |

**Table 11** Initial values of parameters in the left atrial activation function

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Parameters |  |  |  |  |  |  |  |  |  |
|  | 0 | 0 | 0.9 | 0 | 0 | 0 | 0 | 0 | 0 |
|  | 0.1 | 0.05 | 0.038 | 0.07 | 0.1 | 0.045 | 0.04 | 0.07 | 0.1 |
|  | 0.005 | 0.08 | 0.136 | 0.25  25 | 0.32 | 0.375 | 0.45 | 0.6 | 0.78 |

In the model of LVDD, the left ventricular end-diastolic pressure is increased by linearly increasing the parameters of  and . The P-V relations of vessels in the pulmonary circulation are changed, the PVR is increased too. The P-V relation and activation function of the left atrium are revised to compensate for the increased left atrial pressure and volume. The simulation results are shown in **Fig. 19(a)-(d) and Fig. 20**. Compared these with the normal hemodynamic conditions, the left ventricular diastolic dysfunction leads to an increased left ventricular end-diastolic pressure. The left atrium needs to increase the pressure to ensure the blood returns to the left ventricle. Long-term blood return is blocked, causing blood to accumulate in the left atrium and its volume increase consequently. The right ventricular systolic pressure would increase to overcome the increased pulmonary artery pressure. As shown in **Fig. 20**, the blood pressures in pulmonary vessels are also increased. Compared these with the simulation results of DPAS model, the pulmonary vein pressure is higher than that in PH caused by DPAS. The reason is in the mechanism to PH. For LVDD case, the pressure in the left atrium and the pulmonary veins rises, which in turn leads to an increase in the distal pulmonary artery blood pressure.



**Fig. 19** P-V loops of four chambers for PH caused by LVDD. The red loop is for normal, the black ones are for developing PH and the blue is for this PH at late stage. (a) P-V loops of left ventricle; (b) P-V loops of left atrium; (c) P-V loops of right ventricle; (d) P-V loops of right atrium.



**Fig. 20** Development of key pulmonary blood pressures for PH due to LVDD.

4. 3 Simulation Results of PH Caused by Ventricular Septal Defect

In the simulation of PH caused by VSD, the P-V relations of proximal, distal pulmonary arteries and pulmonary veins are given in **(31a)-(31f)**. The values of , , , , , , , , , ,  and  are shown in **Table 8**. The adjustable parameters in the model of VSD are given in **Table 12**. The modified activation function of left atrium consists of three Gaussian functions by **(43)-(44c)**, and its initial values of parameters in the activation function are given in **Table 13**.

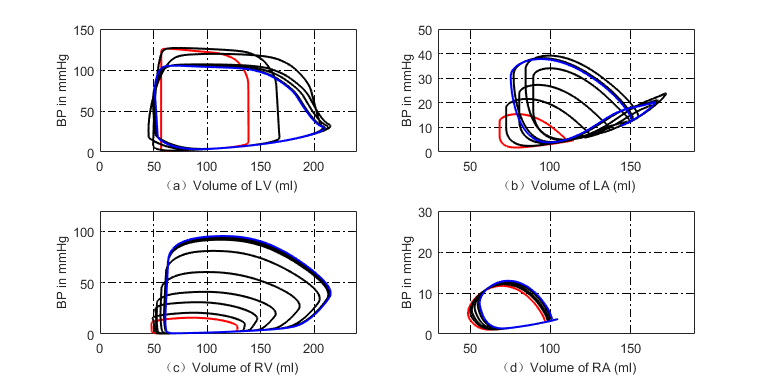
**Table 12** Values of adjustable parameters inthe model of VSD

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| Parameter | Value | Parameter | Value | Parameter | Value | Parameter | Value |
|  | 0.00015 |  | 0.0002 |  | 0.00025 |  | 0.1 |
|  | 0.00448 |  | 0.000056 |  | 0.000056 |  |  |

**Table 13** Initial value of parameters in the activation function of left atrium

|  |  |  |  |
| --- | --- | --- | --- |
| Parameters |  |  |  |
|  | 0.9 | 0 | 0 |
|  | 0.038 | 0.05 | 0.05 |
|  | 0.145 | 0.37 | 0.42 |

A branch consisting of a resistor  is used to model blood flow caused by VSD. The decreasing  over cardiac beat number simulates the development of VSD. Both right ventricle and left atrium increase contractibility to adapt the abnormal hemodynamics. Comparing these with those in normal hemodynamic conditions, both the volume and SV of the left ventricle increase greatly, meanwhile the systolic pressure decreases. However, the SV of right ventricle increases. Thus, the SVs of left, right ventricles are out of balance because of the VSD branch flow. The left atrium regulates its pumping function to maintain the circulation system works. **Fig. 21** gives the hemodynamics of the four heart chambers of PH caused by VSD. The corresponding blood pressures of various pulmonary vessels in the progress of PH are shown in **Fig. 22(a)**. As seen in **Fig. 22(b)**, the blood flow between the left and right ventricle,  increases over time. Positive value of  means flow from left to right, and negative value means the contrary. It is seen from **Fig. 22(b)** that the blood flow is unidirectional from left to right at the beginning of VSD. As time goes on, the VSD becomes serious as seen at simulation time greater than 500s. There is small negative blood flow from right ventricle to left ventricle in very short time interval. This PH caused by VSD develops finally into obstructive PH. The flow could be bidirectional and/or right-to-left. However, the further development of this PH is not considered in this study.



**Fig. 21** P-V loops of the four chambers for PH development caused by VSD. The red loop is for normal, the black ones are for developing PH and the blue one is for the late PH at serious condition. (a) P-V loops for left ventricle; (b) P-V loops for left atrium; (c) P-V loops for right ventricle; (d) P-V loops for right atrium.



**Fig. 22** Blood pressures and blood flows in PH development caused by VSD. (a) Key blood pressures in the pulmonary circulation; (b) Corresponding blood flows.

4. 4 Simulation Results of PH Caused by Mitral Stenosis

In this simulation, the P-V relation of proximal, distal pulmonary arteries and pulmonary veins are given in **(31a)-(31f).** The values of , , , , , , , , , ,  and  are shown in **Table 8**. The values of adjustable parameters in the model of MS are given in **Table 14**. The modified activation function of left atrium consists of three Gaussian functions by **(50)-(51c)**, and initial values of parameters in the left atrial activation function are given in **Table 14** and **Table 15**.

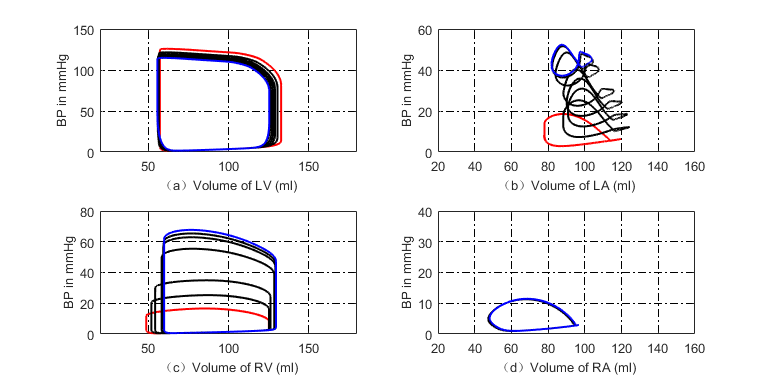
**Table 14** Values of the parameters inthe model of MS

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Parameter | Value | Parameter | Value | Parameter | Value |
|  | 0.0003 |  | 0.00008 |  | 0.0003 |
|  | 0.001 |  | 0.0000056 |  | 0.000336 |
|  | 0.000168 |  | 0.000168 |  |  |

**Table 15** Initial value of parameters in the activation function of left atrium

|  |  |  |  |
| --- | --- | --- | --- |
| Parameters |  |  |  |
|  | 0.9 | 0 | 0 |
|  | 0.038 | 0.05 | 0.05 |
|  | 0.145 | 0.37 | 0.42 |

The increasing resistance  simulates the pathological mechanism of MS. The P-V relations of vessels in the pulmonary circulation, increasing of PVR, contractibility of the right ventricle, left atrium are all together adapt to abnormal hemodynamic flow caused by MS. The simulation results are shown in **Fig. 23(a)-(d)**. Compared these with the normal hemodynamics, the left ventricular P-V loop remains almost no change, and SV decreases slightly. The left atrial systolic and diastolic pressures increase, and the P-V loop of left atrium has typical two loops. The pressures of key pulmonary vessels in this PH development are shown in **Fig. 24**.



**Fig. 23** P-V loop of the four chambers during PH development caused by MS. The red loops are for the beginning of PH, the black ones are for developing PH and the blue ones present the late stage of this PH. (a) P-V loops for left ventricle; (b) P-V loops for left atrium; (c) P-V loops for right ventricle; (d) P-V loops for right atrium.

**Fig. 24** Development of key pulmonary blood pressures for PH due to MS.

5. Discussions

PVR is an important indicator for pulmonary hemodynamics. The irreversible injury, the intima and medial thickening of the vessels leads to thickening of the blood vessel wall and narrowing of the lumen. PVR increases, which may results in PH ultimately. It can be seen from the simulation of DPAS that the pulmonary vascular stenosis leads to increasing resistance at the distal pulmonary arteries and hence results in PH. In the PHs caused by LVDD, VSD and MS, PVR may be normal in the early stage of PH, but become obviously increase with elevating pulmonary artery pressure.

From a physiological point of view, the morphology and structure of right and left ventricle are to adapt their functional requirements for pumping blood. The right ventricle could be considered as a sidewall that attaches additional muscles to the left ventricular wall. The wall of the right ventricle is much thinner than that of the left ventricle. Therefore, it cannot maintain normal contractile function when the mPAP increases. However, it can be well adapt to the increase of blood volume due to right ventricular reflux. When the right ventricular afterload increases rapidly, it can cause a significant expansion of the right ventricle. However, if the mPAP increase gradually over a long time, the right ventricle reform to ventricular hypertrophy by increasing the thickness of one side of the wall to meet the needed contractile force. As a result, the right ventricle can accommodate a sustained and significant increase in mPAP. A question is that the mPAP rises usually faster than the right ventricle adaptability does, the contractility does not meet the needed force, this leads obstacles in right ventricular motor function. In the simulation of the four typical PHs, it is found that the P-V loop of right ventricle gradually changes from the normal to a P-V loop with very high systolic pressure, and the right ventricle volume increases with the disease development.

6. Conclusions

A platform consisting of analog circuit elements for simulating human circulation system is setup in this study. The developments of four typical PHs caused by different pathogenesis are separately simulated in the platform. On PH caused by distal pulmonary artery stenosis, the thick, stiff distal arteries are modeled by increasing resistances. On PH due to left ventricular diastolic dysfunction, PH develops under the proposed model of the decrease of left ventricular myocardial compliance, filling disorder. On PH caused by ventricular septal defect, a branch is proposed to simulate the branch flow between the left and right ventricles. On PH caused by mitral stenosis, an increasing resistor is used to simulate the degree of stenosis. For each PH development, the regulation rules for heart chambers, arteries and veins are proposed to meet the hemodynamic abnormalities. The simulation results are close to clinical investigations. These works could be powerful to understand the causes that lead to PH and regulation mechanism in PH development.

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Declaration of Interests

The authors declare no conflict of interests.

Supplementary Materials

The matlab codes for these simulations can be accessed at :

https://github.com/tanghongdlut/An-Analog-Circuit-Platform-for-Simulating-Typical-Pulmonary-Hypertensions-from-Point-of-Hemodynamics. Those who are interested reproducing the results can downloaded the codes freely.

Reference

1. Prins KW, Thenappan T: **World health organization group I pulmonary hypertension epidemiology and pathophysiology.** *Cardiology Clinics* 2016, 34(3): 363-374.
2. Barnett CF, Alvarez P, Park MH: **Pulmonary arterial hypertension diagnosis and treatment.** *Cardiology Clinics* 2016, 34(3): 375-389.
3. D'Alto M, Dimopoulos K, Coghlan JG, et al: **Right heart catheterization for the diagnosis of pulmonary hypertension controversies and practical issues.** *Heart Failure Clinics* 2018, 14(3): 467-477.
4. Xiao DW, Xu BL: **Hemodynamic recovery from heart failure with left ventricular assist device: a lumped-parameter simulation**. *Beijing Biomedical Engineering* 2016, 35(4): 367-380.
5. Zeng Y, Gu KY, Gao M, et al: **Simulation of cardiovascular system at heart failure stage.** *Journal of Beijing University of Technology* 2013, 39(12): 1911-1915.
6. Liu LL, Li L, Qian KX: **Modeling and simulation of a fifth-order lumped parameter cardiovascular system.** *Chinese Journal of Biomedical Engineering* 2012, 31(1): 13-19.
7. Korurek M, Yildiz M, Yuksel A: **Simulation of normal cardiovascular system and severe aortic valve stenosis using equivalent electronic model.** *The Anatolian Journal of Cardiology* 2010, 10(6): 471-478.
8. Tsalikakis DG, Fotiadis DI, Sideris D: **Simulation of cardiovascular diseases using electronic circuits.** *Computers in Cardiology* 2003, 30: 445-448.
9. Dolenšek J, Podnar T, Runovc F, et al: **Analog simulation of aortic and of mitral regurgitation.** *Computers in Biology and Medicine* 2009, 39(5): 474-481.
10. Luo C, Ramachandran D, Ware DL, et al: **Modeling left ventricular diastolic dysfunction: classification and key in dicators.** *Theoretical Biology and Medical Modelling* 2011, 8:14.
11. Korurek M, Yildiz M, Yuksel A, Sahin A: **Simulation of Eisenmenger syndrome with ventricular septal defect using equivalent electronic system.** *Cardiology in the Young* 2012, 22(3): 301-306.
12. Olansen JB, Clark JW, Khoury D, et al: **A closed-loop model of the canine cardiovascular system that includes ventricular interaction.** *Computers and Biomedical Research* 2000, 33(4): 260-295.
13. Chung DC, Niranjan SC, Clark JW, et al: **A dynamic model of ventricular interaction and pericardial influence**. *American Journal of Physiology Herat and Circulatory Physiology* 1997, 272(6): H2942-H2962.
14. Lu K, Clark JW, Ghorbel FH, et al: **A human cardiopulmonary system model applied to the analysis of the Valsalva maneuver.** *American Journal of Physiology Heart and Circulatory Physiology* 2001, 281(6): H2661-H2679.
15. Hong T, Jiao G, Yongwan P: **Heart valve closure timing intervals in response to left ventricular blood pressure.** *Journal of Biomedical Science and Engineering* 2013, 6(1): 65-75.
16. Sunagawa K, Kawada T, Nakahara T: **Dynamic nonlinear vago-sympathetic interaction in regulating heart rate.** *Heart and Vessels* 1998, 13(4): 157-174.
17. Perros F, Humbert M: **Physiopathology of** **pulmonary arterial hypertension - cellular and** **molecular aspects.** *Presse Medicale* 2005, 34(3): 232-242.
18. Yildiz P: **Molecular mechanisms of pulmonary hypertension.** *Clnica Chimica Acta* 2009, 403: 9-16.
19. Lankhaar JW, Westerhof N, Faes TJ C, et al: **Pulmonary vascular resistance and compliance stay inversely related during treatment of pulmonary hypertension.** *European Heart Journal* 2008, 29(13), 1688–1695.
20. Lankhaar JW, Westerhof N, Faes TJC: **Quantification of right ventricular afterload in patients with and without pulmonary hypertension**. *American Journal of Physiology Heart and Circulatory Physiology* 2006, 291(4): H1731-H1737.
21. Salazar E, Knowles JH: **Analysis of pressure-volume characteristics of lungs.** *Journal of Applied Physiology* 1964, 19(1): 97-104.
22. Hardy HH, Collins RE: **On the pressure-volume relation in circulatory elements.** *Medical & Biological Engineering & Computing* 1982, 20(5): 565-570.
23. Shang XK, Xiao SN, Dong NG,et al: **Assessing right ventricular function in pulmonary hypertension patients and the correlation with the New York Heart Association (NYHA) classification.** *Oncotarget* 2017, 8(52): 90421-90429.
24. Komamura K: **Similarities and differences between the pathogenesis and pathophysiology of diastolic and systolic heart failure.** *Cardiology Research and Practice* 2013, 1-6.
25. Chatterjee, K; Massie B: **Systolic and diastolic heart failure: differences and similarities.** *Journal of Cardiac Failure* 2007, 13(7): 569-576.
26. Aurigemma GP, Zile MR, Gasch WH: **Contractile behavior of the left ventricle in diastolic heart failure-with emphasis on regional systolic function.** *Circulation* 2006, 113(2): 296-304.
27. Kurt M, Wang JW, Torre-Amione G, et al: **Left atrial function in diastolic heart failure.** *Circulation Cardiovascular Imaging* 2009, 2(1): 10-15.
28. Teo SG, Yang H, Chai P, Yeo TC: I**mpact of left ventricular diastolic dysfunction on left atrial volume and function: a volumetric analysis.** *European Journal of Echocardiography* 2010, 11(1): 38-43.
29. Rossi A, Gheorghiade M, Triposkiadis F, et al: **Left atrium in heart failure with preserved ejection fraction structure, function, and significance.** *Circulation Heart Failure* 2014, 7(6): 1042-1049.
30. Melenovsky, V; Hwang, SJ; Redfield, MM, et al: **Left atrial remodeling and function in advanced heart failure with preserved or reduced ejection fraction.** *Circulation Heart Failure* 2015, 8(2): 295-303.
31. Raeisi-Giglou P, Lam L, Tamarappoo BK, et al: **Evaluation of left ventricular diastolic function profile in patients with pulmonary hypertension due to heart failure with preserved ejection fraction.** *Clinical Cardiology* 2016, 40(6): 356–363.
32. Vonk Noordegraaf A, Westerhof BE, Westerhof, N: **The relation between the right ventricle and its load in pulmonary hypertension.** *Journal of the American College of Cardiology* 2017, 69(2): 236–243.
33. Acosta S, Puelz C, Riviere B, et al: **Cardiovascular mechanics in the early stages of pulmonary hypertension: a computational study.** *Biomechanics and modeling in Mechanobiology* 2017, 16(6): 2093-2112.
34. Zile MR, Baicu CF, Gaasch WH: **Diastolic heart failure-abnormalities in active relaxation and passive stiffness of the left ventricle.** *New England Journal of Medicine* 2004, 350 (19): 1953- 1959.
35. Donal E, Raud-Raynier P, Place CD, Gervais R, et al: **Resting echocardiographic assessments of left atrial function and filling pressure interest in the understanding of exercise capacity in patients with chronic congestive heart failure.** *Journal of the American Society of Echocardiography* 2008; 21(6): 703–710.
36. Perloff, JK, Rosove MH, Child JS, Wright GB: **Adults with cyanotic congenital heart disease: hematologic management.** *Annals of Internal Medicine* 1988, 109(5), 406-413.
37. Ammash NM, Warnes CA: **Ventricular septal defects in adults.** *Annals of Internal Medicine* 2001, 135: 812-824.
38. Granton JT, Rabinovitch M: **Pulmonary arterial hypertension in congenital heart disease.** *Cardiology Clinics* 2002, 20(3): 441–457.
39. Daliento L, Somerville J, Presbitero P, et al: **Eisenmenger syndrome factors relating to deterioration and death.** *European Heart Journal* 1998, 19(12): 1845–1855.
40. Vongpatanasin W, Brickner ME, Hillis LD, Lange RA: **The eisenmenger syndrome in adults.** *Annals of Internal Medicine* 1998, 128: 745-755.
41. Yan T, Zhang G, Li B, et al: **Pulmonary artery haemodynamic properties in patients with pulmonary hypertension secondary to rheumatic mitral stenosis.** *Heart,* *Lung and Circulation* 2012, 21(12): 782–786.
42. Erturk M，Aksu HU, Celik O, et al: **Evaluation of the effect of mitral stenosis severity on the left ventricular systolic function using isovolumic myocardial acceleration.** *Cardiology Journal* 2014, 21(4): 442–448.
43. Wroblewski E, James F, Spann JF, Bove AA: **Right ventricular performance in mitral stenosis.** *The American Journal of Cardiology* 1981, 47(1): 51–55.
44. Stefanadis C, Dernellis J, Stratos C, et al: **Effects of balloon mitral valvuloplasty on left atrial function in mitral stenosis as assessed by pressure–area relation.** *Journal of the American College of Cardiology* 1998, 32(1): 159–168.

APPENDIX A: PARAMETERS AND INITIAL CONDITIONS OF THE NORMAL HUMAN CIRCULATION SYSTEM CIRCUIT

The values of parameters for the normal human circulation system circuit model are given in **Table A1-A3.** The initial conditions of the blood volumes in the four chambers, vessels and the blood flows in the inductors are shown in T**able A4**.

**Table A1**. Resistors and diodes of the normal human circulation system circuit model

|  |  |  |
| --- | --- | --- |
| Parameter | Description | Value |
| ***Flow Resistances*** | | |
|  | Mitral valve | 0.015 mmHg·s·ml-1 |
|  | Aortic valve | 0.02 mmHg·s·ml-1 |
|  | Head and arm artery | 13 mmHg·s·ml-1 |
|  | Left neck artery | 16 mmHg·s·ml-1 |
|  | Left clavicular artery | 16 mmHg·s·ml-1 |
|  | Proximal aorta | 1.2 mmHg·s·ml-1 |
| and | Right (Left) upper limb artery | 0.4 mmHg·s·ml-1 |
| and | Right (Left) internal carotid artery | 0.4 mmHg·s·ml-1 |
|  | Proximal systemic artery | See **Eq.11** |
|  | Right subclavian vein | 0.17 mmHg·s·ml-1 |
| and | Right (Left) internal jugular vein | 0.2 mmHg·s·ml-1 |
|  | Left subclavian vein | 0.2 mmHg·s·ml-1 |
|  | Systemic veins | 0.2 mmHg·s·ml-1 |
|  | Vena cava | See **Eq.9** |
|  | Tricuspid valve | 0.02 mmHg·s·ml-1 |
|  | Pulmonary valve | 0.01 mmHg·s·ml-1 |
| and | Right (Left) proximal pulmonary artery | 0.02 mmHg·s·ml-1 |
| and | Right (Left) distal pulmonary artery | 0.03 mmHg·s·ml-1 |
| and | Right (Left) pulmonary veins | 0.045 mmHg·s·ml-1 |
| ***Viscoelastic Resistances*** | | |
|  | Head and arm artery | 0.01 mmHg·s·ml-1 |
|  | Left neck artery | 0.01 mmHg·s·ml-1 |
|  | Left clavicular artery | 0.01 mmHg·s·ml-1 |
|  | Proximal aorta | 0.01 mmHg·s·ml-1 |
| and | Right (Left) proximal pulmonary artery | 0.005 mmHg·s·ml-1 |
| and | Right (Left) distal pulmonary artery | 0.005 mmHg·s·ml-1 |
| and | Right (Left) pulmonary veins | 0.005 mmHg·s·ml-1 |

**Table A2**. Inductors of the normal human circulation system circuit model

|  |  |  |
| --- | --- | --- |
| Parameter | Description | Value |
|  | Proximal aorta | 0.001 mmHg·s2·ml-1 |
| and | Right (Left) proximal pulmonary artery | 0.001 mmHg·s2·ml-1 |

**Table A3**. Capacitors of the normal human circulation system circuit model

|  |  |  |
| --- | --- | --- |
| Parameter | Description | Value |
|  | Head and arm artery | 1 ml·mmHg-1 |
|  | Left neck artery | 1 ml·mmHg-1 |
|  | Left clavicular artery | 1 ml·mmHg-1 |
|  | Proximal aorta | 0.8 ml·mmHg-1 |
|  | Right upper limb artery | 3 ml·mmHg-1 |
|  | Left upper limb artery | 2 ml·mmHg-1 |
|  | Right internal carotid artery | 2 ml·mmHg-1 |
|  | Left internal carotid artery | 4 ml·mmHg-1 |
|  | Proximal systemic artery | See **Eq.10** |
|  | Right subclavian vein | 10 ml·mmHg-1 |
| and | Right (Left) internal jugular vein | 10 ml·mmHg-1 |
|  | Left subclavian vein | 10 ml·mmHg-1 |
|  | Systemic veins | See **Eq.7** |
|  | Vena cava | See **Eq.8** |
| and | Right (Left) proximal pulmonary artery | 10 ml·mmHg-1 |
| and | Right (Left) distal pulmonary artery | 23 ml·mmHg-1 |
| and | Right (Left) pulmonary veins | 25 ml·mmHg-1 |

**Table A4**. Initial conditions of the normal human circulation system circuit model

|  |  |  |  |
| --- | --- | --- | --- |
| Compartment | Value | Compartment | Value |
| Total blood volume | 4711 ml |  |  |
| ***Volume*** | | | |
| Left ventricle | 123 ml | Right ventricle | 110 ml |
| Left atrium | 63 ml | Right atrium | 53 ml |
| Head and arm artery | 111 ml | Left neck artery | 117 ml |
| Left clavicular artery | 117 ml | Proximal aorta | 64 ml |
| Right upper limb artery | 29 ml | Left upper limb artery | 19 ml |
| Right internal carotid artery | 20 ml | Left internal carotid artery | 37 ml |
| Proximal systemic artery | 217 ml | Systemic veins | 2526 ml |
| Right subclavian vein | 66 ml | Left subclavian vein | 66 ml |
| Right internal jugular vein | 69 ml | Left internal jugular vein | 66 ml |
| Vena cava | 170 ml | Right proximal pulmonary artery | 64 ml |
| Left proximal pulmonary artery | 64 ml | Right distal pulmonary artery | 140 ml |
| Left distal pulmonary artery | 140 ml | Right pulmonary veins | 130 ml |
| Left pulmonary veins | 130 ml |  |  |
| ***Flow*** | | | |
| Proximal aorta | 40 ml·s-1 | Right proximal pulmonary artery | 16 ml·s-1 |
| Left proximal pulmonary artery | 16 ml·s-1 |  |  |