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Computational modeling of human physiology: the simulation of aortic stenosis in cardiac circulation

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CHAPTER **PAGE**

Overview:

Traditionally, bench testing, animal studies, and clinical trials have been the main sources of evidence for bringing medical devices to market in the U.S. In recent years, however, computational modeling has become an increasingly powerful complementary tool for evaluating medical devices alongside bench, animal and clinical methods.

This thesis represents a small part of a broader project aimed at developing a simulation model of the pulmonary and systemic circulation systems for use in demonstrating the efficacy of pharmaceuticals and medical devices such as artificial valves.

Specifically, my thesis is focused on the aortic valve component of the model, for which I set out to provide proof of concept and preliminary model validation.

Stenosis consists in a narrowed valve that does not open properly and may be caused by progressive calcification or a congenital bicuspid formation. This reduces blood flow from the heart into the main artery, diminishing the flow from the ventricle to the systemic arterial components of the standard cardiovascular model. Aortic stenosis is a common cause of aortic valve replacement, impacting approximately 1.5 million people in the U.S today. Without valve replacement, death is a likely outcome.

The primary measure of stenosis is the resistance of the aortic valve. While this can be measured directly, the measurement method is highly invasive given that it requires catheterization. Therefore, it is generally not performed on patients due to the risks involved. Instead, surrogate measures may be obtained via a Doppler ultrasound test that is not invasive and easy to perform. This provides surrogate values including the peak/mean pressure gradient across the valve (which is a time-varying property). Another surrogate measure is valve area.

The aim of the present research was to use the proposed model of the cardiac circulation system to convert observed peak pressure gradients into valve resistances for a set of clinical patients.

The cardiovascular model comprises six components, namely the left ventricle, systemic arteries, systemic veins, right heart, pulmonary arteries, and pulmonary veins, plus two valves for each ventricle. A series of physics equations derived from first principles provide the foundation for modelling the cardiopulmonary system. These equations are time-varying and often direct relationships between variables are not realistic.

The model includes certain parameters that are controlled and other values that may only be observed. Specifically, valve resistance is a controlled parameter and pressure gradient is an observed value. This prevents us from merely inputting a pressure gradient and retrieving valve resistance.

Real patients' clinical data provide us with peak pressure gradient measures. Based on this data, the simulation could be run repeatedly to find the appropriate resistance in each case. In contrast, we constructed a table of values converting pressure gradients to aortic resistances via the proposed model. I then used linear interpolation to estimate valve resistance values corresponding to peak pressure gradient measures falling between points in the table.

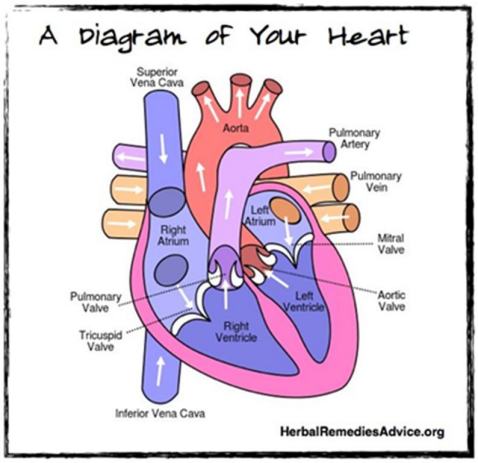
This demonstrates the capacity of simulation techniques to convert the observed surrogate measures to the desired endpoint of valve resistance values.

Chapter 1

1.1 A brief description of cardiac circulation

The task of the heart is to pump blood around the body. A description of cardiac circulation can begin at any point within the system which forms a closed loop. Starting from the left side, the left ventricle of the heart receives blood and pumps it into the systemic arteries. These form a tree of progressively smaller vessels and from the smallest of the systemic arteries, blood flows into the systemic capillaries. Leaving the systemic capillaries, the blood enters the systemic veins, through which it flows in vessels of progressively increasing size toward the right side of the heart. The right heart pumps blood into the pulmonary arteries, which form a tree that distributes the blood to the tissues of the lung. The smallest branches of this tree are called pulmonary capillaries. Leaving the pulmonary capillaries, the blood is collected in the pulmonary veins, through which it flows back to the left heart. This completes circulation. The average time required for a blood cell to complete the described circuit is about 1 minute.

There is a key symmetry in the design of the circulatory system: The blood that leaves the left heart flows through the arteries, capillaries, and veins of the systemic circulation circuit before returning to the right heart. Similarly, the blood that leaves the right heart flows through the arteries, capillaries, and veins of the pulmonary circulation circuit before returning to the left heart. Because of this symmetry between the systemic and pulmonary circulation circuits, equations modelling systemic circulation take the same form as equations modelling pulmonary circulation. Analogously, the equations for the right and left heart take the same form, while the relationship between the right heart and the systemic circulation circuit mirrors the relationship between the left heart and the pulmonary circulation circuit. However, the parameters in the equations for pulmonary circulation bear different values to the corresponding parameters of systemic circulation. Indeed, systemic blood volume is about 10 times pulmonary blood volume, and systemic arterial pressure is about 6 times pulmonary arterial pressure.



1.2 The physical variables of cardiac circulation

The three physical variables that are required to quantitatively describe circulation are pressure, volume, and flow.

Blood volume offers a convenient measure of the amount of blood in any part of the circulation system. Volume here will be measured in liters and represented by the symbol *V*.

Blood flow is defined as the volume of blood passing a given point in the circulatory system per unit time. Blood flow will here be measured in liters/minute and represented by the symbol *Q*. The most crucial flow in circulation is cardiac output, which is defined as the volume of blood pumped per unit of time by either side of the heart. Cardiac output may be calculated as the product of stroke volume, which is the volume of blood pumped per beat, and heart rate, defined as the number of beats per unit time.

The definition of pressure is force per unit area. The conventional unit of pressure in physiology is mmHg (millimeters of mercury), which expresses the height of a column of mercury that can be supported by the pressure in question. When considering pressure, it should be taken into account that only pressure differences produce observable effects. A particularly convenient reference pressure in physiology is atmospheric pressure because this is the pressure outside most of the blood vessels in the circulation system. Pressure will be represented here by the symbol *P*, which will stand for pressure measured with respect to the atmosphere.

1.3 Two proprieties of blood vessels: *compliance and resistance*

A vessel has an upstream pressure P_1 and a downstream pressure P_2. To explain how *Q*, P_1, P_2, and *V* are related, two separate properties of the blood vessel must be considered: its resistance to blood flow and its compliance, or ability to respond to an increase in pressure by distending and increasing the volume of blood that it is holding. If we assume a vessel to be rigid, then the volume of the vessel is known and constant. Thus, we only need to identify the relationship between flow (*Q*), upstream pressure (P_1), and downstream pressure (P_2). Given that only pressure differences matter, it is safe to assume that *Q* is determined by pressure difference $P_1 - P_2$. This relationship may be expressed as follows:

$$Q = \frac{P_1 - P_2}{R}$$

where R is a constant representing the vessel's resistance. If a vessel satisfies this equation, we refer to it as a resistance vessel.

On the other hand, if we assume that the vessel is elastic but its resistance to blood flow is equal to zero, then the upstream pressure (P_1) and downstream pressure (P_2) at the two extremities of the vessel will be equal for all flows (*Q*). Because the vessel is elastic, there is a relationship between distending pressure $P = P_1 = P_2$ and volume (*V*). The simplest relationship of this kind is:

$$V = CP$$

where *C* is the compliance of the vessel. Alternatively, if we wish to take into account the non-zero residual volume of the vessel at zero pressure, we could use the following relationship:

$$V = V_d + CP$$

where V_d is the "dead" volume of the vessel at P = 0. A vessel satisfying either of the last two equations is called a compliance vessel.

In practice, a real vessel will exhibit both resistance and compliance properties simultaneously. However, the circulatory system does seem to produce a clear separation between the resistance and compliance functions of its different vessels. Thus, the large arteries and veins are primarily compliance vessels, in the sense that only small pressure differences are needed to drive the cardiac output through them, while their changes in volume are highly significant. On the other hand, the main site of resistance is in the tissues themselves (primarily at the level of the smallest arteries, the arterioles), where volume changes are less important but where large pressure drops are observed.

Although the linear relationship used above to describe blood vessels may be too simple, as an approximation of a linear relation between flow and pressure differences, it is a good approximation when we allow for changes in resistance. Finally, in terms of the linear compliance relations that we have assumed, it is an excellent approximation to say that the volume of a blood vessel is determined by the internal pressure, but the relationship between volume and pressure becomes progressively less compliant as it is distended. The linear model is a simplification.

1.4 Stroke volume and the relationships between pressure, inflow, and outflow in a vessel.

A pump is a device that can accept fluid at low pressure (P1) and transfer it to a region where the pressure is high ($P_2 > P_1$). Let us consider the left side of the heart: The left ventricle is equipped with an inflow (mitral) valve and an outflow (aortic) valve. When the ventricle is relaxed (diastole) the inflow valve is open, and the outflow valve is closed. During this period, the left ventricle receives blood from the left atrium at a pressure that is essentially the same as that of the pulmonary veins. Thus, for the left ventricle, $P_1 = Ppv$ (pressure in the pulmonary veins). When the ventricle contracts (systole), the inflow valve closes and the outflow valve opens, and the chamber pumps blood into the systemic arterial tree. Thus, for the left ventricle, $P_2 = Psa$ (pressure in the systemic arteries). The terms “systolic” and “diastolic” refer to the phases of the cardiac cycle. In the absence of stenosis, because the aortic valve is open during systole, the systolic pressure in the systemic arteries is essentially the same as the systolic pressure in the left ventricle. In contrast, the diastolic pressure in the ventricle is much lower than diastolic pressure in the arteries. This is due to the closure of the aortic valve throughout this phase.

To understand what determines the output of the ventricles, let us consider the left and right ventricles as compliance vessels whose compliance changes with time. Thus, the ventricle may be described using the following expression:

$$V(t) = V_d + C(t)P(t)$$

where *C(t)* is a given function. The important point is that *C(t)* takes on a small value during systole ($C_{systole}$), which is when the ventricle is contracting, and a much larger value during diastole ($C_{diastole}$), which is when the ventricle is relaxed. The maximum volume of the ventricle is achieved at end-diastole and is expressed as follows:

$$V_{\mathrm{ED}} = V_{\mathrm{d}} + C_{\mathrm{diastole}} P_{\mathrm{v}}$$

while the minimum volume is achieved at end-systole and is given by:

$$V_{\mathrm{ES}} = V_{\mathrm{d}} + C_{\mathrm{systole}} P_{\mathrm{a}}$$

where P_a is the pressure in the arteries supplied by the ventricle and P_v is the pressure in the veins that fill it. Thus, stroke volume is given by the difference between these two quantities

$$V_{\mathrm{stroke}} = V_{\mathrm{ED}} - V_{\mathrm{ES}}$$

In our own model, we simplified the calculation of stroke volume by assuming $C_{systole} = 0$. This gives a stroke volume equal to:

$$V_{\mathrm{stroke}} = C_{\mathrm{diastole}} P_{\mathrm{v}}$$

As earlier stated, our proposed model for the simulation of cardiac circulation treats the ventricle as a compliance vessel. A compliance vessel that is not in the steady state has an inflow $Q_1(t)$ that is not equal to outflow $Q_2(t)$ at every time point. When inflow and outflow are not equal, the volume of the vessel changes with time. In fact, if *V(t)* denotes the volume of the vessel at time *t*, this yields a differential equation:

$$V = Q_1 - Q_2$$ (where, from this point on, $\mathrm{V} = \frac{d}{d(t)} V$)

This equation (expressing the conservation of volume) may be converted into that relating the pressure in the vessel to the flows in and out of it, by using the compliance vessel equation:

$$\frac{d}{d(t)} C \dot{P} = Q_1 - Q_2$$

This last equation will be used to solve a linear system of *N* differential equations in *N* unknowns.

1.5 Developing a model to simulate cardiac circulation

We are interested here in building a computer model of the entire circulation cycle, although our focus will be on the left side of the heart. As mentioned above, we treat the two ventricles of the heart as compliance vessels, whose compliance is not constant but rather is some given function of time that will drive our model. The compliance function that we assume for the left ventricle takes time zero to be at end-diastole (when the left ventricle reaches its maximum volume), is periodic with period *T*, and is written as follows:

$$C_{\mathrm{LV}}(t) = \begin{cases} C_{\mathrm{LVD}} \left(\frac{C_{\mathrm{LVS}}}{C_{\mathrm{LVD}}} \right)^{\frac{1-\exp(-t/\tau_S)}{1-\exp(-T_S/\tau_S)}}, & 0 \le t \le T_S, \\ C_{\mathrm{LVS}} \left(\frac{C_{\mathrm{LVD}}}{C_{\mathrm{LVS}}} \right)^{\frac{1-\exp\left(-(t-T_S)/\tau_D\right)}{1-\exp\left(-(T-T_S)/\tau_D\right)}}, & T_S \le t \le T. \end{cases}$$

where T_s denotes the time at the end of systole.

We next require a MATLAB function that may be summoned to evaluate compliance in the ventricle at time *t*. The function must be general enough to be called for either side of the heart given the appropriate arguments:

```
%ventricular compliance as a function of time: here we take time
%zero to be at the end of
%diastole, when the left ventricular compliance has its maximum
%value.
%The following function drives the cardiac cycle
function CV = CV_now(t, CVS, CVD)
global T TS tauS tauD;%tauD/S are two constants of time, smaller
%values yield faster transitions.
tc=rem(t,T);%time of current cycle measured from start of %systole
if(tc<TS)
    e= (1-exp(-tc/tauS))/(1-exp(-TS/tauS));
    CV = CVD*(CVS/CVD)^e
else
    e= (1-exp(-(tc-TS)/tauD))/(1-exp(-(T-TS)/tauD));
     CV = CVS*(CVD/CVS)^e
end
%This function is general so that we can call it for either side
%of the heart.
%When this function is used to model the left side of the heart
%then  CVD,CVS are set equal to CLVD, CLVS and the output CV %will
%be the left ventricular compliance CLV.
```

In this project, how we treat the valves of the heart will be of particular importance. The left ventricle has an inflow valve called the mitral valve, and an outflow valve called the aortic valve. When these valves are healthy, they present a very low resistance to forward flow but completely block backflow. Valve diseases may alter either or both properties. Resistance to forward flow may be increased and cause stenosis, or the valve may become leaky and allow backflow and cause regurgitation. The MATLAB script that we developed may be used to study some of the consequences of heart valve malfunction in cardiac circulation. In the present case, we are interested in aortic stenosis. Furthermore, the model must be very general so that it will be readily adaptable to a variety of circumstances. Therefore, we model the generic situation of an arbitrary collection of *N* compliance vessels connected by resistance vessels equipped with valves. In fact, we assume that each pair of compliance vessel is connected by two such resistance vessels, with the valves pointing in opposite directions. If any of these connections is not actually wanted, we can make the corresponding resistance infinite. By assigning the resistances in different ways, we can model any kind of connection that we want, including no connection at all. The equations of the general network that we have just described are as follows. First, we have the equation for conservation of volume:

$$\dot{V}_i = \sum_{j=1}^{N} (Q_{ji} - Q_{ij}), \quad i = 1, \ldots, N,$$

where V_i and P_i are the volume and pressure of compliance chamber i, respectively, and Q_{ij} is the outflow from chamber i into chamber j. Next, we have the compliance relationship for each chamber:

$$V_i = (V_\mathrm{d})_i + C_i P_i, \quad i = 1, \ldots, N,$$

where C_i and $(V_d)_i$ are the compliance and "dead volume" (volume when $P_i = 0$) of compliance chamber i. Note that C_i will be constant for arteries and veins, but time-dependent for chambers of the heart.

Finally, we have the pressure-flow relationship for each of the valve-equipped resistances that connects any pair of chambers in our model:

$$Q_{ij} = \frac{S_{ij}}{R_{ij}}(P_i - P_j) = S_{ij} G_{ij} (P_i - P_j), \quad i, j = 1, \ldots, N,$$

where S_{ij} is the state of the valve (closed or open) and where we have introduced the notation $G_{ij} = 1/R_{ij}$ to cover the case $R = \infty$. Whether a valve is open or closed depends on the direction in which the flow is attempting to go and on the sign of the pressure difference across the valve. Thus, we have:

$$S_{ij} = \begin{cases} 1, & P_i > P_j, \\ 0, & P_i \leq P_j, \end{cases}$$

Note that if $S_{ij} = 0$, then the flow through that valve will be equal to zero, given that this means that the valve is closed.

One approach to solving the equations of cardiac circulation is to first combine these equations to obtain:

$$\begin{aligned} \frac{d}{dt}(C_i P_i) &= \sum_{j=1}^{N} \left(S_{ji} G_{ji} (P_j - P_i) - S_{ij} G_{ij} (P_i - P_j) \right) \\ &= \sum_{j=1}^{N} \left(S_{ij} G_{ij} + S_{ji} G_{ji} \right) (P_j - P_i), \end{aligned}$$

This is a system of N differential equations in the N unknowns, P_1, ... , P_N. A numerical method of solving these equations is obtained by replacing the time derivative with a backward difference quotient:

$$\frac{C_i(t)P_i(t) - C_i(t-\Delta t)P_i(t-\Delta t)}{\Delta t}$$
$$= \sum_{j=1}^{N} \left(S_{ij}(t)G_{ij} + S_{ji}(t)G_{ji}\right)\left(P_j(t) - P_i(t)\right)$$

If we temporarily regard the valve states $S_{ij}(t)$ as known quantities, this is a linear system in the unknowns $P_i(t)$. It may be expressed in standard form as follows:

$$\sum_{j=1}^{N} A_{ij}(t)P_j(t) = C_i(t-\Delta t)P_i(t-\Delta t), \quad i = 1, \ldots, N,$$

where

$$\begin{aligned} A_{ij}(t) &= -\Delta t\left(S_{ij}(t)G_{ij} + S_{ji}(t)G_{ji}\right), \quad i \neq j, \\ A_{ii}(t) &= C_i(t) - \sum_{j:j\neq i} A_{ij}(t), \end{aligned}$$

The following MATLAB program solves this linear system and calculates, at each step (heartbeat), N values of pressure, one for each chamber:

```
%This function finds the pressure given the states of the valves
function P=P_new(P_old,C_old,C,S)
global G dt CHECK N;
A=-dt*((S.*G)+(S.*G)');
A=diag(C-(sum(A))')+A;
P=A\(C_old.*P_old);
if (CHECK)
    for i=1:N
        CH(i)=-(C(i)*P(i)-C_old(i)*P_old(i))/dt;
        for j=1 :N
            CH(i)=CH(i)+S(j,i)*G(j,i)*(P(j)-P(i));
            CH(i)=CH(i)-S(i,j)*G(i,j)*(P(i)-P(j));
        end
    end
CH %Write out the values of CH,
%which should be zero to within roundoff.
end
```

The function *P*_new finds the pressures given the state of the valves (1 = opened, 0 = closed), and it is easy to set the state of the valves if we are given the pressures. There is a circular dynamic going on here, given that the pressures can only be determined when the state of the valves is known yet we also know that the valve states are determined by the pressures. What we need to look for here is a self-consistent choice of the valve states and the pressures. One approach to identifying such a choice is by trial and error. This would involve starting the script with any state of the valves and solving for the pressures; then resetting the valves according to the pressures, solving for the pressures again, and so on, until the valve states stop changing. We can write a program that finds self-consistent valve states and pressures by setting each according to the other until the valve states stop changing:

```
%script to find self-consistent valve states and pressures:
done=0; %not done yet!
while(~done) %if not done, keep trying
    S_noted=S; %note valve states, at start S is a NxN zero
%matrix--> all valves are closed
%set pressures based on valve states:
    P=P_new(P_old,C_old,C,S);
%then set valve states based on pressures:
    P_matrix=P*ones(1,N);
    S=((P_matrix) > (P_matrix'));
%done if all valve states are unchanged:
    done=all(all(S==S_noted));
end
```

The main program for simulating the entire circulation cycle is as follows:

```
%main program for the whole circulation simlation
global T TS tauS tauD;
global G dt CHECK N;
in_circ_2 %initialize
for klok=1:klokmax
    t=klok*dt;
    P_old=P;
    C_old=C;
%find current values of left and right ventricular compliance and
store each
%of them in the appropriate slot in the array C:
    C(iLV)=CV_now(t,CLVS,CLVD);
    C(iRV)=CV_now(t,CRVS,CRVD);
%find self-consistent valve states and pressures:
    set_valves
%store variables in arrays for future plotting:
    t_plot(klok)=t;
    C_plot(:,klok)=C;
    P_plot(:,klok)=P;
    V_plot(:,klok)=Vd+C.*P;
    Pdiff=P(iU)-P(iD); %pressure differences for flows of
interest:
    Q_plot(:,klok)=(Gf.*(Pdiff>0)+Gr.*(Pdiff<0)).*Pdiff;
```

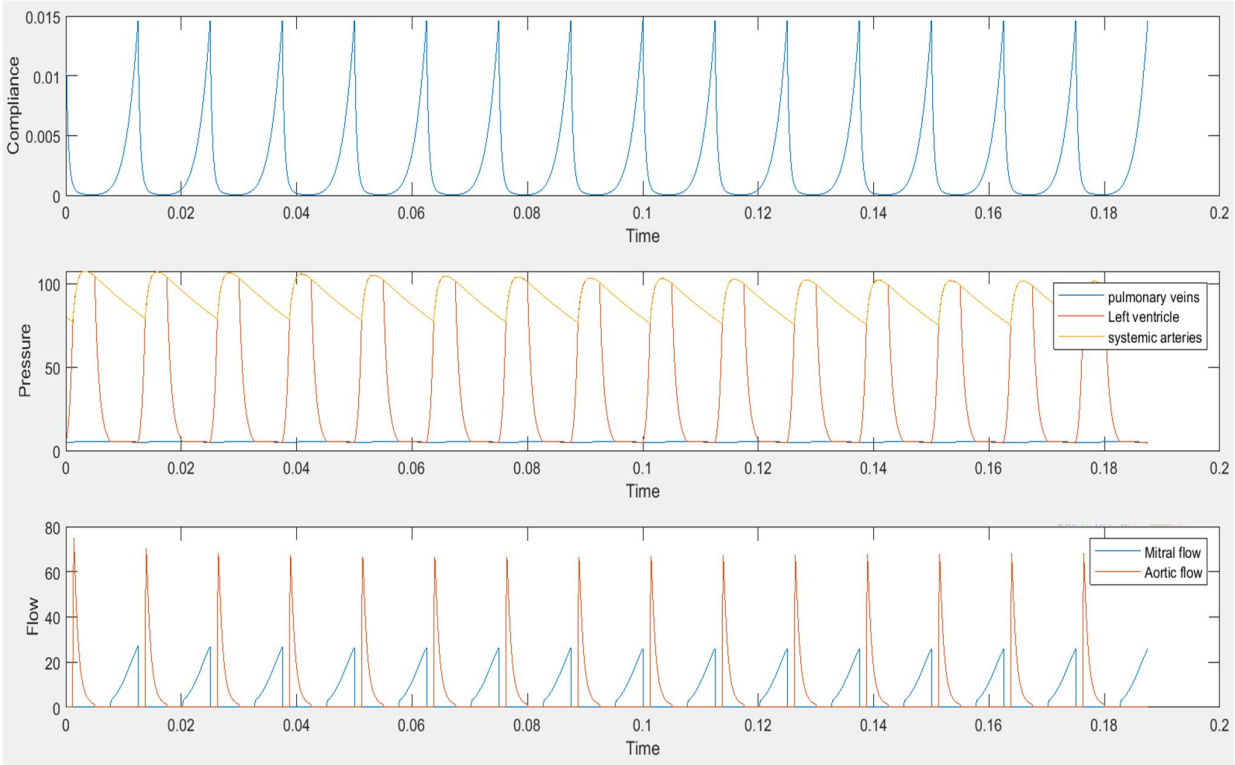
```
    Pdiff_plot(:,klok)=Pdiff;
%(the net flow is computed in each case)
end
%plot results:
plots
```

Chapter 2: The outputs of the simulation

2.1 Physical variable outputs in the left ventricle

In our model, compliance is a function of time that drives cardiac circulation. Indeed, the three physical variables needed to describe cardiac circulation change as compliance changes with time. The next figure comprises three plots, in which time is always on the *x* axis with a physical variable on the y-axis, that illustrate how compliance (plot 1), pressures (plot 2) and flows (plot 3) change with time in the left ventricle over 15 heart beats. We take time zero to be at end-diastole, when left ventricle compliance reaches its peak value.

Figure1

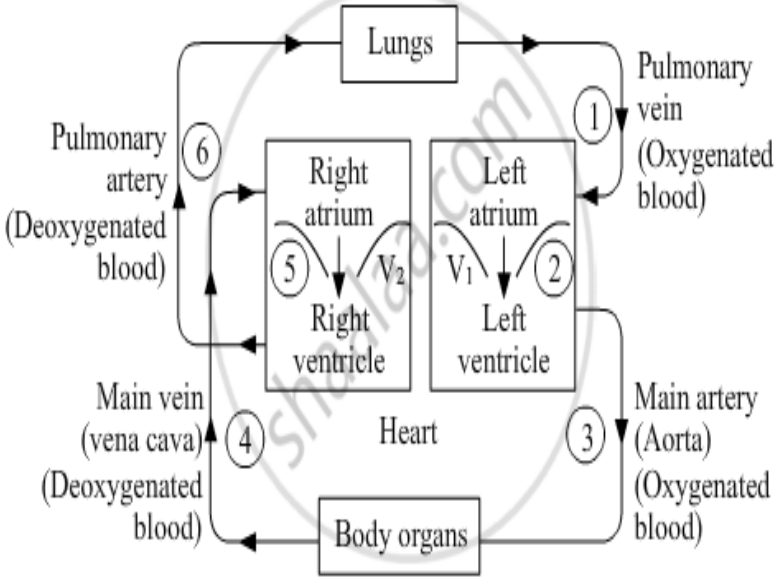


Diastole:

For instance, let us consider time 0.02. In our model, at this time on the x-axis, cardiac circulation enters the diastole phase. Thus, the compliance function in plot1 begins to rise until it reaches its peak, which corresponds to the end of diastole. Throughout this period, from 0.02 to peak, the states of the aortic valve and mitral valve in our MATLAB script are: S_{Ao}=0 (closed), S_{Mi}=1 (open). This is due to the values that the pressure in the systemic arteries, left ventricle, and pulmonary veins takes on during diastole: throughout this time interval, the pressure in the systemic arteries is higher

than the pressure in the left ventricle, while the pressure in the pulmonary veins is also higher than pressure in the left ventricle ($P_{sa} > P_{lv} > P_{pv}$). A valve opens when upstream pressure is higher than downstream pressure.

Because of the states of the aortic and mitral valves (*aortic closed, mitral open*), any blood that enters the left atrium from the venous pulmonary circulation circuit passes directly into the left ventricle, hence the steady rise in ventricular volume during the diastolic portion of the cardiac cycle. Diastole ends when the ventricle reaches its maximum volume. It is crucial to note that in our model we do NOT simulate the left and right atriums; nevertheless, the levels of pressure in the systemic arteries and pulmonary veins during diastole are essentially the same as the levels of pressure in the right and left atriums, respectively.



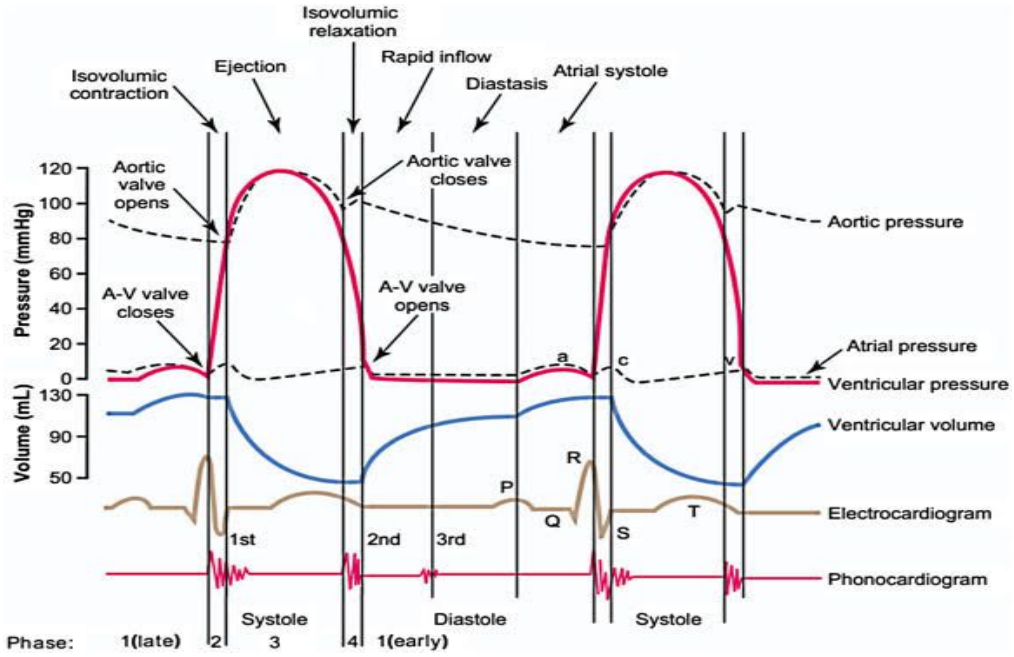
Systole:

At the end of diastole, contraction of the ventricle begins (*systole*) as its pressure starts to increase. In early systole, as shown in plot2 just before time 0.04, for a very short interval of time the systematic artery pressure (*orange*) is higher than the ventricular pressure (*red*) which is higher than the pulmonary vein pressure (*blue*). Thus, the ventricle contracts with no corresponding volume change (*isovolumetrically*). This brief portion of the cardiac cycle takes place while both mitral and aortic valves are closed, and we refer to this event as isovolumetric contraction. During this short period, the left ventricle contracts until its pressure exceeds systemic artery pressure, which happens at time 0.04 in plot 2, when the red function rises above the orange function. At this point, the aortic valve opens, resulting in ventricular ejection.

During late systole, the pressure in the systemic arteries is still lower than ventricular pressure, so that blood continues to be ejected out of the heart. Toward the end of systole, the aortic valve closes because left ventricular pressure drops below systemic artery pressure, and the ventricle enters the isovolumic relaxation phase (*both valves closed*), marking the beginning of diastole. At the beginning of diastole, the pressure in the ventricle drops, once again falling below pulmonary vein pressure, implying the opening of the mitral valve. At this point, diastole continues until the ventricle begins to contract and the mitral valve closes once again. As mentioned above, during the entire diastolic phase, the left ventricle is filling with blood.

From plot 2 it is very clear that the diastole phase lasts much longer than systole. Indeed, the pressure in the ventricle is higher than the pressure in the systemic arteries for a very limited range of values on the x-axis, while the inverse holds for a far greater number of values.

Our simulation offers a very good match for the theoretical model represented below (Ali Ostadfar, PhD in Biofluid Mechanics, 2016). The main differences are due to the fact that we have chosen to model pulmonary vein pressure instead of the atrial pressure. Moreover, we do not simulate electrocardiogram or phonocardiogram readings.



From A.C. Guyton, J.E. Hall, Textbook of Medical Physiology, eleventh ed., Elsevier, Inc., Philadelphia, PA, 2006

2.2 Left ventricle volume

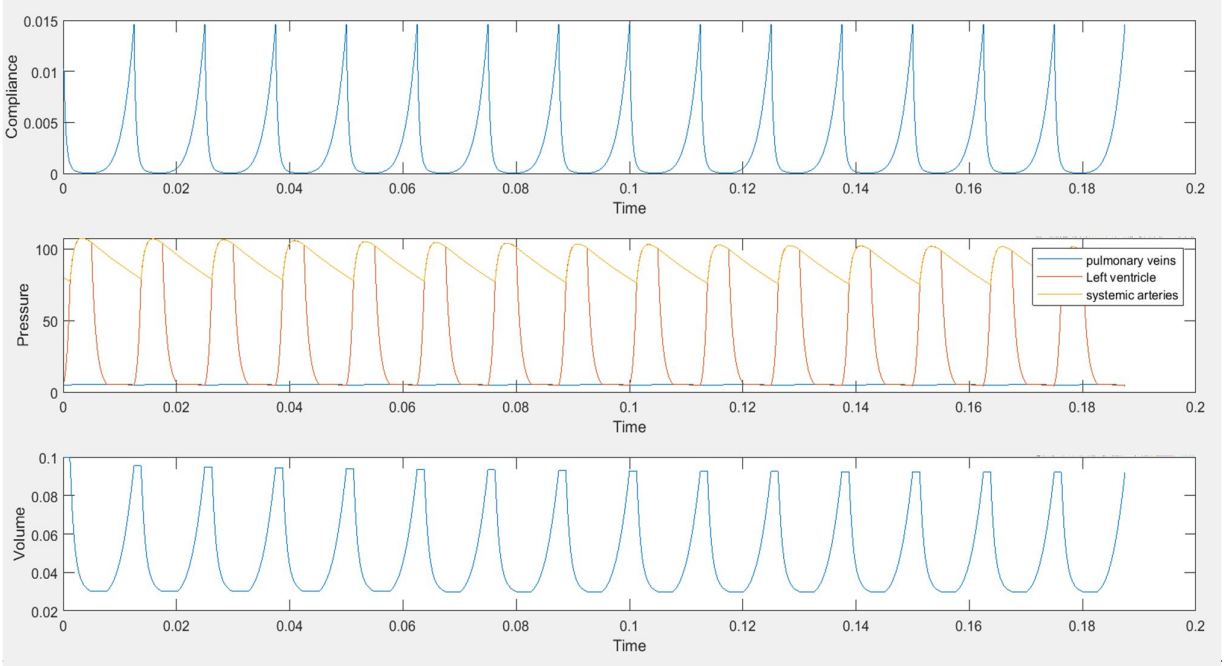
Initially, ventricular filling is very rapid because of the relatively large pressure gradient between the pulmonary veins and the ventricle. The pressure in the ventricle continues to slightly decrease after the mitral valve opens because of continued ventricular relaxation (*see in figure 2, plot 2 beginning*

at time 0.02 when the red function drops below the blue function). Its subsequent increase slows down ventricular filling.

During diastole, the mitral valve is open, and the left atrium forces any blood into the left ventricle, effectively priming the ventricle for contraction. This priming action occurs because during much of left ventricular diastole, pulmonary vein pressure is higher than the left ventricular pressure. Any blood that enters the left atrium from the venous pulmonary circulation passes directly into the left ventricle, hence the steady rise in ventricular volume during the diastolic portion of the cardiac cycle. At the beginning of systole, there is a rapid increase in ventricular pressure due to ventricle contraction. This is associated with the closing of the mitral valve and isovolumic contraction of the ventricle. The left ventricle contracts for a short amount of time without losing volume because both the mitral valve and the aortic valve are closed. As the pressure in the ventricle rises above the pressure in the systemic arteries, the aortic valve opens, and thus the left ventricle ejects blood into the systemic circulation circuit, thereby losing most of its volume. Toward the end of systole, the ventricle enters the **isovolumic relaxation phase** (*both valves are closed*) and its volume remains constant until its pressure falls below the pressure in the pulmonary veins.

Plot 3 in the following figure shows how the volume in the left ventricle changes with time.

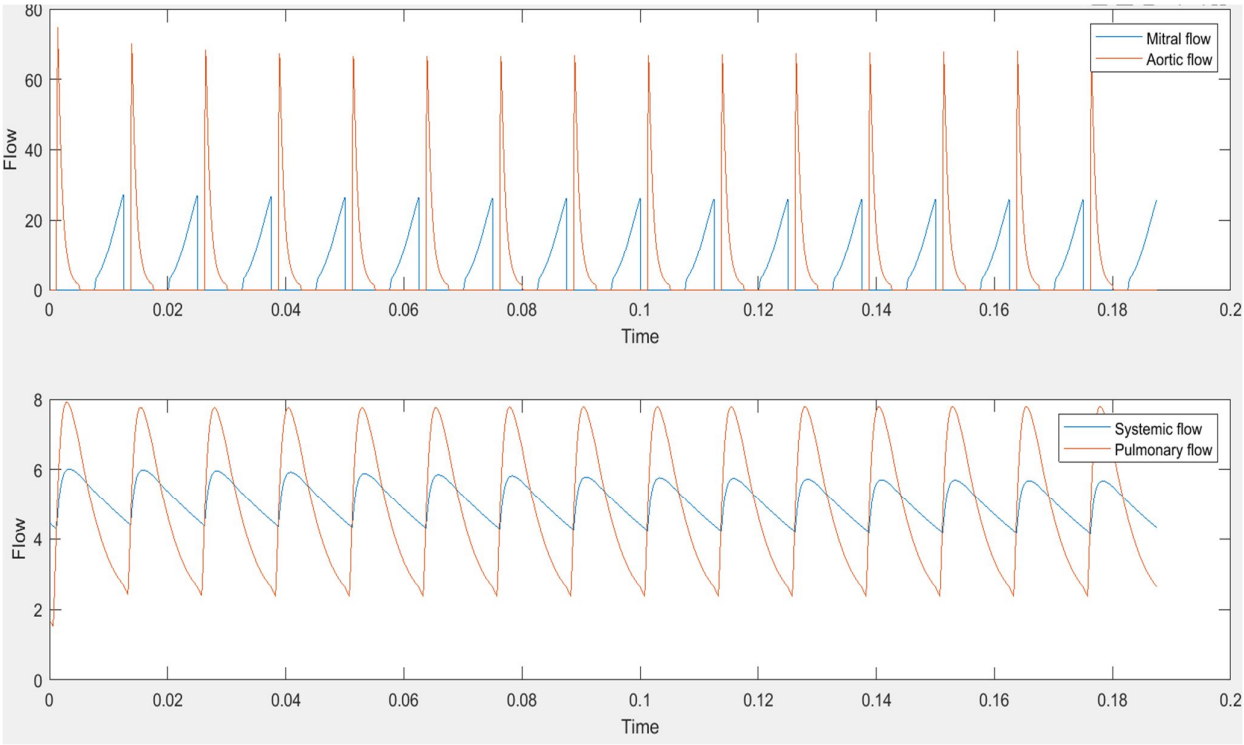
Figure 2



2.3 Inflow and outflow outputs in the left ventricle

This entire process is confirmed by the functions of the flows (see figure 3, plot1) . This plot shows how the mitral and aortic flows change with time. Throughout diastole (from time 0.02), as mentioned above, the aortic valve is closed and the mitral valve open, which means that the aortic flow is zero (red function) while the mitral flow increases rapidly (blue function). At the beginning of systole, during isovolumetric contraction, both functions are zero because both valves are closed. This confirms what we illustrated above. As the left ventricle's pressure rises above systemic artery pressure, the aortic valve opens, and the left ventricle ejects blood into the arteries, which explains why aortic flow rises rapidly. Obviously, the mitral flow stays equal to zero throughout systole given that the mitral valve is closed.

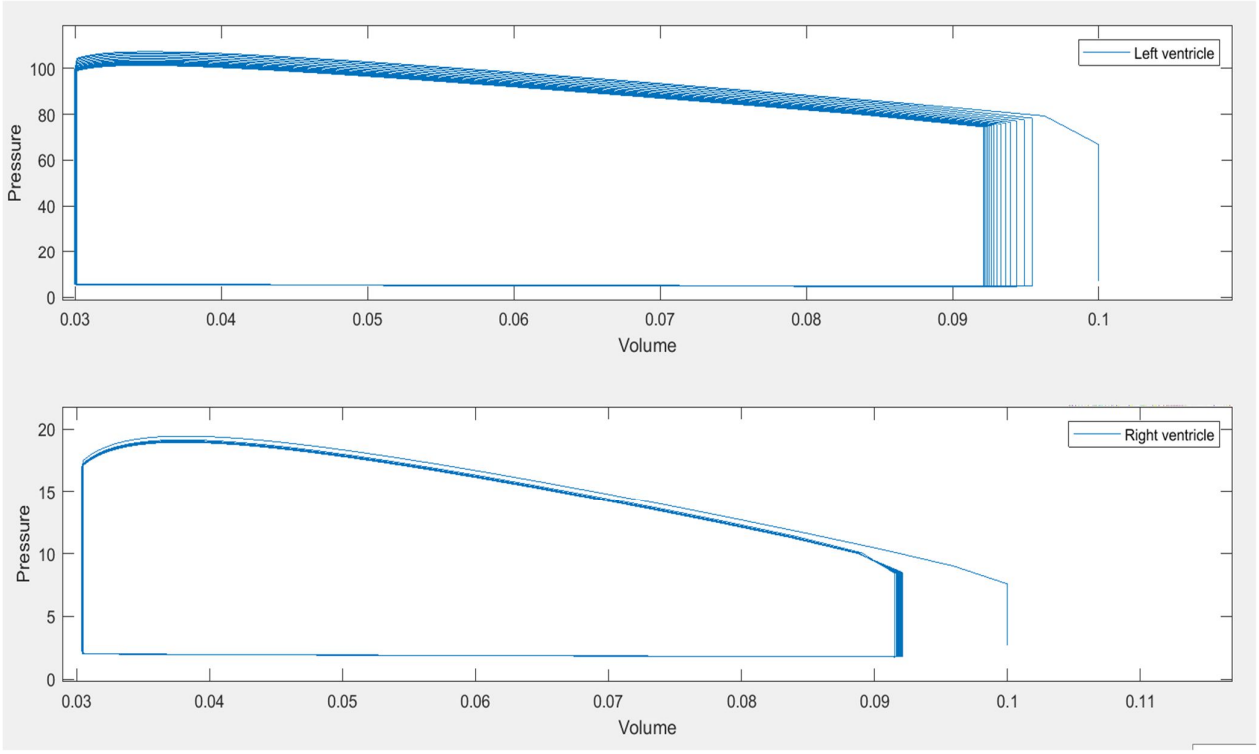
Figure 3



2.4 Pressure-volume loops

The following figure shows how the volumes of the left and right ventricles vary with pressure over 15 heart beats, shown as 15 loops. The bottom plot is for the right ventricle while the top plot is for the left ventricle.

Figure 4



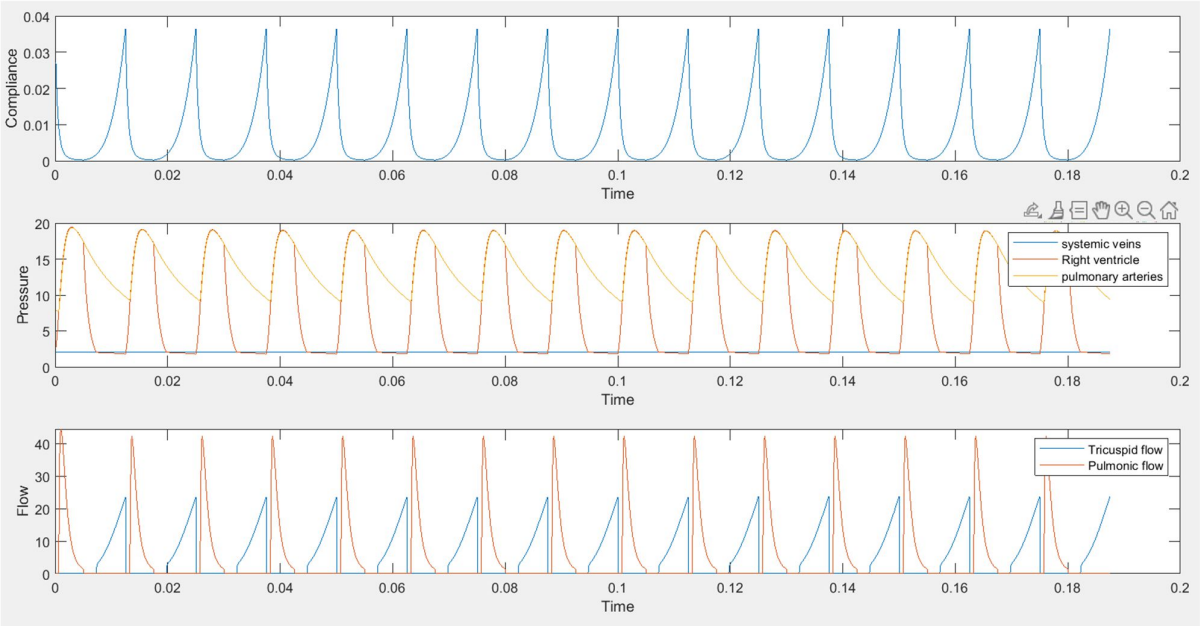
The two plots show volume on the x-axis and on the y-axes the pressure in the left and right ventricles, respectively. Let us now describe the plot1 from the beginning of systole, when volume has already peaked. As discussed, at the very beginning of systole, both valves are closed (isovolumetric contraction) and, as pressure rises, the ventricle starts to contract with no corresponding volume change. We can observe this in the plot: for each loop, the function rises vertically (on the right side of the plot) meaning that volume is not changing while pressure is rising very fast. Then the function continues to rise on the y-axis but, in contrast, to fall on the x-axis. This happens because when pressure gets high enough, the aortic valve opens and the volume in the ventricle starts to decrease until pressure stops rising and the cardiac circulation cycle reaches the isovolumic relaxation phase. The latter event is shown on the left side of the plot, where for each loop the function decreases vertically, meaning that the volume is remaining constant while pressure is falling rapidly. This marks the beginning of diastole. It may be observed that the function at this point runs parallel with the x-axis. Indeed, when pressure goes low enough, the mitral valve opens and the ventricle starts filling with blood and increasing its volume. This is possible because the ventricle is relaxed (pressure is very low) during diastole. The filling continues until the ventricle begins to contract and the mitral valve closes once again.

2.5 The right ventricle

The process in the right ventricle is very similar. Pressure may be also be expressed as a function of the pump coefficient of the ventricle (*K*) and the flow rate of the system (*Q*) by the following relation: P = Q/K

If *Q* is assumed to be constant, then as *K* increases, the pressure decreases. The pump coefficient for the right side of the heart is 2.8, which is more than double that of the left heart (1.12). Thus, the pressures on the right side of the heart should be much lower, which is what we can observe in the following figure:

Figure 5



In the left ventricle, peak pressure attains values in excess of 100. In the right ventricle, for each heartbeat, pressure is lower than 20.

Chapter 3: Simulation of aortic stenosis

3.1 How to simulate aortic stenosis

Let us recall that the left heart has an inflow (mitral) and an outflow (aortic) valve. A heart valve can malfunction in either of two distinct ways (or in some combination of the two). These are "stenosis," in which the valve is narrowed and presents a high resistance to forward flow, and "incompetence" or "insufficiency," in which the valve is leaky and fails to prevent backflow. In our model of the left heart and systemic arteries, stenosis is easy to model given that the necessary parameters are already included in the model: R_{Mi} (resistance of the mitral valve) and R_{Ao} (resistance of the aortic valve). These two values can be controlled in our model, thus increasing either of these resistances simulates stenosis of the corresponding valve. After we have done this, we can observe the effects on stroke volume, left ventricular blood pressures, and systemic arterial blood pressure.

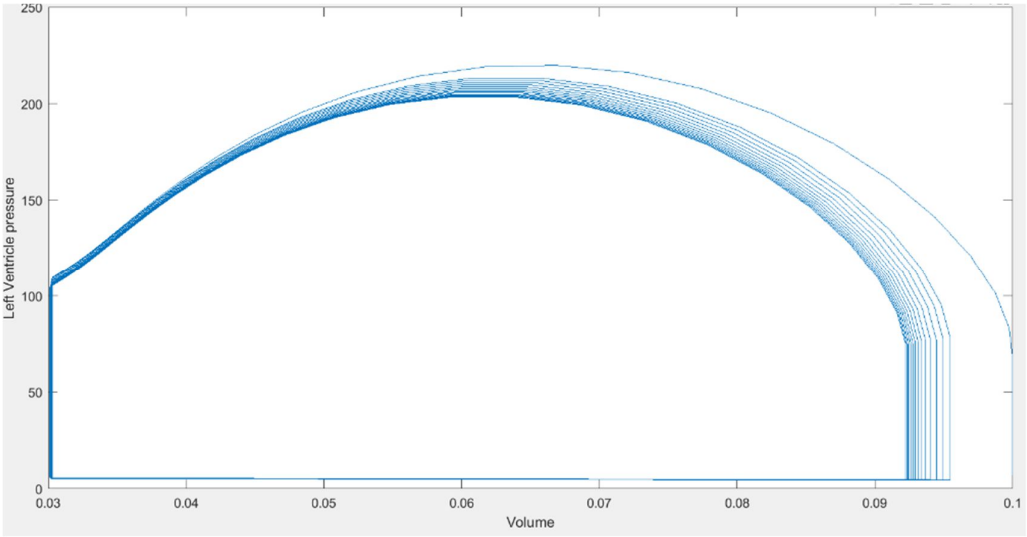
In the present project, our focus is on aortic stenosis. One of the main complications caused by a narrower aortic valve is outflow obstruction from the left ventricle. This requires the left heart to generate excess pressure to pump enough blood into the systemic arteries. In other words, if the valve is tighter than usual, then the pressure in the left ventricle must be raised significantly to pump the 'normal condition stroke volume' into the next chamber.

Pressure overload in the left ventricle may be used to evaluate the intensity of aortic stenosis. Thus, the difference between peak pressure in the left ventricle and systemic arteries, or peak pressure gradient, is a good surrogate measure of aortic stenosis severity.

The following plots show how stroke volume, left ventricular pressure, systemic artery pressure, and aortic peak pressure gradient change, if we set aortic valve resistance equal to 3 (this value corresponds to an extreme case of aortic stenosis).

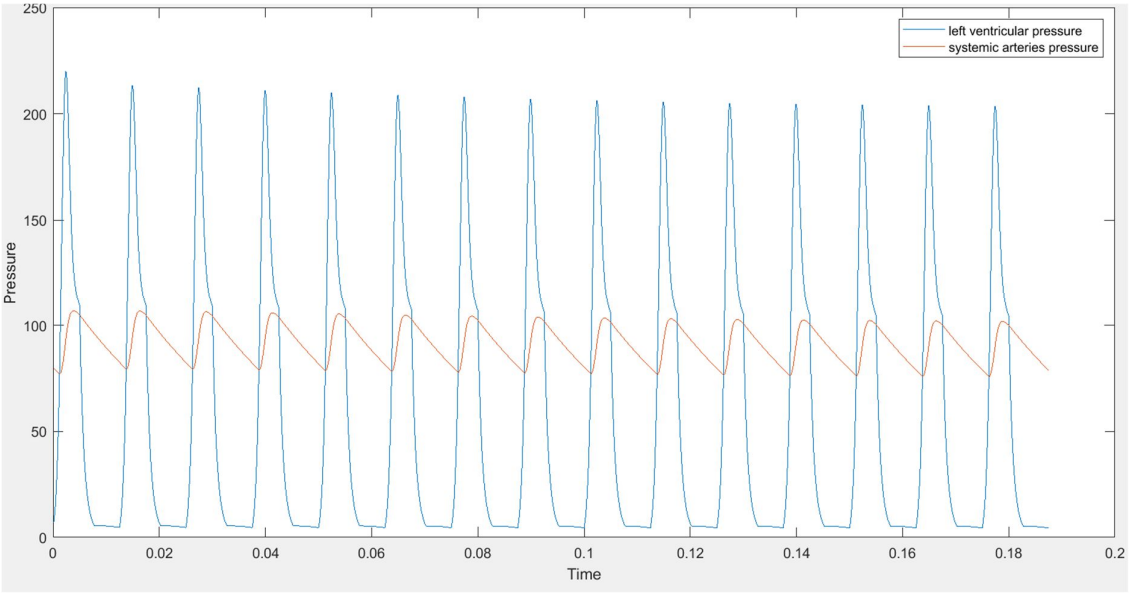
In the following figure, we may observe how, in order to maintain a regular left ventricular outflow of blood, pressure needs to be a lot higher than under normal conditions. (See Figure 4, plot1 for a representation of how pressure in the left ventricle behaves in the absence of aortic stenosis).

Figure 6



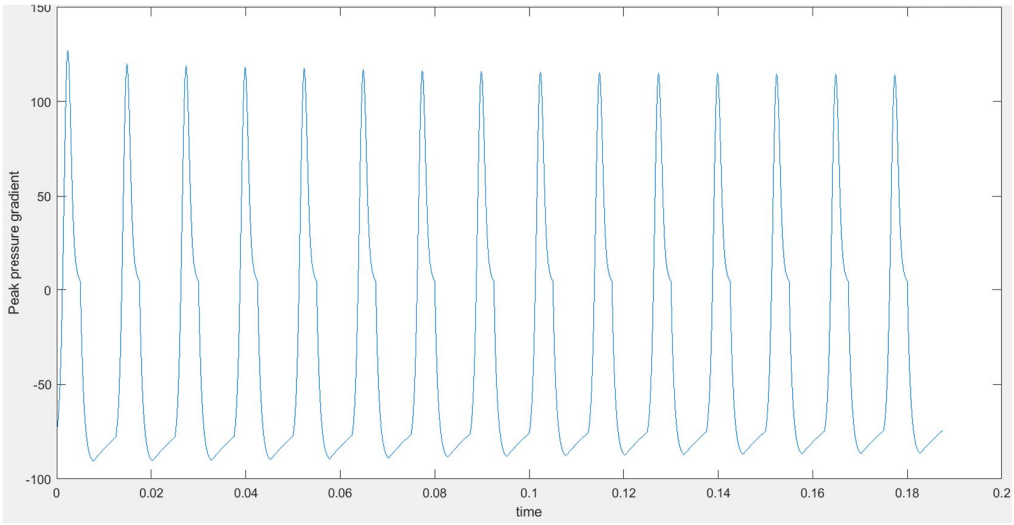
The next figure shows how left ventricular pressure and systemic artery pressure change with time. If we look at Figure 1 (plot2), it is evident that the difference between these two quantities gets much greater when the aortic valve is narrower, just as in this case.

Figure 7



Obviously, this implies that aortic peak pressure gradient is greater during systole. Under normal conditions, peak pressure gradient should be lower than 10. Here we can observe that the difference between peak pressures in the left ventricle and systemic arteries is over 100 for each heartbeat:

Figure 8



Thus, by changing aortic valve resistance in our model, we can simulate different values of peak pressure gradient. While we should keep in mind the fact that the primary measure of stenosis is the resistance of the aortic valve, this variable can only be directly measured via a highly invasive procedure that is not generally performed on patients due to the risks involved. Instead, surrogate measures such as peak pressure gradient are used. These are based on a Dopploer ultrasound measurement that is not invasive and easy to perform.

3.2 An alternative to clinical trials

Moreover, in many cases, aortic stenosis leads to aortic valve replacement with artificial valves. This procedure can be quite risky given that it involves the insertion of a catheter in the patient's chest and heart. Other issues include the fact that some people with aortic valve disease may not be candidates for traditional open-heart surgery due to other health problems.

Hence the importance of computational modelling and simulations. First, simulations can reduce our reliance on animal models and human data for proving the efficacy and safety of medical products. They can be useful to measure parameters that are difficult to evaluate in real patients (such as aortic resistance in our case) and they can offer an opportunity to address questions that we cannot address clinically. Furthermore, simulations facilitate assessment of a medical device, such as an artificial valve, in populations that cannot be investigated clinically, such as patients with rare diseases or pediatric patients.

The next steps in the project consist in using our model to convert peak pressure gradient from real patient clinical data into aortic resistance values and testing the model used to do this. Once this has been done, we may use the simulation to test new devices. For instance, suppose a client has experience with Valve A and a modified version Valve A.1. Then a new valve design is developed (Valve B) that is completely different and would require a new series of studies with hundreds of subjects to demonstrate its efficacy. Instead, we can test hundreds of valves in a lab, and obtain the distribution data of the resistances of hundreds of valves. We can then use the model (since it has been tested) to convert this data into simulated trial results demonstrating that peak pressure gradient (PPG) performance is similar to that of past devices. A small study of 40 subjects will then be sufficient to validate the simulated results.

3.3 Model verification by linear interpolation

To progress towards this goal, we next analyze a dataset from three different studies in which each row represents a subject. For each observation, two values of PPG are reported: a preoperative measurement (before valve replacement) and a discharge measurement (after valve replacement). Using SAS software, we created two tables, one for preoperative values and one for discharged values, where we evaluated for each study the mean, standard deviation, median, interquartile range, minimum, maximum, 95% confidence interval, and missing values for the observed Peak Pressure Gradient.

ANALYSIS AT PREOPERATIVE EXAMINATION: PEAK PRESSURE GRADIENT

	Overall N	Mean (SD)	Median (IQR)	Min, Max	95% Confidence Interval
Preoperative					
Peak Pressure Gradient - Simple Method (mmHg)					
Study 1	484	76.41(24.907)	72.20(33.20)	22.60,157.00	74.18, 78.63
Study 2	999	75.26(25.677)	74.00(31.00)	3.00,190.00	73.67, 76.86
Study 3	412	82.19(22.207)	77.62(26.40)	25.00,200.00	80.04, 84.34
Pooled - Fixed Effect	1895	77.06(24.903)	74.00(29.90)	3.00,200.00	75.94, 78.18

ANALYSIS AT DISCHARGE EXAMINATION: PEAK PRESSURE GRADIENT

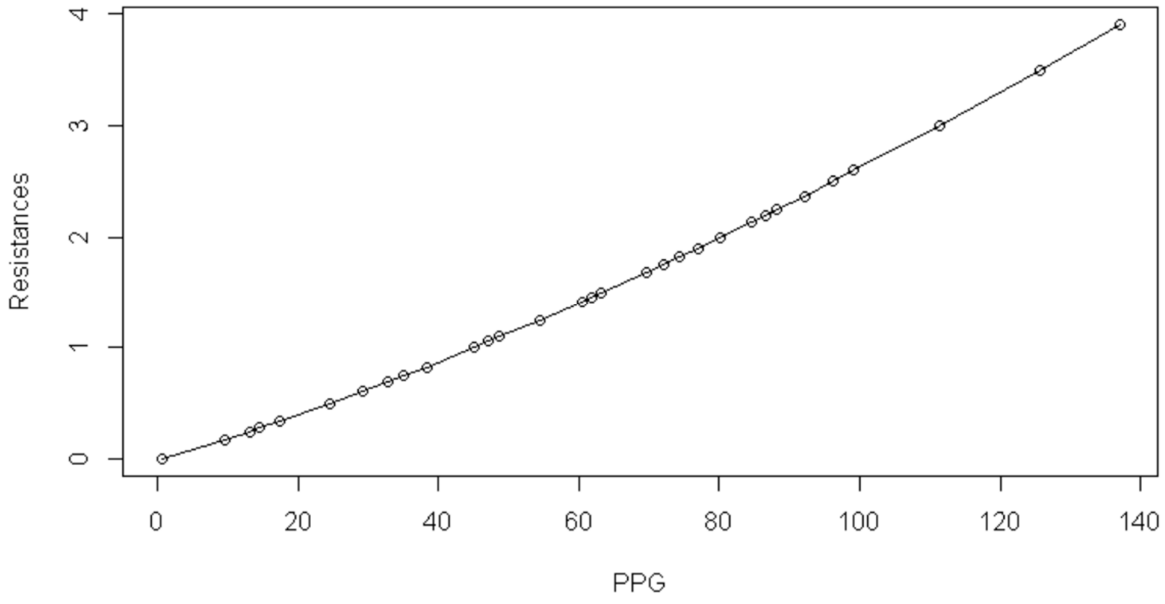
	Overall N	Mean (SD)	Median (IQR)	Min, Max	95% Confidence Interval
Discharge					
Peak Pressure Gradient - Simple method (mmHg)					
Study 1	495	25.61(9.172)	24.00(11.30)	6.70,64.50	24.67, 26.29
Study 2	574	24.43(10.357)	23.00(11.10)	4.00,129.00	23.76, 25.46
Study 3	257	28.82(10.480)	27.60(12.30)	9.60,70.00	27.59, 30.17
Pooled - Fixed Effect	1733	25.55(9.774)	24.00(11.03)	4.00,129.00	25.09, 26.01

Now we wish to run the simulation to build a curve that gives resistance as a function of PPG. After converting preoperative and discharge PPGs into resistances, we can produce a summary table of resistances similar to the PPG tables.

As mentioned earlier, our model includes controlled parameters such as resistance that may be changed freely to simulate various scenarios, and parameters such as peak pressure gradient that can only be observed. Our model is composed of nine equations and 9 unknown parameters and it would be challenging to estimate the inverse formula in order to arrive at resistance as a function of peak pressure gradient. This prevents us from simply inputting peak pressure gradient values and retrieving valve resistances.

Instead, we simulated 31 different values of PPG by varying the aortic resistance parameter in our model. In doing this, we wished to make sure that the PPG values obtained via the simulation were close enough, and that representative of the entire range of PPG values observed in the three clinical studies. The output of this procedure was a table comprising two columns: one column with 31 different aortic resistance values and one column with the corresponding PPG values. This table enabled us to build a curve that gives resistance as a function of PPG. To estimate valve resistance values that would correspond to peak pressure gradients falling between points in the table, we used linear interpolation. We adopted the latter strategy because each pair of consecutive PPG values in the table were close enough to assume that the curve between them was linear. The curve takes a quadratic form for the entire range of PPG values:

Figure 9



The following R-script converts Peak Pressure Gradient measures into resistances via the strategy outlined above:

```
#resistances values

y <- c(0.01, 0.18, 0.25, 0.28, 0.34, 0.5, 0.61, 0.7, 0.75, 0.83, 1,
1.06, 1.1, 1.25, 1.42, 1.46, 1.5, 1.68, 1.75, 1.82, 1.9, 2, 2.14,
2.2, 2.25, 2.37, 2.5, 2.6, 3, 3.5, 3.9)

# corresponding PPG values

x <- c(0.6, 9.6, 13.2, 14.6, 17.4, 24.6, 29.3, 32.9, 35, 38.4, 45,
47, 48.6, 54.4, 60.4, 61.8, 63.2, 69.6, 72, 74.4, 77, 80.08, 84.55,
86.65, 88.26, 92.25, 96.2, 99.2, 111.4, 125.7, 137)

#PPg values from a specific study

PPG_list <- data$AVAL

PPG<-rep(NA,length(PPG_list))

Resistance<-rep(NA,length(PPG_list))

#estimation of corresponding resistances

j=1

for (element in PPG_list) {
  if (j > length(data$AVARCOL)) {j = length(data$AVARCOL)}
  x_now = PPG_list[j]
  i=1
  while (i <= length(x)) {
    if (x[i] <= x_now && x_now <= x[i +1]) {
      new_resistance    =    y[i+1]    -    (x[i+1]-x_now)/(x[i+1]-
x[i])*(y[i+1]-y[i])
      PPG[j]<-x_now
      Resistance[j]<-new_resistance
      i = length(data$AVARCOL) + 5
    } else {i = i+1}
  }
  j = j+1
}
```

Once we had converted all PPG values from the dataset into resistances, we proceeded by generating two summary tables of resistances similar to the PPG tables.

ANALYSIS AT PREOPERATIVE EXAMINATION: AORTIC RESITANCE

	Overall N	Mean (SD)	Median (IQR)	Min, Max	95% Confidence Interval
Preoperative					
Peak Pressure Gradient - Simple Method (mmHg)					
Study 1	484	1.71(0.63)	1.73(0.88)	0.72,3.82	1.66, 1.77
Study 2	999	1.79(0.58)	1.74(0.93)	0.86,3.52	1.75, 1.82
Study 3	412	1.97(0.86)	1.86(1.17)	0.51,3.62	1.88, 2.05
Pooled - Fixed Effect	1895	1.82(0.74)	1.74(0.98)	0.51,3.82	1.78, 1.85

ANALYSIS AT DISCHARGE EXAMINATION: AORTIC RESITANCE

	Overall N	Mean (SD)	Median (IQR)	Min, Max	95% Confidence Interval
Discharge					
Peak Pressure Gradient - Simple method (mmHg)					
Study 1	495	0.51(0.15)	1.73(0.88)	0.72, 3.83	0.49, 0.52
Study 2	574	0.59(0.27)	0.53(0.26)	0.06,1.32	0.56, 0.61
Study 3	257	0.45(0.2)	0.39(0.17)	0.15,0.92	0.42, 0.47
Pooled - Fixed Effect	1733	0.54(0.25)	0.49(0.3)	0.06,3.83	0.52, 0.55

Conclusions

We constructed a general model capable of simulating the entire cardiac circulation cycle in various circumstances such mitral, pulmonic, or tricuspid valve disease, although our focus here has been on aortic stenosis and healthy conditions. Moreover, the model that we developed was tested on real patient clinical data which means that we could now use it as a complementary method of evaluation alongside animal models and clinical trials. Indeed, to demonstrate the efficacy of a new artificial valve, we could measure hundreds of resistances from hundreds of valves in a lab, then use the simulation to convert the resistances into simulated trial results and evaluate whether the peak pressure gradient performances were similar to past devices. Using a simulation eliminates, in new studies, the requirement to test a large number of subjects to demonstrate the efficacy of new devices. Instead, a much smaller study would be sufficient to validate the simulated results.

Computational modeling is a valuable regulatory tool because of the potential it offers to obtain significant cost-savings in evaluating medical devices, simulating performance under scenarios that may not be possible with human use or that can more effectively be evaluated via simulation. It can be used to simulate and better understand medical devices in several ways. For instance, by simulating the device under a variety of conditions that mimic some aspect of the clinical or use environment to investigate some aspect of the device's performance. An example of computational modeling as a medical device is the use of personalized simulation to indicate whether a patient is a candidate for a medical device or a pharmaceutical, for example, by simulating the effects of an invasive clinical procedure or a given dosage of a drug to predict an outcome before the therapy is selected.

Computational modeling can also be used to simulate treatment outcomes. Thus, modeling and simulations can offer a pathway towards exposing fewer patients to experimental therapies by drawing on other sources of evidence. It can offer an opportunity to address questions that we cannot address clinically due to financial or ethical considerations, and to investigate aspects of device performance in larger numbers of clinically relevant cases (hundreds of thousands as opposed to hundreds). Computational modeling can facilitate the exploration of using a medical device in populations that cannot be investigated clinically, such as in patients with rare diseases or pediatric patients. Computational modeling has also enabled the complete "in silico" simulation of clinical trials for medical imaging systems. This means having the possibility to implement different computational models to simulate the entire clinical evaluation of an imaging system, creating a "virtual clinical trial," where no patients are physically exposed to the imaging system. Lastly, knowledge-based tools may be harnessed to develop data-driven models from big data sources, such as real-world data, and deep learning methods deployed to gain key insights into medical device use and performance.

The rapid advance of technology has drastically changed the power and availability of computational modeling tools. With this increased capability and power, evidence from computational modeling has the potential to replace traditional data collection from other models. The power of this approach lies in the ability to replace expensive and lengthy clinical trials with completely in silico trials, where all aspects of the evaluation cycle can be simulated

with sufficient confidence to allow us to replace each step with simulation. The main objective of this approach is to achieve the same regulatory conclusion with virtual clinical trials as with a large 600-patient clinical trial. The success of this approach relies on statistical models, deep learning, and artificial intelligence. Such advanced analyses and statistical methods have the potential to dramatically transform the use of medical devices.

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