Influence of the coronary microcirculation on the epicardial pressure and flow dynamics: a model study

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Abstract

Coronary heart diseases is one of the main causes of death in the Western World. Currently, most quantitative diagnoses are based on indices based on the time-average of the pressure and flow signals. However, it is thought that also the dynamics of the pressure and flow signal in the large coronary arteries are influenced by some coronary diseases. Even diseases involving deterioration of the microcirculation from which the pressure and flow cannot be assessed. So dynamic measuring of the pressure and flow in those artery might reveal underlying diseases. Therefore, the aim of this study is to develop a model of the heart and the coronary circulation in order to investigate the influence of some diseases on the pressure and flow dynamics in the larger coronary arteries. The heart is modelled by the 1-fiber model, the vasculature by a lumped parameter model and the diseases can be modelled by varying some parameters of those models.
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Introduction

Coronary diseases are one of the main causes of death since 1990. Therefore much effort has been made to understand these diseases better in order to improve prevention, diagnosis and treatment. This resulted among others, in an improved diagnosis of the severity of a vessel narrowing (stenosis) in the coronary artery because the severity of a stenosis is no longer based on angiographic (2D projection) images but on quantitative indices based on time average coronary blood pressure and flow. In the introduction we will first discuss the anatomy, physiology and the influence of disease on those two (pathology). Then we will discuss the above mentioned quantitative indices in more detail to end with the aim of this report and how to achieve it.

Anatomy, physiology and pathology

Anatomy

The cardiac muscle receives its blood via the coronary arteries. The two (main) coronary arteries originate right behind the aortic valves; the right and (main) left coronary artery delivers blood to the right and left ventricle (LV) respectively. The left coronary artery splits into the left anterior descending (LAD) and the left circumflex (LCX) artery, which, respectively, supply the front and the back of the LV.

![Diagram of heart and coronary circulation](image)

**Figure 1:** The heart and the coronary circulation. Left the left ventricle, right the right ventricle. AV = atrioventricular, AVGA = atrioventricular groove artery, PDA = posterior descending artery, RCA = right coronary artery, RV = right ventricular, SA = sinoatrial from Sunil et al.

The main coronary arteries are all situated at the epicardium (epicardial coronary arteries). Smaller vessels originate from those arteries and penetrate into the myocardium. Close to the epicardium and endocardium they are respectively referred to as subepicardial and subendocardial coronary arteries. The coronary arteries and mainly the arterioles (small arteries) can change their radius by contracting the muscles in the vessel wall. These contractions regulate the amount of blood that flows through that artery and are regulated by chemical and mechanical demands of the heart. The state in which the arterioles are maximally relaxed is called hyperaemia. In a healthy heart, the coronary flow in hyperaemia is fivefold the flow at rest.
Physiology
Pressure and flow dynamics

The pressure and flow dynamics in the coronary circulation differ from the rest of the body because flow in the coronary artery is highest in diastole and the lowest in systole (as shown in Figure 2), while the flow in the coronary veins is (extra) high in systole and small in diastole. The reason for these dynamics is that due to the contraction of the heart muscle the pressure in the myocardium, $p_m$, increases. Several models exist to explain this behaviour.

According to the intramyocardial pump model the pressure in the vessel increases in systole because $p_m$ exerts on the vessel wall. This results in a smaller (or even negative) pressure gradient in the coronary arteries which results in an impeded (or even reversed) flow and causes a larger pressure gradient in the veins which enhances venous flow. Hence blood is squeezed out of the myocardium in systole. Furthermore, the resistance of the myocardial vessels increases due to the fact that their diameter reduces due to the rising extra vascular pressure.

Another way to describe the dynamics of the flow is the waterfall model, which state that vessels, mostly veins, might even collapse due to the extra vascular pressure. When the veins collapse, no blood can flow through so it impedes arterial flow.

In diastole the pressure in the myocardium falls rapidly due to the relaxation of the left ventricle. Hence blood is sucked back in to the myocardium which enhances arterial flow and impedes (or even reverses) venous flow. In fact this arterial flow in diastole is larger than in systole, which is the reason that a shorter diastole might cause heart complaints.

These characteristics of the flow in coronary arteries and veins are not seen in the subepicardial microcirculation (left pane of Figure 2). Although there is also negative flow in the microcirculation during early systole, still the most blood is transported, contrary to coronary arteries, during systole. Because the diameter of these vessels did not change much compared to the change in velocity the left figure of Figure 2 reflects the flow dynamics of the coronary microcirculation.

Pathologies

Several diseases affect the coronary microcirculation. Examples are Hypertrophic CardioMyopathy (HCM), diabetes, atherosclerosis and ischemic heart disease, which will be shortly discussed below.
HCM refers to a state of the heart in which the myocardium has substantially thickened (mild (13-15 mm) to massive (30 mm)) compared to normal (12 mm) and is mostly the result of arterial hypertension. Many symptoms can be associated with HCM; a high LV pressure, the existence of arterioles with abnormally thick walls and lumen and a decreased capillary density, which are likely to result in ischemia. HCM is also associated with a diastolic dysfunction in which impaired LV relaxation, increased chamber stiffness, and compromised left atrial systolic function impede filling, leading to elevated left atrial and LV-end-diastolic pressures with reduced stroke volume and cardiac output. It is also associated with a decrement of CFR, which is an index that will be discussed in the following section.

Diabetes can result in diabetic cardiomyopathy and is diagnosed when ventricular dysfunction develops in absence of atherosclerosis, hypertension and significant valvular disease. Left ventricular systolic and diastolic dysfunction, left ventricular hypertrophy, and alterations in the coronary microcirculation, like abnormal capillary permeability, micro aneurysm formation, subendothelial matrix deposition, endothelial dysfunction and fibrosis surrounding arterioles, have all been observed, although not consistently, in diabetic cardiomyopathy. Furthermore, stiffening of the arteries has been reported.

(Diffuse) atherosclerosis is the forming of plaques on the endothelium but does not necessarily result in obstruction of the epicardial coronaries. Still it impairs the microcirculation due to endothelium dysfunction. Typically the compliance is decreased which increases pulse pressure.

Ischemia is a result of a lack of oxygen and thus dying myocardial cells, which can be caused by many reasons, for example the diseases named above or a stenosis. Death myocardial cells are replaced by scar tissue which experiences no active stress due to contraction of the heart muscle and has different mechanical properties. Kohl et al. found that acute myocardial ischemia impaired left ventriculo-arterial coupling due to a combination of augmented arterial elastance, secondary to early vasoconstriction later associated with decreased arterial compliance, and decreased LV contractility.

Indices

In order to be able to quantify the severity of diseases, quantitative indices based on the time-average intracoronary pressure and flow signal have been developed. This was possible due to the fact that new techniques to measure flow and pressure in the coronary circulation have become available.

Examples of these quantitative indices are CFR (Cardiac Flow Reserve), FFR (Fractional Flow Reserve), IMR (Index of Microcirculatory Resistance) and HSR (Hyperaemic stenosis Resistance Index).

CFR is defined as the ratio between the resting to hyperaemic coronary flow. Hence, it is a measure for the ability of the heart to increase its coronary flow. Drawbacks of this index relate to the determination of resting flow and its dependency on heart rate and pressure. Furthermore, this index makes no distinction between a diminishing flow due to coronary arterial occlusion or declining micro circulatory functioning.

An index with a superior reproducibility compared to CFR, is FFR, which is a measure for the decline of flow due to a stenosis. FFR is defined as the ratio between the hyperaemic flow with and without a stenosis, which can be approximated by the ratio between the pressure proximal and distal to a stenosis.

Another index with comparable reproducibility is IMR. IMR relates to the true resistance of the microcirculation and is therefore a measure for the condition of the microcirculation. IMR is determined with thermodilution. With thermodilution, the temperature is measured at two places in the artery: at the shaft of the catheter and distal to the shaft, at the tip of a wire coming out of the catheter (see Figure 3). Then a cold bolus of saline is injected proximal to the first thermistor: the first thermistor registers when the saline enters the coronary tree and from the temperature-time curve of the second thermistor (thermodilution curve) it can be calculated on average, how much time it takes for the flow to get from the first to the second thermistor: the mean transit time. The mean transit time is a measure for the flow.
IMR is then defined as the distal coronary pressure divided by the inverse of the mean transit time in hyperaemia. When the coronary pressure is measured distal or in absence of a stenosis and simultaneously with the mean transit time in hyperaemia, the microvascular resistance is evaluated independent of epicardial stenoses.

Another index which uses both flow and pressure is HSR. Flow and pressure are simultaneously measured with a 0.014-inch dual-sensor (pressure and Doppler velocity) guidewire, which has become only recently available\textsuperscript{25}. HSR is defined as the ratio of mean transstenotic pressure gradient to the average peak flow velocity and has better predictive abilities then FFR and CFR\textsuperscript{29}.

So the possibility of measuring flow and pressure simultaneously has led to indices which can better quantify the severity of a stenosis or the deterioration of the microcirculation. In addition to the preceding time-averaged parameters, it is, only since recently, possible to measure continuously and simultaneously both pressure and flow\textsuperscript{33,34}. This enables the investigation of the dynamics of the pressure and flow and their relation with coronary diseases.

It is hypothesized that the dynamics of the epicardial pressure and flow can predict the condition of the coronary microcirculation and thus diseases that alter the microcirculation. Krams et al. already showed for HCM\textsuperscript{35} that, by observing the dynamics of coronary pressure and flow, it is possible to find an index related to the degree of HCM. Because this might be possible for other diseases that alter the coronary microcirculation, like diabetes\textsuperscript{36}, hypertrophic cardiomyopathy (HCM)\textsuperscript{37,38}, (diffuse) atherosclerosis\textsuperscript{39} and ischemic heart disease\textsuperscript{40}, more knowledge about the microcirculation and how these diseases influence the microcirculation, is required. The diseases mentioned here are of particular interest because 10-30\% of the patients with angina pectoris who underwent angiography have no sign of obstructive stenosis and cannot be diagnosed\textsuperscript{41}.

Furthermore, it should be investigated how these changes change the dynamics of the epicardial arteries because it is not possible measure pressure and flow dynamics directly in the microcirculation but only in the epicardial arteries.

Therefore, the aim of this report is to develop a model of the coronary circulation in which the effect of microvascular diseases on epicardial pressure and flow dynamics can be investigated and to make a start with the actual modelling of those diseases.
To that end, a lumped parameter model of the circulation is constructed using the DISCO\textsuperscript{57} software. Parameters in this model can be altered in order to simulate coronary diseases, in this study it is chosen to model HCM. Furthermore, because the time-signals of coronary pressure and flow are highly influenced by the contraction of the heart muscle, the contraction should be modelled as well. Several models are available which try to do so; in this study the model as proposed by Bovendeerd et al.\textsuperscript{42} is used because of the small amount of parameters. These few parameters can also be changed to model some coronary diseases.
Method

Circulation model

A lumped parameter model
The model of the blood circulation divides the complete circulation into different segments. See Figure 4.

![Diagram of blood circulation](image)

Figure 4: Schematic representation of the blood circulation

Every segment of vein or artery can be modelled by three elements: 1 resistance, inertia and compliance element (see Figure 5).

![Diagram of blood vessel segment](image)

Figure 5: Electric representation of a blood vessel segment
By varying the values of the elements, it is possible to give each segment the fluid-dynamical properties of the type of artery or vein they should represent. For some segments the inertia is small enough to be neglected. Furthermore, the segments of the systemic circulation are modelled as symmetric elements. This means that the value of the compliance of the segment is divided over its two capacitors, in order to reduce the error made by lumping of the parameters\(^3\). The electric representation of the model is shown in Figure 6.

In each node, which are all numbered in Figure 6, the pressure and flow will be determined. All compliances are grounded, meaning zero pressure outside the vessel wall; except for the nodes 11 and 15 because left ventricular and intramyocardial pressure are respectively prescribed on those nodes. Hence the intramyocardial pump model\(^4\) is used to model the coronary pressure-flow dynamics. The valves are modelled as diodes with a resistance of 5 MPa·s/m\(^3\) for aortic valve and 0.5 MPa·s/m\(^3\) for the mitral valve. The mitral valve resistance is about equal and aortic valve resistance is 2-5 times higher compared to values found in literature\(^5,6\) in order to obtain a stable solution. All other values are chosen according to Bovendeerd\(^7\).

**Implementation**

From the electric scheme of Figure 6, it is possible to derive a set of linear differential equations which should agree with:

\[
\dot{p}_c = \frac{V - V_0}{C} \quad (1)
\]

\[
\Delta p_R = Rq \quad (2)
\]

\[
\Delta p_L = L\dot{q} \quad (3)
\]
Where \( \dot{p}_C \) is the time derivative of the pressure drop over a capacitance, \( q \) is the flow, \( C \) is the capacitance, \( \Delta p_R \) and \( \Delta p_L \) are the pressure drop over a resistance and inertia element, respectively. \( R \) is the resistance, and \( L \) is the inertia constant.

Every element (capacitor, inductance, resistance) is associated with two nodes, namely the one before and the one after the element. For those nodes, Equations (1) - (3) can be written as the following equation

\[
A \ddot{p} + B \dot{p} + Cp = \dot{q}
\]  

(4)

Where \( A = \begin{bmatrix} -1 & 1 \\ 1 & -1 \end{bmatrix} \), \( B = \begin{bmatrix} -1 & 1 \\ 1 & -1 \end{bmatrix} \), \( R = \begin{bmatrix} -1 & 1 \\ 1 & -1 \end{bmatrix} \), \( L = \begin{bmatrix} -1 & 1 \\ 1 & -1 \end{bmatrix} \), \( \dot{q} \) is the flow and \( ?, ?, ? \) are the pressure and its first and second order derivative in the nodes respectively, \( C \) is the compliance, \( R \) is the resistance and \( L \) is the inductance of the element.

DISCO\textsuperscript{47} assembles these equations of all the nodes in one equation and solves this equation with the implicit Euler method as integration scheme, taking in account the boundary conditions (\( p = p_{in} \) at node 11, \( p = p_{out} \) at node 15 and \( p = 0 \) at node 3, 7, 9, 13 and 17) iteration is performed using the Newton-Rhapson method with a convergence criterion of \( 10^{-3} \). The time step is 5 ms.
Heart model

From preceding sections is clear that it is necessary to determine p\textsubscript{LV} and p\textsubscript{m} to model the coronary pressure-flow dynamics. Both p\textsubscript{m} and p\textsubscript{LV} are determined as in the heart model developed by Arts et al.\textsuperscript{48} and extended by Bovendeerd et al.\textsuperscript{42}. Their model couples the behaviour of the sarcomeres to the change of left ventricle volume, by determining the stress and strain in one myofiber and extrapolates the strain to change of volume of the whole LV. The change of volume changes LV pressure. Advantages of this model are its simplicity and small amount of necessary parameters. The resulting equation and the main assumptions are presented below. The reader is referred to Bovendeerd et al.\textsuperscript{42} for the derivation of this model.

Left ventricle pressure

The LV is represented as a thick walled sphere of thin nested shells and the p\textsubscript{LV} as the sum of the radial stress of all these shells. Together with the assumption that the fibre stress is equal through the wall, Bovendeerd et al. derived the following equation for the p\textsubscript{LV} in which macroscopic values as p\textsubscript{LV} and V\textsubscript{LV} are coupled to the microscopic stresses \(\sigma_f\) and \(\sigma_{m,r}\):

\[
p_{LV} = (\sigma_f - 2\sigma_{m,r}(\bar{r})) \ln \left( \frac{r_{out}}{r_{in}} \right) = \frac{1}{3}(\sigma_f - 2\sigma_{m,r}) \ln \left( 1 + \frac{V_w}{V_{LV}} \right)
\]

(5)

Here are \(\sigma_f\), \(\sigma_{m,r}\), and \(\sigma_{m,w}\) the fiber stress, the stress of the matrix in radial direction and the stress of the matrix in radial direction at a representative distance \(\bar{r}\). \(r_{in}\) and \(r_{out}\) are the radii of the shells containing the LV and the LV together with the wall respectively.

Intra myocardial pressure

Arts et al.\textsuperscript{48} showed that a relation between stretch ratio of the fibres and V\textsubscript{w} and V\textsubscript{LV} exists. Namely, the stretch ratio of the sarcomeres (l/l\textsubscript{0}) corresponds to the circumferential stretch ratio of a shell that contains the V\textsubscript{LV} and one third of the V\textsubscript{w}. The latter stretch ratio is represented in the right hand side of the following relation under the assumption that the LV is a sphere.

\[
\lambda_f = \frac{l}{l_0} \approx \left( \frac{V_{LV} + \frac{1}{3}V_w}{V_{LV0} + \frac{1}{3}V_w} \right)^{\frac{1}{3}}
\]

(6)

With \(\lambda_f\) the fibre stretch ratio, l\textsubscript{0} the sarcomere length, l\textsubscript{0} and V\textsubscript{LV0} the sarcomere length and the cavity volume of the LV at zero transmural pressure.

V\textsubscript{LV}, V\textsubscript{w} and p\textsubscript{LV} are coupled to the strain of fibres and matrix. Their stress is modelled according to Bovendeerd\textsuperscript{42}. Hence, the passive stress in fibre direction, \(\sigma_{m,f}\):

\[
\sigma_{m,f}(\lambda_f) = \begin{cases} 
\sigma_{f,0}(\exp[c_f(\lambda_f - 1)] - 1) & \lambda_f \geq 1 \\
0 & \lambda_f < 1 
\end{cases}
\]

(7)

and the passive stress in radial direction, \(\sigma_{m,r}\):
\[ \sigma_{m,r}(\lambda_r) = \begin{cases} \sigma_{r0}(\exp[c_r(\lambda_r - 1)] - 1) & \lambda_r \geq 1 \\ 0 & \lambda_r < 1 \end{cases} \]  

(8)

With \( \sigma_{f0}, \sigma_{r0}, c_f \) and \( c_r \) scaling parameters and \( \lambda_f \) and \( \lambda_r \), the strain in fibre and radial direction, respectively. Assuming incompressibility it follows that \( \lambda_r = \lambda_f^{-2} \).

The active stress of the fibres, \( \sigma_a \), depends on 4 properties: contractility \( c \) which is always between one and zero and indicates how well the heart can contract, sarcomere length \( l_s \), time elapsed since activation \( t_a \) and sarcomere shortening velocity \( v_s \). Hence:

\[ \sigma_a(c, l_s, t_a, v_s) = c \sigma_{ar} f(l_s) g(t_a) h(v_s) \]  

(9)

Here is \( \sigma_{a,0} \), a scaling constant, and the functions \( f \), \( g \) and \( h \) describe how \( \sigma_a \) depends on \( l_s \), \( t_a \) and \( v_s \) respectively:

\[ f(l_s) = \begin{cases} 0 & l_s \leq l_{s,0} \\ \frac{l_s - l_{s,0}}{l_{s,ar} - l_{s,0}} & l_s > l_{s,0} \end{cases} \]  

(10)

\[ g(t_a) = \begin{cases} 0 & t_a < 0 \\ \sin^2\left(\frac{\pi t_a}{t_{max}}\right) & 0 \leq t_a < t_{max} \\ 0 & t_a > t_{max} \end{cases} \]  

(11)

\[ h(v_s) = \frac{1 - (v_s / v_0)}{1 + c_r (v_s / v_0)} \]  

(12)

With \( l_{s,0} \) the sarcomere length below which active stress becomes zero, \( l_{s,ar} \) represents the sarcomere length to which the reference state \( \sigma_{ar} \) refers to. \( t_{max} \) is the duration of the twitch, \( v_0 \) is the unloaded sarcomere shortening velocity and \( c_r \) determines the shape of stress-velocity curve. All parameters are chosen in agreement with experimental data\(^2\).

To be able to model the intramyocardial pressure \( (p_{im}) \) it is assumed that \( \sigma_r \) varies linearly through the left ventricular: \( \sigma_r = p_{LV} \) at the endocardium to \( \sigma_r = 0 \) at the epicardium, so

\[ \sigma_r = -\beta \cdot p_{LV} \]  

(13)

Furthermore, \( \sigma_r \) can be divided into two parts: intramyocardial hydrostatical pressure and the radial stress in the matrix:
\[ \sigma_r = -p_{im} + \sigma_{m,r} \]  

(14)

Combining equation (13) and (14) results in equation (15) where \( p_{im} \) is only determined at a representative radial distance \( \bar{r} \).

\[ p_{im}(\bar{r}) = \bar{\sigma}_{m,r} + \frac{r_{out} - \bar{r}}{r_{out} - r_{in}} p_{LV} = \bar{p}_{im} \]  

(15)

Where \( \bar{p}_{im} \) is a short notation for \( p_{im}(\bar{r}) \).

\[ \bar{r} = \left( \frac{3(V_{LV} + V_w / 3)}{4\pi} \right)^{\frac{1}{3}} \]  

(16)

Now both \( p_{im} \) and \( p_{LV} \) can be determined to serve as input for the lumped parameter model.

**Pathology: HCM**

In order to investigate the influence of HCM on the pressure and flow dynamics in the larger coronary arteries, its pathologies should be modelled correctly. As described before, patients with HCM have a thickened left ventricular wall volume and a smaller ventricle lumen which can be modelled respectively with an enlarged wall volume \( (V_w) \) and a decreased left ventricular volume \( (V_{LV}) \). Increased chamber stiffness, also associated with HCM, can be described by changing the passive constitutive behaviour of the myocardial tissue by increasing the stiffness in radial \( (\sigma_{r0} \text{ and } c_r) \) and fibre direction \( (\sigma_{f0} \text{ and } c_f) \). Impaired LV ventricle relaxation might be modelled the same way.

Changes to the coronary circulation due to HCM are thicker vessel walls and narrowed lumen which might be modelled by decreased compliance and increased resistance respectively. The decreased capillary density cannot be described by the model used in this study.

Due to increased chamber stiffness, the pressure peak will rise and fall less sharp in all of the systemic arteries. The increase of the resistance of the coronary circulation will lead to larger pressure drop over the heart and a decreased perfusion of the heart. The increased compliance of the coronary circulation will result in a sharper rise and fall of the pressure and flow peak.

<table>
<thead>
<tr>
<th>Heart model:</th>
<th>Mild HCM</th>
<th>Massive HCM</th>
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<tbody>
<tr>
<td>( V_w )</td>
<td>↑</td>
<td>↑↑</td>
</tr>
<tr>
<td>( V_{LV} )</td>
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<td>( \sigma_{f0} )</td>
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<td>( \sigma_{r0} )</td>
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<td>( c_r )</td>
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<tr>
<td>( c_f )</td>
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</tbody>
</table>

**Circulation model, coronary microcirculation:**

| Compliance | ↓        | ↓↓          |
| Resistance | ↑        | ↑↑          |

Table 1: relative change of parameters to model HCM compared to healthy heart and circulation.
Results

The results of the model described above are presented in this section. The pressure in the LV, arteries (or aorta) and veins (or left atrium) are referred to as $p_{LV}$, $p_{art}$ (or $p_{Ao}$) and $p_{ven}$ (or $p_{RA}$) respectively. In Figure 7 they are plotted as function of time: the left and right graph show the pressure as according to the model and literature\(^49\) respectively. The shape of the curves are equal, but the pressures of the model is higher everywhere and its systole slightly longer. From the $pV$-loop of the LV (Figure 8) it is seen that $p_{LV}$ is mainly too high during systole.

![Figure 7: Pressure in systemic circulation as predicted by the model (left) compared with literature\(^49\) (right).](image)

In Figure 9 the flow through the aortic and mitral valve ($q_{av}$ and $q_{mv}$ respectively) are shown according to the model (left) and according to literature\(^50\) (right). The flows through the aortic valve are equal, but the model yields $10^2$ times higher flow through the mitral valve compared to reported values\(^50\). The influence of these flaws of the model on the behaviour of the heart is well illustrated by the flow-volume diagram\(^51\) in Figure 10: the flow-volume diagram has neither the correct shape nor the correct values. The flow in the flow-volume diagram is defined as the time derivative of the volume, so during the systolic emptying of the LV there is a negative flow while the filling in diastole has a positive flow. The flow in the flow-volume loop from literature, however, does not comply with the valve flows illustrated in the right figure of Figure 16.
9. The maximal flow through the mitral and aortic valve are 500 ml s\(^{-1}\) in Figure 9 while they are about 200 ml s\(^{-1}\) in Figure 10. The flows in Figure 10 are probably underestimated.

![Flow in systemic circulation](image1)

![flow through the aortic and mitral valve](image2)

**Figure 9:** flow through the aortic and mitral valve \(q_{av}\) and \(q_{mv}\) respectively as predicted by the model (left) compared to literature (left, adapted from Van de Vosse).  

**Figure 10:** Flow-Volume diagrams of the LV as found in literature (left)\(^6\) and as predicted by the model (right). Note that the range of the vertical axis is an order of magnitude of 10 higher in the right figure than the left figure. Furthermore should be noted that the diagram follows the heart cycle counter clockwise (diastole and systole positive and negative flow respectively).

Combining values from literature used for the pV and flow-volume diagrams it is seen that the volume of the LV falls within the physiological range.

**Coronary circulation**

Figure 11 shows the dynamics of the coronary pressure and flow according to the model. The pressure and flow of the coronary artery and begin-microcirculation are out of phase, while they are in phase for end-microcirculation and veins. The mean coronary flow in rest for healthy people is about 225 ml/min\(^3\); the model yields 285 ml/min so the model overestimates the flow slightly. End-diastolic values of 35 and 10 mmHg at begin and end of the capillary bed respectively, are found in literature\(^5\), and compare to the corresponding pressure, \(p_{cor mc1}\) respectively \(p_{cor mc2}\) of the model.

Figure 2 shows the course of the flow and pressure for different parts of the coronaries for dogs as found in literature\(^7\). Comparing those characteristics with Figure 11 reveals that the model predicts correctly that most of the inflow of the coronary arteries occurs during diastole and that most of the venous outflow occurs during systole.
Furthermore, the model shows in early systole correctly a decrease of flow at the beginning of the microcirculation, \( q_{\text{cor mc1}} \), while the flow at the end of the microcirculation, \( q_{\text{cor mc2}} \), erroneously, lacks this decrease. On the other hand, there is, erroneously, no large flow in mid- and end systole at the beginning of the microcirculation, while it is, correctly, present at the end of the microcirculation. In early diastole there is a non-physiological increase of \( q_{\text{cor mc1}} \) and decrease of \( q_{\text{cor mc2}} \). Also most of \( q_{\text{cor mc1}} \) flows during diastole instead of systole, \( q_{\text{cor mc2}} \) shows correctly most flow during systole. Consequently, the dynamics of \( q_{\text{cor mc1}} \) and \( q_{\text{cor mc2}} \) differ quite much from each other, which is also in contradiction with literature (Figure 2).

![Pressure in coronary artery, microcirculation and vein](image1)

![Flow through coronary artery, microcirculation and vein of a normal LV of about 300 g](image2)

Figure 11: Coronary pressure (upper) and flow (middle) under normal conditions.
Stability

Figure 12: No stable solution of the volume LV is achieved after many (+400) heart beats. Figure 12 shows that there is no stable solution for even over 500 heart beats. The LV volume keeps increasing suggesting that there is no conservation of mass.

Figure 13 shows the difference between net inflow and volume change for the systemic vein segment (blue) and the LV segment (green). Every beat there is a large spike while the difference should be zero in order to have conservation of mass. The spikes coincide with the opening of mitral valve. The red line indicates the difference between the volume that should be added according to equation 1 \((dV/dt)\) at increment ic and the actual added volume \((V(ic + 1) - V(ic))\). This difference should also be zero, but the difference is large every beat at the moment the mitral valve opens. So Figure 13 also shows that the conservation of mass does not hold here.

As the valves close, instabilities can be seen. This is most apparent in the \(p_{ao} \) pressure curve when the aortic valves close (see Figure 14) and decrease with decreasing aortic inertia (not shown).
Figure 14: Aortic pressure at closing of the aortic valve
Discussion

It is already shown that the dynamics of the coronary circulation can indeed be modelled with a lumped parameter model and the heart model of Arts et al., extended by Bovendeerd et al. In this report it was tried and succeeded to use that model and mimic their results. The global dynamics of the coronary arteries and veins comply with theirs and other reported physiological dynamics. Only the values are not correct as most values are higher than physiologic values. For example peak LV pressure is 156 mmHg instead of 120-130 mmHg and mean coronary flow is 285 mL min\(^{-1}\) instead of 215 mL min\(^{-1}\). This could be fine tuned by changing the value of some resistances, but it turned out that values of resistance, inertia or compliance could not be easily altered. A change of R-, I or C-value prevents the model to find a solution as some values get larger then machine precision, even if the change falls in a physiological range.

Reason for these instabilities might be the valves. The valves are modelled as pressure driven diodes with an internal resistance. The value of the resistance of the diode changes from 5MPa m\(^{-3}\) when the pressure gradient is positive to 5 \(10^3\) MPa m\(^{-3}\) when the pressure gradient is negative. Due to this changing of the resistance in time, the linear system becomes a highly non-linear system. This non-linear system is still solved as a set of linear equations by DISCO, which will lead to instabilities as shown in Figure 14 and artefacts as shown in Figure 14. The influences of these instabilities increases with increasing flow through the valves at the moment the resistance changes and might even get larger than the machine precision. To counter that, the closure of the valves should not only be pressure, but also flow driven. Thus the valves will only close (the resistance multiplied by \(10^3\)) when both the pressure gradient is negative and the flow is negative. This way the resistance only changes when the flow is about zero so non-linearity can be well approximated by a linear system. This reasoning is supported by the observation that the system was stabilized by a smaller aortic inertia but yields, again, no solution when the aortic inertia was too small (2 times smaller).

Another reason might be DISCO itself, because even very simple electric schemes did not converge to a solution and the LV volume increases with every heart beat suggesting that something goes wrong with the conservation of mass.

Because the model yielded no solutions when the R-, C- and L-values were changed, no diseases could be modelled.

The flow and pressure of the systemic circulation and the coronary arteries and veins are modelled quite correctly and the same holds for the pressure in the coronary microcirculation. The flow in the coronary microcirculation, however, is modelled rather wrong as there is a phase shift between the flow through the arterioles and venules.

Reason might be that it is assumed that the intramyocardial pressure has no influence on the intravascular pressure at the beginning and end of the microcirculation, hence boundary condition for the pressure at node 13 and 17 (\(p_{13}\) and \(p_{17}\) respectively) is \(p_{13} = p_{17} = 0\). But when it is assumed that \(p_{im}\) has as much influence on the intravascular pressure there as it has in the capillaries, the boundary condition should change to \(p_{13} = p_{17} = p_{im}\) instead. This might also be physiological since both the arterioles, capillaries and venules lie in the myocardium. This change of boundary condition will cause the flow through the beginning of the microcirculation to decrease less during systole because the pressure on node 12 and thus the pressure gradient between node 12 and 14, will increase due to emptying of the capacitor due to the increase of pressure at node 13, \(p_{im}\), during systole. In other words, the change of boundary conditions will change the flow through the beginning of the microcirculation to decrease less because the blood will be squeezed out of the vessel as the volume decreases under the influence of the increased extramural pressure (\(p_{13} = p_{im} > 0\)). In diastole, the flow will decrease because the vessel (capacitor) will be refilled with blood again because the extramural pressure (\(p_{im}\)) is decreased.

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The flow through the end of the microcirculation, $R_{myo2}$ between node 14 and 16, will decrease during systole because the pressure gradient will be smaller as the pressure at node 16 ($p_{16}$) will be larger under influence of the extramural pressure at $p_{17}$ ($p_{17} = p_{im} > 0$). The flow through $R_{myo2}$ will be about the same during diastole because the pressure gradient over $R_{myo2}$ will be equal during diastole ($p_{14} = p_{im} = 0$) or maybe less because the vessel will be filled with blood again because the decreasing extramural pressure. Consequently will the flow through the coronary arterioles and venules be less out of phase with each other which is a better resemblance of experimental data of Ashikawa et al.\textsuperscript{9}.

About their results should be noted though that they only measured the subepicardial microcirculation. Yada et al.\textsuperscript{53} however, report a change of diameter of about 20% of the microvasculature during the cardiac cycle for the subendocardial microvasculature while it stays the same for the subepicardial microvasculature. This gives rise to the thought that the flow through the myocardium is heterogeneous for different layers. Therefore, extrapolation of the results of Ashikawa to the whole cardiac microcirculation might be invalid.

An advantage of the heart model used in this report is the small amount of parameters needed due to its simplicity. This simplicity however, might also be a drawback, since it might not be able to describe certain diseases correctly. An example is ischemia of the LV because it consists of different types of tissue, namely myocardial and scar tissue. Because the LV is in the current model represented as an extrapolation of one fibre, it cannot have both tissues properties. This problem might be solved by representing one LV as a combination of an ischemic LV and a healthy LV. This is of course not physiological and therefore might lack the ability to describe the behaviour of cardiovascular system and might as well be hard to implement. So, generally, only changes of global left ventricular properties like contractility and volume can be modelled with the model used in this report. This should be kept in mind in further research, when more diseases are modelled using this model.
Conclusion

In this study it is shown that it is possible to develop a model which describes the behaviour of the flow and pressure of the coronary system with the model of Arts and Bovendeerd as was already done by Bovendeerd. But some adjustments are still necessary to make the model of this study more stable and more in accordance to physiological values before the influences of microcirculatory pathologies on the epicardial arteries can be investigated. Especially in the algorithm to solve the set of linear equations: DISCO.
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