Autoregulatory Mechanisms in Chagasic Dilated Cardiomyopathy: A Mathematical Approach

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Abstract

Chagas is a vector borne tropical disease caused by the protozoan parasite *Trypanosoma cruzi* and transmitted by *Rhodnius prolixus*. Approximately from 8 to 12 million people are infected in Central and South America, 120 million are at risk and there are 50,000 deaths per year from this disease. In Colombia around 438,000 people are infected and 4,800,000 in risk of infection. Chagas disease is a major cause of heart disease and cardiovascular-related deaths in areas where it is endemic; all these aspects makes the chagas disease an important public health problem, with no vaccines available and only a few anti parasite drugs. Chagas’ heart disease displays certain characteristics that differentiate it from other cardiac conditions. In the natural course of the disease, the cardiac abnormalities appear around 20 to 30 years after infection. Knowing this, our aim is to expose the mechanisms involved in the silent development of Chagasic dilated cardiomyopathy that take place along the evolution of this pathology.

To achieve this, a mathematical model was proposed based on fluid mechanics. We assumed the cardiovascular system as a circuit with two pumps (Right and Left Ventricles) and 8 resistances: 4 that represent the cardiac valves (Tricuspid, Pulmonary, Mitral and Aortic), 2 representing the entrances to atriums (cavoatrial and pulmonary atrium) and the systemic and pulmonary capillaries. Each parameter was determined according to anatomical and physiological properties found in the literature. The model was implemented in MATLAB and the equations were solved to the steady state. The simple mathematical model was helpful to understand the normal functioning of the cardiovascular system. The model was used to simulate the different stages of chagasic cardiovascular disease and to identify the compensation mechanisms.

**Key Words:** Chagas Disease, Dilated Cardiomyopathy, Cardiovascular System Model.

Introduction

Chagas is a vector borne tropical disease caused by the protozoan parasite *Trypanosoma cruzi* and transmitted by *Rhodnius prolixus*. Approximately from 8 to 12 million people are infected in Central and South America, 120 million are at risk and there are 50,000 deaths per year from this disease; of these deaths, 60% are related to sudden cardiac death (SCD), 25% to heart failure and 15% to stroke. Chagas disease is one of the major causes of heart disease and cardiovascular-related deaths in areas where it is endemic; also migratory population movements from endemic countries have led to the disease being diagnosed in non-endemic areas. All this makes chagases disease a concern for public health.
health authorities, with no vaccines available and only a few antiparasitic drugs. It primarily affects low-income populations and is a major cause of chronic morbidity and mortality. (Mora, 2016).

Heart disease caused by *T. cruzi* displays certain characteristics such as left ventricle apical fibrosis, conduction system alterations, and abnormalities in contractility, which differentiate it from other cardiac conditions. It has a tendency towards the formation of aneurysms, particularly in the apical region. In addition, it has powerful arrhythmogenic potential, commonly giving rise to ventricular arrhythmias, and it is associated with a high rate of thromboembolic events (Gascon et al. 2007). The specific differential characteristics of chronic chagasic cardiomyopathy makes cardiac failure or sudden death the frequent manifestations of the disease, generating the need of developing diagnostic and therapeutic protocols for earlier detection.

When *T. cruzi* enters the body it travels through the bloodstream; this acute phase of the infection usually does not have clinical manifestation. After approximately two months the parasite leaves the bloodstream and infects the myocytes and muscle cells of the gastrointestinal tract. For decades the patient remains asymptomatic while the parasite reproduce, during this time 20-30% of the patients suffer a myocardial remodeling; this process starts with a hypertrophy of the cardiac muscle that throughout the years will end up in fibrosis and finally in heart failure (Bern, 2015). Another 10% of the patients present digestive complaints or both, and less than 5% of patients develop a neurologic form of the disease; the remaining stay asymptomatic. (WHO, 2017)

Given the lack of diagnostic tools, some studies have been performed in order to obtain qualitative models as predictors used to assist diagnosis, prognosis and treatment. These models statistically estimate the likelihood of clinical events taking into account complementary tests and physiological measures. In 2016, Brasil et al. developed a logistic regression model that uses basic measurements to calculate the risk of having a *T. cruzi* infection (Brasil, Xavier, Holanda, Hasslocher-Moreno, & Braga, 2016). Another model developed in 2015 predicted severe or moderate systolic dysfunction in Chagas disease. It was used based on the following clinical, electrocardiographic and radiologic data: sex, chest X-ray, right bundle branch block, anterior superior divisional block, ventricular extrasystole, pathologic Q-wave, primarily ventricular repolarization alterations, left bundle branch block, and pacemaker rhythm. This model is recommended for ordinary use in urban and rural populations (Souza, et al., 2015). Another interesting model studied the risk of sudden death in chronic Chagas' heart disease. Four independent predictors were identified, each of which was assigned a number of points proportional to its regression coefficients: QT-interval dispersion, syncope, ventricular extrasystoles and severe dysfunction of the left ventricle. The risk scores for each patient were divided in three groups: low risk, intermediate, and high risk. This study showed that a simple model can predict sudden death with a good clinical relevance of the model with C statistic score of 0.84. (Souza, y otros, 2015).

Even though there are some characteristic signs and symptoms in the cardiovascular effect generated by Chagas, infected patients do not present any pathognomonic signs that allow an accurate and early diagnosis. However, it is known that during the first stage of the infection, the heart could be affected but the usual measurements do not show
alarming changes. As mentioned earlier, there are models to estimate Chagas risk, but these are based on statistical analysis that do not allow us to understand the disease and compensatory mechanisms in the body during the asymptomatic stage. Therefore, the aim of this study is to analyze and expose the mechanisms involved in the silent development of Chagasic dilated cardiomyopathy, including not only the well-known cardiac remodeling but also the systemic process, such as renal, portal and lungs circulations. Based on fluid mechanics we developed a mathematical model for the normal and chagasic cardiovascular system.

Methods

The model is based on the interpretation of the cardiovascular system as a circuit. It has two bombs, corresponding to the left and right ventricles, and six vessel systems that are both compliant and resistant: left and right atrium, systemic arterial vessels, systemic venous vessels, pulmonary arterial vessels and pulmonary venous vessels. In addition, we consider the systemic and pulmonary capillary beds as resistive vessels. The blood flux will move from the left ventricle to the systemic capillary bed through the arteries, and from here to the right bomb through the veins and right atrium. Blood will be ejected from the right ventricle to the pulmonary capillary bed through the pulmonary arteries. In the lung the blood will be oxygenated and move back to the left heart through the pulmonary veins and left atrium. The diagram of the model is presented in Figure 1.

To summarize we are dividing the circulatory system in the following 8 segments:

1. **Segment 1**: starts at the left ventricle (pump) passing through the aortic valve (resistance).
2. **Segment 2**: once the blood passes through the aortic valve it gets to the second segment that begins at the end of the aortic valve and ends in the systemic
capillary bed (resistance).

3. **Segment 3**: this area begins after the systemic capillary bed, passing through the venous circulation and ending at the right atrium. This transition is modeled as a resistance.

4. **Segment 4**: the right atrium passes the blood to the right ventricle through the tricuspid valve (resistance).

5. **Segment 5**: the right ventricle (pumps) blood to the pulmonary artery through the pulmonary valve (resistance) and into the pulmonary artery.

6. **Segment 6**: from pulmonary artery to pulmonary capillary bed, the blood moves through the pulmonary artery and then the exchange of oxygen occurs in the capillaries of the lungs (resistance).

7. **Segment 7**: after passing the lung resistance, flow goes through the pulmonary vein into the left atrium. This transition is modeled as a resistance.

8. **Segment 8**: once in the left atrium the flow must goes through the last resistance (mitral valve) before getting back to the first segment.

In the construction of the model, we took into account the law of mass conservation, the definition of a compliant vessel and the Ohm’s law to understand the dynamics of the flow. Figure 2 shows an example of how the main equations were used for each one of the segments.

![Equation Diagram](image)

\[ \dot{V}_{sa} = Q_{Ao} - Q_s \]  
\[ V_{sa} = C_{sa}P_{sa} + V_0 \]  
\[ Q_s = \frac{P_{sa} - P_{sv}}{R_s} \]

**Figure 2. Equations explaining the dynamics for the first segment of the circulatory system, used also in the other segments.** Equation 1 represents the law of mass conservation, equation 2 the definition of a compliant vessel and equation 3 the Ohm’s law.

The following assumptions were considered to build the model:

I. Dead volumes are neglected due to the fact that the heart does not stop and the pressure never goes to zero.

II. Data was based on a man with 70 Kilograms weight, 80 ml/(kilogram*min) of flow for a total flow by minute of 5.6 liters/minute.

III. Gravity force is neglected.

IV. Systemic and pulmonary capillary beds are resistive.
V. Systemic and pulmonary arteries and veins are distensive.
VI. Blood is an incompressible fluid and has constant viscosity.
VII. The blood flux is laminar.

Equations 4-11 show the compliances, resistances, pressures, and switches for each segment based on equations 1-3. Switches were established as a control for the valves, in order to create an autoregulatory mechanism based on the differential pressure at the sides if each valve. Therefore the valves open when the pressure in one camera exceeds the pressure in the next segment, and closes when the pressure drops avoiding regurgitant flux.

\[
[C_k(t) \ast P_{lv}] = \frac{P_{nv}-P_{lv}}{R_{MI}} \ast S_{MI} - \frac{P_{nv}-P_{lv}}{R_{ao}} \ast S_{ao} \quad (4)
\]

\[
[C_{sa} \ast P_{sa}^\prime] = \frac{P_{nv}-P_{sa}}{R_{ao}} \ast S_{ao} - \frac{P_{nv}-P_{va}}{R_s} \quad (5)
\]

\[
[C_{sv} \ast P_{sv}^\prime] = \frac{P_{nv}-P_{va}}{R_s} - \frac{P_{nv}-P_{sa}}{R_{TRI}} \ast S_{TRI} \quad (6)
\]

\[
P_{ra}^\prime = \frac{P_{nv}-P_{ra}}{R_{TRI}} - \frac{P_{nv}-P_{ra}}{C_{ra}} \ast S_{TRI} \quad (7)
\]

\[
[C_{rv}(t) \ast P_{rv}] = \frac{P_{nv}-P_{rv}}{R_{TRI}} \ast S_{TRI} - \frac{P_{nv}-P_{pv}}{R_{pv}} \ast S_{pv} \quad (8)
\]

\[
[C_{pa} \ast P_{pa}^\prime] = \frac{P_{nv}-P_{pa}}{R_{pv}} \ast S_{pv} - \frac{P_{nv}-P_{pa}}{R_p} \quad (9)
\]

\[
[C_{pv} \ast P_{pv}^\prime] = \frac{P_{nv}-P_{pa}}{R_p} - \frac{P_{nv}-P_{pv}}{R_{MI}} \ast S_{MI} \quad (10)
\]

\[
P_{la}^\prime = \frac{P_{nv}-P_{la}}{R_{MI}} - \frac{P_{nv}-P_{lv}}{C_{la}} \ast S_{MI} \quad (11)
\]

**Parameters**

The parameters in the model were calculated based on pressures and volumes obtained from literature (Delgado, 2010). Compliance was estimated with \( c = \Delta V/\Delta P \), using a constant stroke volume (93.33 mL), and the normal physiological pressures in each segment (Annex A, Table 1 and 2). Resistances were calculated with \( R = \Delta P/Q \), where the flux \( Q \) remained constant and equal to the cardiac output (336,000 ml/seg).

**Results and discussion**

Simulations were performed using de ODE function from the software MATLAB 2016 for 0.8 s and 1 heart beat. The normal heart rate was 60 bpm in a healthy person of 70 kg weight and the normal systemic arterial pressure was 120/80 mmHg.
The results obtained in this model are consistent with the physiological functioning of the cardiovascular system as is evidenced in the opening and closure of the valves (Aortic, Pulmonary, Tricuspid and Mitral) when the differential pressure is positive and negative respectively. Therefore, the opening of valves not only allows an increase in pressure, but also a positive flux gradient into the atrium and ventricles during diastole.

Figure 3 shows the pressure dynamics during the heartbeat. There is a decrease in the pressure of the left ventricle and an increase in the pressure of the right atrium, both curves of pressure intersect and in that point occurs the opening of the mitral valve, the same phenomena occurs in the right atrium and ventricle with the opening of the tricuspid valve (Fig. 4). The systemic arterial pressure, as it is in physiological behavior, is equal to the left ventricle systolic pressure and decreases through time. There is no decreasing in pressure near or under 80 mmHg as was expected to occur in normal functioning, this could be associated to the parameter estimation that needs to be optimized. Pressures of the pulmonary circulation starting in the right atrium and finishing in the left atrium were simulated. High precision results were obtained, with an increase in pressure in each atrium that facilitates the opening of the valves (Tricuspid and Mitral), and a decrease pressure through the pulmonary circulation that allows the oxygen exchange in the capillaries lungs.
Figures 5 shows the fluxes of the eight segments during the heartbeat. There is a change in the behavior of the ativoventricular valves flux (Tricuspid and Mitral) when they open, simulating the correct physiological mechanism of the heart. In the same way semilunar valves (Aortic and Pulmonary) show a controversial behavior due to the drop of flux in the pulmonary artery, while there is an increase in flux at the aorta. However, there is an abnormality in the model related to the opening of the valves, more specifically...
associated to the time at which this process happens. The opening of mitral and tricuspid valves should be simultaneous as it must be in the aortic and pulmonary ones, but in this model that synchronization at the opening and close is lost.

The model shows no volume conservation due to a small variation of 50 ml in the model through time (Figure 6). This variation can be attributed to the numerical estimation of the compliances and resistances of the heart in every single heartbeat. However, the model only shows 1 second in the timeline and it is not possible ensure a good pattern in time.

![Figure 6. Volume vs time](image)

**Conclusion**

The simple mathematical model of the cardiovascular system proposed as a circuit of two pumps and eight resistances was helpful for simulating the physiological functioning of the normal system. Physiological fluxes, volumes and pressures were obtained with the simulations, with a nearly accurate values. The model gave us an approximation based on every single heart beat.

A number of parameters need to be modified in the future in order to obtain a better model in terms of accuracy.

**References**


## Annex A

### Table 1. Variables and parameters used in the model

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Right heart compliance</td>
<td>0.01 liter/mmHg</td>
</tr>
<tr>
<td>Left heart compliance</td>
<td>0.01 liter/mmHg</td>
</tr>
<tr>
<td>Mitral valve resistance</td>
<td>22.8 mmHg*seg/liter</td>
</tr>
<tr>
<td>Pulmonary venous compliance</td>
<td>0.08 liter/mmHg</td>
</tr>
<tr>
<td>Aortic valve resistance</td>
<td>321.6 mmHg*seg/liter</td>
</tr>
<tr>
<td>Systemic arterial compliance</td>
<td>0.01 liter/mmHg</td>
</tr>
<tr>
<td>Systemic resistance</td>
<td>1232.4 mmHg*seg/liter</td>
</tr>
<tr>
<td>Systemic venous compliance</td>
<td>1.75 liter/mmHg</td>
</tr>
<tr>
<td>Tricuspid valve resistance</td>
<td>10.8 mmHg*seg/liter</td>
</tr>
<tr>
<td>Pulmonary valve resistance</td>
<td>53.4 mmHg*seg/liter</td>
</tr>
<tr>
<td>Pulmonary arterial compliance</td>
<td>0.00667 liter/mmHg</td>
</tr>
<tr>
<td>Pulmonary resistance</td>
<td>85.8 mmHg*seg/liter</td>
</tr>
<tr>
<td>Right atrium resistance</td>
<td>0.026 mmHg*seg/liter</td>
</tr>
<tr>
<td>left atrium resistance</td>
<td>0.036 mmHg*seg/liter</td>
</tr>
</tbody>
</table>

### Table 2. Pressures (systole/diastole/mean) in each segment

<table>
<thead>
<tr>
<th>Segment</th>
<th>Systole</th>
<th>Diastole</th>
<th>Mean</th>
</tr>
</thead>
<tbody>
<tr>
<td>Right atrium</td>
<td>-</td>
<td>-</td>
<td>2-8 mmHg</td>
</tr>
<tr>
<td>Left atrium</td>
<td>-</td>
<td>-</td>
<td>2-10 mmHg</td>
</tr>
<tr>
<td>Right ventricle</td>
<td>15-30 mmHg</td>
<td>2-8 mmHg</td>
<td>-</td>
</tr>
<tr>
<td>Left ventricle</td>
<td>100-140 mmHg</td>
<td>3-12 mmHg</td>
<td>-</td>
</tr>
<tr>
<td>Pulmonary vein</td>
<td>-</td>
<td>-</td>
<td>2-10 mmHg</td>
</tr>
<tr>
<td>Pulmonary artery</td>
<td>15-30 mmHg</td>
<td>4-12 mmHg</td>
<td>4-12 mmHg</td>
</tr>
<tr>
<td>Aorta</td>
<td>100-140 mmHg</td>
<td>60-90 mmHg</td>
<td>60-90 mmHg</td>
</tr>
</tbody>
</table>

*All the values were taken from: revista española cardiología. 2010;63(03):334*