Czech Technical University in Prague
Faculty of Electrical Engineering

Department of Cybernetics

Master Thesis

Simulation of Flow and Pressure Pattern in Patients with Different Body Size Supported by Pulsatile Ventricular Assist Devices

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Abstract

This thesis deals with the use of adult-size pulsatile flow ventricular assist device in patients of different size. Hereby, I try to prove basic concept, that substantially larger VAD stroke volume, than to what the patient is used to, would lead to hypertension. This concept has been already multiple times considered (for instance in [39, 35]). There are discussed general properties of human circulatory system, then an overview of mechanical circulatory support devices with emphasize on ventricular assist devices is presented. Based on a paper from Conlon et al.(2006)[8], a mathematical model of systemic circulation is designed and implemented in Modelica language. This model is adjusted to represent either a small, normal-sized or a large patient. Consecutively, there is conducted an experiment on this model, where different VAD stroke volumes are used in *patients* of different size. According to hypothesis, the hypertension is really caused.

Also, an user interface application for this model is designed and implemented in Silverlight environment, to serve as a learning aid and demonstrational tool.

Keywords

Model, pulsatile, VAD, circulation, Modelica

Abstrakt

Tato práce se zabývá pou¸itím pulsatilních srdečních podpor určených primárně pro dospělé, u různě velikých pacientů. Sna¸ím se zde prokázat základní koncept, ¸e výrazně vy¨¨í stroke volume (objem vypuzený za jednu ejekci) ne¸ na který je pacient zvyklý, povede k hypertenzi. Touto zále¸itostí se ji¸ zabývalo několik klinických studií (například [39, 35]), ale je¨tě nebyla potvrzena.

V první části se zabývám základními vlastnostmi oběhové soustavy, následuje přehled mechanických podpor cirkulace a shrnutí problematiky malých pacientů. Na základě práce Conlon et al. (2006)[8] je navrhnut model oběhové soustavy s pulsatilní pumpou a je na něm demonstrován experiment s různě velikým objemem pumpy. Podle předpokladu skutečně dojde u malého pacienta při výměně pumpy za vět¨í (z 35 ml na 65 ml) k hypertenzi.

Dále byla navrhnuta aplikace jako u¸ivatelské rozhraní k tomuto modelu a implementována na platformě Silverlight. Tato aplikace má slou¸it jako učební a demostrační pomůcka.

Klíčová slova

Model, pulzatilní, VAD, cirkulace, Modelica

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Last, but not least, I would like to acknowledge Department of Cybernetics, Czech Technical University in Prague, for financial support to allow me to visit Medical University Vienna and to gain valuable experience there.

[1] Laboratory of Biocybernetics and Computer Aided Teaching, Institute of Pathological Physiology, First Faculty of Medicine, Charles University in Prague

Contents

Nomenclature

Bi-VAD Two ventricular assist devices are supporting both right and left heart.

BMI Body mass index

BSA Body surface area

BTB Bridge to bridge

BTD Bridge to decision

BTR Bridge to recovery

BTT Bridge to transplant

CHF Chronic heart failure - a life-threatening disease.

CI Cardiac index – total blood flow in liters per minute

CS-VAD Constant flow ventricular assist devices

DT Destination treatment

ECMO Extracorporeal membrane oxygenation, a way to provide body with oxygenated blood during acute heart and/or lungs failure.

EKG Electrocardiogram, a method to get heart rhytm by measuring its electrial field.

FDA Food and drug administration – American regulation authority

FFFE Full fill - full eject: control mode of ventricular assist device

FR fixed rate control mode of ventricular assist device

HR Heart rate – number of beats per second

HS Hemodynamically significant stenose – a vessel, which inner diameter is narrowed in some point by more than 50

IABP Intra-aortic balloon pump counter-pulsation

IKEM Institut klinické a experimentální medicíny, Praha (Institute of Clinical and Experimental Medicine, Prague), http://www.ikem.cz

LVAD Left ventricular assist device supports just left heart.

MCS Mechanical circulatory support devices

PF-VAD Pulsatile flow ventricular assist devices

PP Pulse pressure

RVAD Right ventricular assist device supports just right heart.

SV Stroke volume - the volume of blood which is ejected in each revolution

TAH Total artificial heart, is replacing native heart as a whole.

VAD Ventricular assist device. An artificial pump, which helps heart mrdat.

Chapter 1

Introduction

This thesis is motivated by five-year clinical experience of supervisor, MUDr. Ing. David Macků in Institute of Clinical and Experimental Medicine in Prague (IKEM). The problem, which he faced, was a neglected adverse effect of pulsatile ventricular assist device in small-sized patients. The basis of this problem is published in [23].

Major producer of VAD, the Thoratec Corporation does offer many solutions for adult patients, including pulsatile flow VAD, but their use for pediatric patients is limited.

In Europe there are approved systems such as Berlin Heart with different stroke volume tailored for pediatric patients, but their use is still not approved in USA, where there are performed approximately $350 - 400$ pediatric heart transplantations annually [19].

This thesis deals with the use of adult-size pulsatile flow ventricular assist device in patients of different size. Hereby, I try to prove basic concept, that substantially larger VAD stroke volume, than to what the patient is used to, would lead to hypertension. This concept has been already multiple times considered in clinical practise (for instance in [39, 35]), but has not been proven yet.

1.1 Project background

In the United States (as well as in other developed), the cardiovaascular diseases are the leading cause of death [50]. The gold standard treatment of end-stage chronic heart failure (CHF) is heart transplantation. However, not all patients are eligible for a transplant due to their age or other reasons. Even if the patients are eligible for the transplant, due to the severely limited supply of donor heart only small part of patients may undergo heart transplantation each year. Therefore, since 1960, the artificial circulatory support devices are employed to save some lives of end-stage CHF patients[50], where the standard medicaments therapy is not sufficient. Artificial heart support devices have several advantages - they are less costly and not limited by the availability of heart donors and they could serve also as a destination treatment for patients which are not eligible for transplantation.

Heart failure Heart failure is a complex clinical syndrome. It is be a result of any structural or functional heart damage, which leads to filling or ejecting disorders. We distinguish acute and chronic heart failure (CHF). In major part of patients, CHF is the induced by atherosclerotic defects of coronary arteries, the rest are cardiomyopathitis with either identified (e.g. systemic hypertension, heart valves disorders, myocarditis etc.) or unidentified cause. CHF is a progressive process, which could be treated by medicaments therapy, but the prognosis is still unfavourable[20].

Heart failure patients fall into several categories depending on both severity and cause. Therapeutic approaches differ for each subgroup. CHF is classified on New York Heart Association (NYHA) scale from Class I to Class IV, being the most severe. About 65 % of patients are classiffied as Class I and II and a further 30% are designated Class III. These patients are usually treated by drugs or if the disease is of electrical origin, by implantation of a pacemaker. Only 6 – 7% of CHF patients are classified as Class IV, that means that transplantation or implantation of VAD is needed. In US there is about 330,000 of new Class IV cases annually, and around one million worldwide.

Around 2300 of 100,000 americans with chronic heart failure receive heart transplant [25] in the end.

Transplantation and mechanical circulatory support When in final IV phase of CHF, the transplantation is traditionally the only way to reach proper heart function (althgough of different one).

According to [7], as of 2007, 2,210 heart transplantations were performed in US, while there were 2,607 (as of 2008) patients on the transplantation waiting list. As the transplantation is not available immediately and some of the patients have to wait for months, there arised need for mechanical devices, which support human circulation until it recovers or until a transplantation is accomplished. However, each use of a mechanical circulatory support is connected with a set of adverse events, which should be minimized.

Chapter 2

Human circulatory system

The human circulatory system is a blood flow circuit, made of distinct parts. Usually, we speak of two circulatory loops: the small, or pulmonary, circulation leads blood from right heart to lungs and back to left heart, whereas in the big, systemic, circulation the blood flows from the left heart to all other organs and back to right heart. The circulation system satisfies a number of functions ([5]) - the perfusion of organs guarantees:

- oxygen supply
- nutrients supply
- carbon dioxide disposal
- maintenance of proper ions concentration
- hormones transport
- body heat distribution

2.1 Macrocirculation and Microcirculation

This is the macrocirculation point of view, which treats circulatory as a whole. The macrocirculation is defined as that part of the circulation in which inertial forces are not negligible compared to viscous forces. The blood flow in large vessels we can consider as macrocirculation.

Microcirculation, on the other hand, describes flow through small vessels in the vasculature which are responsible for transfer of gases, nutritients and waste. It takes place in capillaries.

When referring to blood flow and pressure, we usually talk about macrocirculation only. Also, this thesis deals with macrocirculation only.

2.2 Blood

Blood is a viscous nontransparent fluid, created of plasma and suspended cells. Plasma, which is more than 50% of volume, consists of water and dissolved

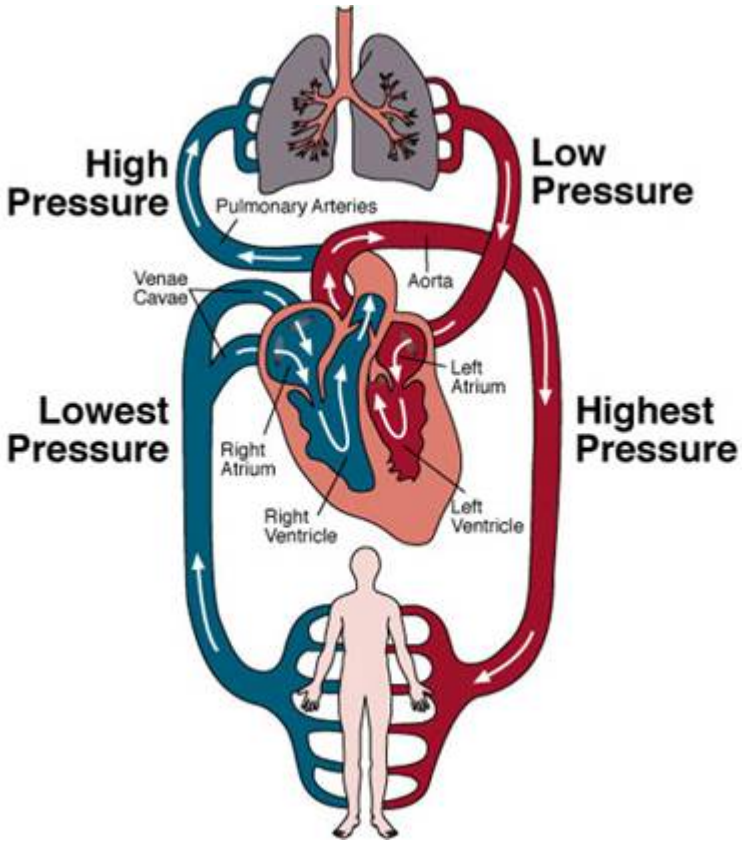

Figure 2.1: Human circulatory structure.
Image from http://www.williamsclass.com/SeventhScienceWork/ImagesCellBricks/OrganSystem.jpg

proteins and minerals (mostly salt). Suspended cells include red blood cells (erythrocytes), which create 99% of the cell mass. Red blood cells are responsible for transport of oxygen and carbon dioxide. Other cells are white blood cells - leukocytes, which plays key role in organism immunity and platelets, which are important in blood clotting and bleeding stopping.

Blood has relatively similar properties to water. It has several folds higher viscosity though (4 to 5.4 times than water [46]), which in addition is non-linear (substantially lower in capillaries). As the blood contains soft cells and dissolved gases, it is partially compressible, but very low in comparisson with vessel's stiffness.

An average human has around 4.5 to 6 liters of blood. Blood is spread all across body in arteries, capillaries and veins. Blood volume depends on body surface area has been empirically found as

$$TotalBloodVolume = 3.290 \cdot S - 1.229 \tag{2.1}$$

, where S stands for body surface area [m^2].

Body surface area Body surface area (BSA) is a widely used paremeter to characterize patient size, especially for parametrization of circulatory system. It employes not only body mass (weight), but also the height. Since measuring BSA directly would be very complicated, various formulae are used. Here I take De Buis formula (adopted from[4], p.28), probably most widely used:

$$BSA = 0.007184 \cdot weight^{0.425} \cdot (height \cdot 100)^{0.725} \tag{2.2}$$

where the weight is in kg and height in m.

Body mass index When defining BSA, one must also mention complementary parameter. Body mass index (BMI) is a relation of height and weight. It is used mainly to define, whether the patient is underweight (BMI$<$18.5), overweight (BMI$>$25, obese from 30), or in normal range. It is computed as:

$$BMI = \frac{weight}{height^2} \tag{2.3}$$

where the weight is in units of kg and height in m^2.

2.2.0.1 Hemostasis

Hemostasis is an arrest of bleeding. It must be quick, in range of milliseconds to minutes. When an artery is injured, blood gushes quickly through the hole. High outflow results in very high shear stress, which initiates hemostasis. Platelet adhesion, which plays major role in hemostasis, is regulated as much by shear stress and by density of controlling substances (glykoprotein Ib receptors, von Willebrand factor concetration and exposed collagen) ([22]). Platelets are also easily activated on contact with foreign surfaces ([25])

Contrariwise, when the blood is stagnant, it will be clotted by a cascade of coagulation proteins [22]. Very high shear stress at stenoses may also contribute to activation of platelets. Resulting thrombus may either cause total occlusion of the stenoses or if it breaks free, an embolus is formed. Also, after stenoses,

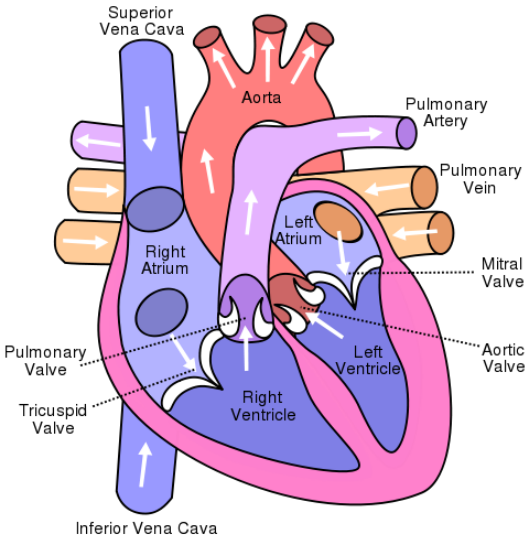

Figure 2.2: Heart schema. Image from commons.wikimedia.com by user Wapcaplet.

where the flow is limited, therefore shear rates low, the contrary phenomena could happen and blood start to clot. This would result in either elongation of stenose (as the clot is added loosely to the end of the stenose) or an embolus could be torn, threatening to clog a vital vessel.

2.3 Heart

Heart is a hollow muscular organ to serve principal purpose: to pump blood through systemic and pulmonary circulation.

In fact, there are two pumps together, separated by muscular wall - the septum. Right heart gets blood from venae cavae and pumps it to lungs (pulmonary circulation). The returned blood is collected then in pulmonary vein and left heart pumps it to all other organs and peripherals (systemic circulation). See figure 2.2 for schematics.

Each heart's side - both left and right consists of atrium and ventricle. Atria collect blood and help to fill the ventricles. Flow is then propelled by rhytmic contraction of the ventricles, which are after atria. This phase of contraction is called *systole*. Ventricles have inlet (mitral and tricuspid) and outlet (aortic and pulmonary) one-way valves, assuring the right flow direction and prevent backflow in filling state after systole. This relaxation period is called *diastole* and the whole process is called *heart revolution*. The pressures are visualized in figure 2.3.

2.3.0.2 Stroke volume

On each revolution, the heart would not eject all volume. Instead, some residual volume stays in the ventricle after systole. The volume, which is ejected is

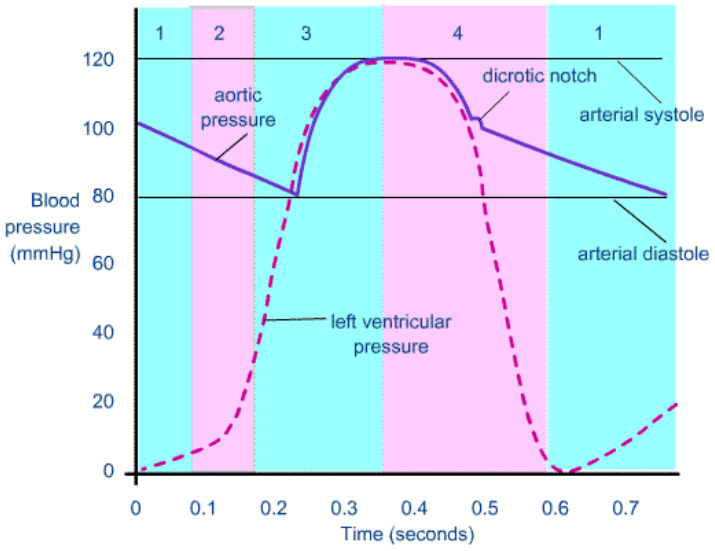

Figure 2.3: Schematics of intraventricle and aortic pressure during heart revolution. Image from http://www.hcc.uce.ac.uk/physiology/circulation02.htm

called stroke volume. It must be the same in both right and left heart in normal conditions. The normal rest value of this stroke volume is empirically dependent on body surface area (Equation 2.2 on page 5) [23] :

$$SV = 40.328 \cdot BSA^{0.93} \tag{2.4}$$

which means, that normal rest stroke volume rises with body weight and height. For a patient with BSA of 1.7 m^2 it is around 65 ml. This volume may change with excercise or changes in mental state.

Higginbotham et al. (1986)[17] measured stroke volume at rest and during exercise in adult male subjects and came to a conclusion, that normal stroke volume is 57±14 ml per m^2 of BSA, while the patient is at rest at supine position (lying in their back) and 41±9 $ml \cdot m^{-2}$ at upright position. During exercise the SV raises up to 58 $ml \cdot m^{-2}$ at exercise. This means SV of 70 to 98 ml in patient with BSA 1.7 m^2

2.3.0.3 Cardiac index

Cardiac index (CI), one of main indicator of heart work, describes total heart outlet over period of time. It is obtained from heart rate (HR) and stroke volume (SV) as

$$CI = HR \cdot SV$$

Usually it is presented in liters per minute. Normal value is about 5 l/min, which varies with age and during exercise, where it can rise up to eight times ([46]). In normal conditions the cardiac index (or total flow in this case) of left heart must equal that of right heart, otherwise the blood would have to accumulate somewhere and an edema would result.

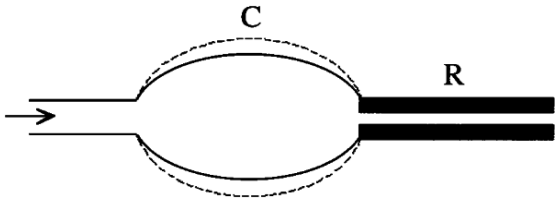

Figure 2.4: Windkessel effect illustration. Image from [22].

2.3.0.4 Coronary arteries

Coronary arteries play vital role in heart function. They lead from ascending aorta, immediately after aortic valve and they promote blood circulation in heart and supplies it with vitally important gases and nutritients. The clotting of these arteries leads to myocard infarct (a necrosis of a part of heart muscle), which impairs the heart function. Also, necrotic tissue is more susceptible to rupture, a life threatening condition.

During systole the flow in coronary arteries are occluded, because the muscle is contracted. Most of the flow happens in diastole. Also because of that, the diastolic pressure is so important. This must be taken into account when employing MCS.

2.4 Arterial and venous system

As mentioned above, arteries are vessels, which lead blood rich in oxygen (on the contrary, in pulmonary circulation the blood in arteries is poor on oxygen) to peripheral organs. Because of pressures up to 120 mmHg, it is often referred to arteries as a high-pressure circulation. Veins are running blood from peripherals back to heart.

2.4.1 Windkessel effect

Windkessel effect is a one-dimensional simplification of arterial pulse propagation and although more complex abstraction exists, it is quite sufficient for the idea.

Relation between blood volume and a pressure waveform could be simplified using a lumped parameter or one dimensional flow model. The best-known is the very Windkessel, which has been used to explain the rapid rise and gradual decrease of the flow and pressure waveforms.

Windkessel is described by compliant section with a resistance (figure 2.4). During systole, the compliant vessel fills with blood. In diastole, when the pressure drops, the blood is expelled using the vessel's wall tension. The pressure and flow waveforms are quite similar to those measured in the body ([22]).

In reality, the arterial wall response is much more complicated. The artery wall does not exhibit itself as elastic structure only, but it varies depending on content of elastic, collagenous and smooth muscle fibers and resembles more a visco-elastic structure. It shows, when we increase pressure (volume in this case) rapidly, the wall tension is much larger, than in the case we increase pressure (volume) slowly [46].

2.5 Peripherals

Peripherals consist of capillars, where microcirculation occurs. That is where the blood interchanges gases and other substances with tissue.

Capillaries and venules have extremely small diameter (around 9 μm), but there are very plenty of them. Together their cross-sectional area is around 700 times larger (around 3500 cm^2) than the diameter of aorta (silbernagl).

2.6 Autoregulation of circulation

There are various means to regulate flow and pressure. Some of them are capable of acting very quick, others are intended for long-time adaption.

Baroreflex acts in very quickly. It is a feedback system based on neuron sensors in aortic arch and in carotid (in neck) arteries, which measure pressure. Its increase (or decrease) is signalized to neural system, which then through sympathetic and parasympathetic nervous systems adapts heart rate, contractility and vasoconstriction. This system is very important to compensate short-term changes, such as standing up (where the hydrostatic pressure suddenly changes). [47]

Renin-angiotensin system acts in longer time scale, when there is significant decrease in blood volume and/or blood pressure. Firstly, it lowers filtration in kidneys, thus lowering amount of urine, thus lowering secretion of blood and salts and more volume means higher pressure. Secondly, angiotensin is mighty mediator in vasoconstriction[36].

2.6.0.1 Regulation of heart

Although the heart works on its own, a number of control mechanism exists. Mainly it is a pump controlled by input, hormonally and neurally.

Regulating *by input* is important because we must realise, that in fact there are two pumps in the system - the right heart and the left heart. In both parts there is a must to keep same amount of blood over long period. In other words, the blood volume could not be shifted from systemic circulation to pulmonary. That is more complicated, since both pumps has the same frequency. So, let us increase e.g. systemic resistance. This would limit inflow in systemic circuit and if the right heart would pump with same performance, consequentially it would shift blood to pulmonary circulation. However, with higher filling pressure, the heart reacts with stronger contraction, resulting in bulkier stroke volume. This phenomena is called the Frank-Starling law.

Heart is also sensitive for *hormones* such as adrenaline, which speeds up its rate and also increases the force of contractions (this parameter is called contractility).

Third way to control heart's rate is through neural control, where sympathetic and parasympathetic nervous systems create the balance to set optimal rate. Those systems are coactivated by many ways, including baroreflex control. Regulation systems are described in section 2.6.

2.6.0.2 Vasoconstriction and vasodilatation

Arterioles have strong muscular wall to completely close or dillate arteriole. Adjustable resistance serves to control perfusion and to selective direct transport to capillaries[22, 29]. All blood vessels (except for capillaries) have receptors to hormones, which signals the vessel to contract or dillate. This phenomenon is called *vasoconstriction* or *vasodillatation*. Different level of vasoconstriction allows to limit inflow into different organs and they also increase the blood pressure (in fact, reducing zero pressure volume). The opposite action, vasodillatation likewise decreases blood pressure, which could result in hypovolemic shock (too low pressure leads to insufficient perfusion). ([36])

Vasoconstriction is usually initiated on various physiological needs to control systemic vascular resistance, venous pooling (e.g. compensate standing-up effect) and intravascular blood volume ([22]).

2.6.0.3 Adaptation and remodelling

Vessels are also able to adapt to long time shear stress. When this increases, it is a signal for a vessel to dillate. Long time dillatation leads to permanent remodeling to larger diameter. This is applicable to time spans of weeks to months, thus is called long-term remodelling. To this, [22] also states:

> Alterations in the pulsatile pressure lead to changes in the organization of the elastin and collagen structure within the media. [...] Increased flow causes the artery to dilate until the wall shear stress reaches the baseline of the artery. Restricted flow through an artery produces a smaller-diameter vessel. A baseline appears to be approximately 15 to 20 $dynes \cdot cm^{-2}$ for most arteries in a wide range of species. (From [22])

That implicates, that in long time scale, the body is quite able to remodelate not only its peripheral resistance, but partially also vessels diameter.

However, long-term hypertension leads to thickening of vessel's medial layer. This means stiff, thick arteries, with possible stenoses development, which restricts blood flow ([22]).

2.7 Pressure and flow patterns

Blood pressure is an important hemodynamics indicator. For instance, too low blood pressure could indicate a failing circulatory, which could result in low organ perfusion and multi-organ failure. On the other hand, too high blood pressure could mean arteriosclerosis (artery hardening) and other symptoms, which could eventually lead to heart failure (and thus to too low pressure).

Unless stated otherwise, I refer to blood flow as volume per second definition, usually in $ml \cdot s^{-1}$.

2.7.1 Pressure

Pressure changes over time in such wave like in figure Figure 2.5 on page 11. Its peak value follows pressure in ventricles. After closure of the aortic valve,

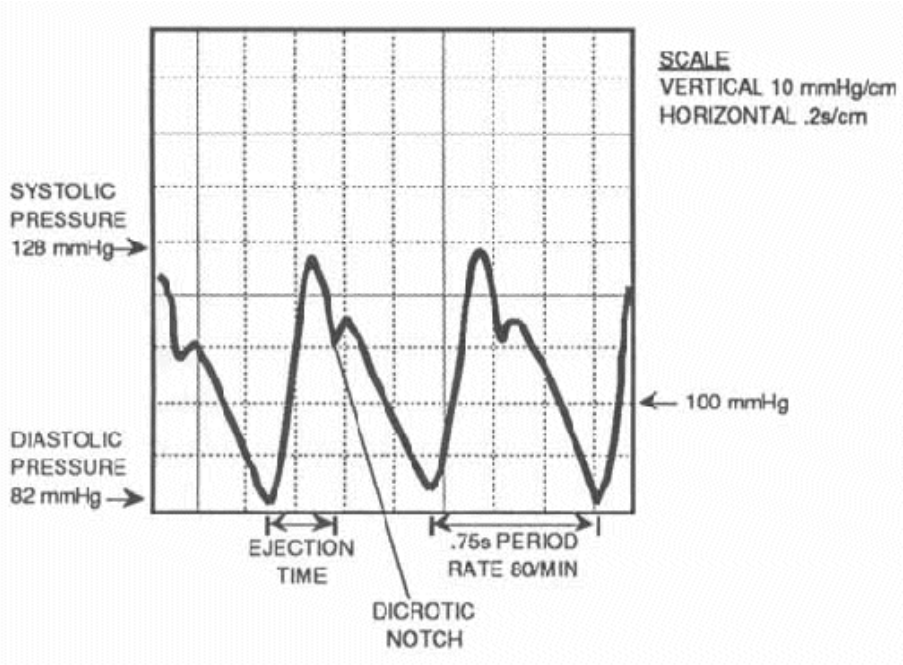

Figure 2.5: Pressure wave in small artery with systolic and diastolic pressure shown. Image from http://domain675291.sites.fasthosts.com/anae/hdmon.htm

another - smaller - peak arises. The notch between the main and the second peak is called dichrotic notch. It was believed, that this is created by savage closing of aortic valve ([36]), but nowadays it is becoming clear, that this second peak arises as the pulse wave recoils from blood bed.

2.7.2 Pressure unit and measurement

Most common mean of measuring arterial pressure is via sphygmomanometer, which was developed in 1881 and came to use after Dr. Korotkoff's invention of auscultation method[5]. This was the first noninvasive method and is used till today.

Although the SI unit for pressure is Pa, which is $N{\cdot}m^{-2}$, it is common among medical professionals to give its value in $torr$ (or $mmHg$) . Their relation is expressed as hydrostatic pressure of mercury:

$$p \quad = \quad \rho \cdot h \cdot g \quad [Pa; kg.m^{-3}; m; m.s^{-2}] \tag{2.5}$$

where p is pressure in Pa, h is height of mercury and ρ is density of mercury (13 595 $kg \cdot m^{-3}$) and g is gravity constant (9.8 $m \cdot s^{-2}$). That yields that 1 $mmHg$ equals hydrostatic pressure of 133 Pa.

This unit is given historically. First attempts to measure blood pressure (in this case pulse pressure) date to 1733 by Stephen Hales. Later in 1847 with development of kymograph by Carl Ludwig, there was possible to record pressure

Category	Systolic pressure		Diastolic pressure
Hypotension	< 90	or	< 60
Normal	$90 - 120$	and	$60 - 80$
Prehypertension	$120 - 139$	or	$80 - 89$
Hypertension, Stage 1	$140 - 159$	or	$90 - 99$
Hypertension, Stage 2	≥ 160	or	≥ 100

Table 2.1: Classification of blood pressure. Values in *mmHg* (After [46, 48])

curve, which changes during time. In 1905 Dr. Korotkoff presented his auscultation method, which opened the door to easy noninvasive measuring. Using sphygmomanometers, this method is in use till today, being the most popular method in public use. Although current versions of sphygmomanometers may be also electronic, the originally the tube was filled with mercury, level of which showed the pressure. Since then, blood pressure is measured in millimeters of mercury (chemical element Hg), thus $[mmHg]$. Also, continuous-time measuring methods are availiable (most precise are the invasive methods).

When referring to a blood pressure, we mean *arterial blood pressure*. Pressure changes greatly across the circulatory system, being highest in heart and aorta and lowest in large veins. Arterial blood pressure is similar in large arteries, such as abdominal aorta, brachial or femoral artery.

2.7.3 Normal values of blood pressure

The arterial blood pressure is considered as physiological, when both systolic (highest) and diastolic (lowest) are within a given range. Table 2.1 gives an overview of pressure classification.

2.7.4 Hypertension issues

Hypertension has been classified into various type, such as arterial, venous and others. Unless stated otherwise, in this thesis I mean by hypertension just the arterial hypertension. As could be seen from table 2.1, arterial hypertension is a chronic condition, when the arterial systolic (or diastolic) pressure is persistently higher than 140 mmHg (or 90, respectively). It may be caused primarily, or as a consequence of another conditions, which affects kidneys, arteries, heart or endocrinne system [26].

Symptoms are usually hidden, but it is connected with many pathological complications, such as ([26])

Artherosclerosis is thickening and hardening the arteries.

Aneurism or a bulge of a vessel. Forms especially in larger arteries, where it could lead to a rupture.

Vessel rupture could be just visible in eyeballs, bothering in nose, but fatal in brain.

Metabolic disorders are caused by modified gradients in microcirculaiton.

Heart failure may develop, as the heart must work against higher pressure and thus develop more strain.

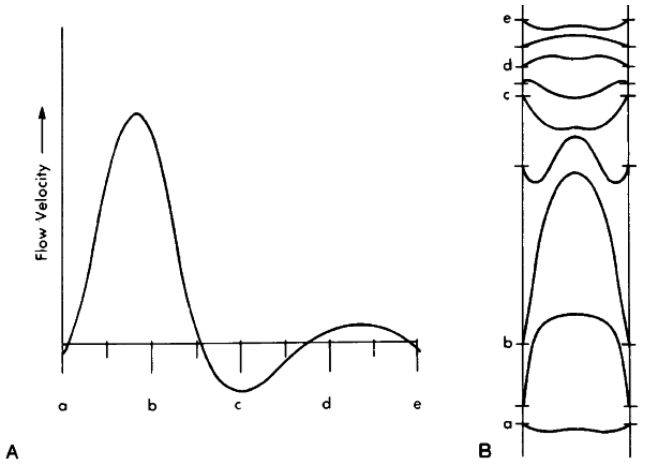

Figure 2.6: Blood flow profile. (A) shows flow velocity waveform in normal femoral artery, (B) shows velocity profile across vessel's diameter at specified time point. (Modified from [22])

and when considering hypertension in pulmonary circulation:

Thromboembolitic issues in lungs, there is increased chance of forming blood clots.

Bleeding into lungs and hemoptysis (coughing up blood) could be potentially fatal.

Edema would normally not appear, because the body is accustumed to overall higher pressure. But inducing acute hypertension may in theory change the pressure gradients in microcirculation level, so the resoprtion is not sufficient, thus forming an edema.

2.7.5 Flow profile

Blood flow is problematic to measure, because it is not constant across the cross-section. Also, on curvatures, bifurcations and junctions the flow profile is quite complicated. On figure 2.6 is shown velocity profile of the flow across the vessel's diameter. Note how the flow is reversed.

In praxis, flow profile is often neglected for simplicity reasons. However, flow profile is very important issue, when there could be diametrically opposite flow near the walls and in the middle of the vessel. Also, as blood is non-Newtonian (non-linear shear rates) fluid, it demonstrates non-linear shear stress [22], which makes flow modelling even more complicated. Especially for design of circulatory support devices the shear stress is very important, because of thromboembolitic issues (see section 2.2.0.1 on page 5).

2.7.6 Arterial pulse

The blood pressure, from aorta as far as to vena cava, has periodic fluctuations, created by heart pumping. These fluctuations manifest themselves on blood

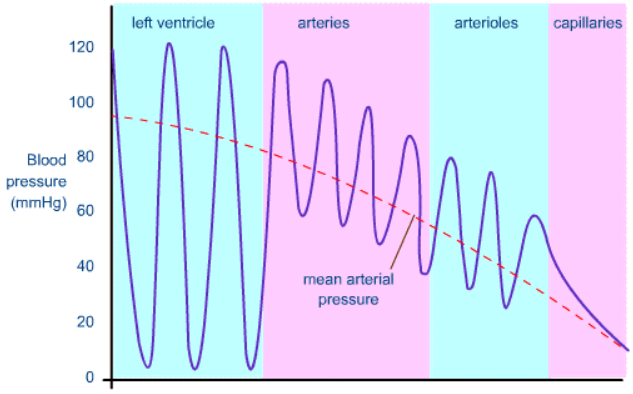

Figure 2.7: Pulsatility in various parts of circulatory system

vessel's wall as volume and pressure pulse. Characteristcs of the wave changes from aorta to arterioles in consequence of different elasticity of vessels due to viscous friction and recoil on large arterial bifurcations (especially brachial aorta). Due to recoils a paradox phenomenon could occur, that for instance the pulse pressure in e.g. femoral or brachial artery could be a bit higher than in aorta ([46]).

Propagation of pulse wave is not the same as blood flow for given systole. The real flow speed of the blood (transported blood volume over one heart revolution) is significantly lower (at rest it is around 50 $cm \cdot s^{-1}$ in aorta) than the propagation of pulse wave (shiver of arterial walls), which fluctuates around few meters per second (precisely around 5 $m \cdot s^{-1}$in aorta and around 10 $m \cdot s^{-1}$in peripheral arterioles) [46]. Velocity of propagation of pulse wave depends on stiffness and varies from person to person. Also, speed is not linearly dependent on flow, because the vessel would stretch during systole.

Arterial pulse pressure (PP) is defined as

$$PP = SP - DP \quad [mmHg; mmHg; mmHg]$$

, where SP is maximal systolic pressure and DP minimal diastolic pressure.

Pulsatility varies a lot from arteries to veins (illustration in figure 2.7)

2.7.7 Mean arterial pressure

Mean arterial pressure (MAP) is the average pressure during the aortic pulse cycle. Exactly the MAP could be expressed as

$$MAP = \frac{1}{APC} \int_{t}^{t+APC} BPW(\tau)d\tau \quad [mmHg; s; mmHg]$$

where APC is length of aortic pulse cycle and BPW is course of blood pressure wave.

At normal resting heart rates when diastole lasts longer than systole, mean arterial presssure could be estimated as

$$MAP = \frac{1}{3}(SP - DP) + DP \quad [mmHg; mmHg; mmHg; mmHg]$$

where SP is systolic pressure and DP diastolic pressure.

2.7.8 Hydrostatic pressure

As consequence of equation for hydrostatic pressure 2.5 on page 11 the pressure depends on height. At foot level there would be higher than at heart level – whole column of height from feet to heart creates this.

2.7.9 Laminar and turbulent flow

Basically, flow of liquid in rigid tube may be laminar or turbulent, as seen in figure 2.8. The flow characteristics are expressed by Reynolds number, which is a dimensionless number corresponding to the ratio of inertial forces to viscous forces. This quantifies the relative importance of these two types of forces for given flow conditions.

$$Re = \frac{inertia\,forces}{viscous\,forces} = \frac{\rho \cdot d \cdot v}{\eta} \tag{2.6}$$

where ρ is the fluid's density, d diameter of the tube, v the fluid's speed and η is viscosity. When Re is below around 2300, the flow is characterized as clearly laminar, higher than 4000 is clearly turbulent. Inbetween it is said to be transition flow, where both laminar and turbulent flows occur. Under normal condition in vascular system dominates laminar flow, with exception of aorta and a few of other arteries.

Taking flow peak $q = 300\,ml \cdot s^{-1}$ and aortic diameter as $d = 2.5\,cm$ we obtain speed v as

$$\begin{aligned} v &= \frac{q}{\pi \cdot r^2} \\ v &= \frac{300}{\pi \cdot (2.5/2)^2} \\ v &\approx 63\,cm \cdot s^{-1} \end{aligned}$$

Now, using the formula 2.6, assuming blood viscosity is 0.0027 and density 1000 kg.m-3, with same diameter 2.5 cmcm^2, it gives us

$$\begin{aligned} Re &= \frac{1000 \cdot 2.5 \cdot 63}{2.7 \cdot 10^{-3}} \\ Re &\approx 6300\,[-] \end{aligned}$$

Thus, blood flow during flow peaks in aorta is turbulent. [22] reports, that the Reynolds number of aortic flow is around 4000. Also, [37] shows, that turbulent flow occurs in ascending aorta. Some studies even treats blood as a non-newtonian fluid, with nonlinear flow profile distributions.

Turbulent flow expresses itself with larger flow resistance and sound (Korotkoff sounds are used in pressure measuring). From mechanical point of view, one tries to avoid turbulent flow near surfaces, as it can increase the risks of thromboembolytic issues.

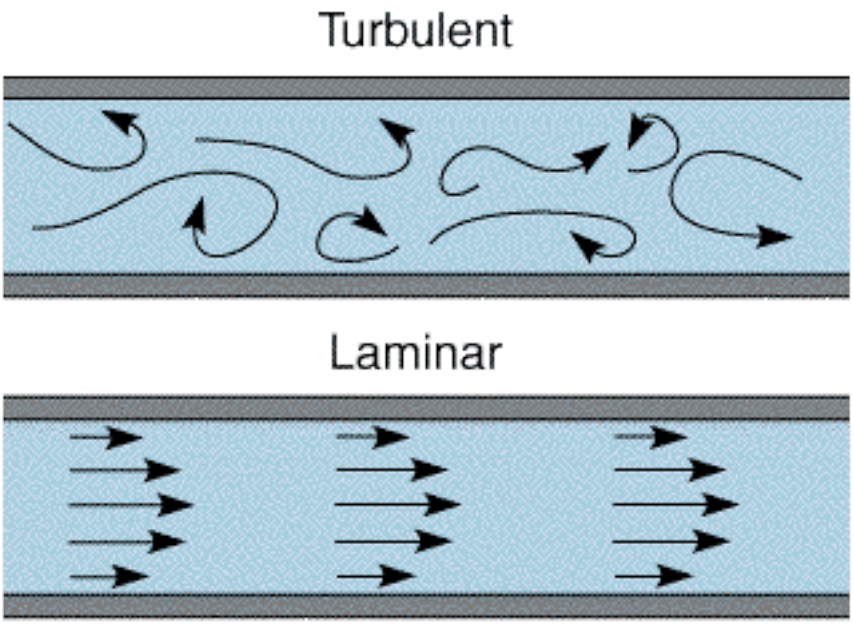

Figure 2.8: Types of flow - laminar vs.turbulent. Image from http://www.cheng.cam.ac.uk/research/groups/electrochem/JAVA/electrochemistry/ELEC/l7html/hydro.html

2.7.10 Hagen–Poiseuille equation

Hagen–Poiseuille equation describes the pressure drop in a fluid, which is flowing through a long cylindrical pipe. It is assumed, that the fluid is incompressible and the flow is laminar and is through a constant circular cross-section that is significantly longer than its diameter.

Hagen-Poiseuille law (or Poiseuille law, Poiseuille equation) characterizes laminar flow in rigid tube, whose length is substantially larger than its diameter as

$$Q = \frac{\pi \cdot r^4 \cdot \Delta p}{8 \eta l}$$

where r is radius, η viscosity, l lenght and p pressure difference. Here it is important, that the flow is propelled by pressure gradient and that the flow depends with power of 4 on its diameter. This is utilized by the body to restrict flow in certain parts by vasoconstriction (more on page 10). In case of turbulent flow, the relationship is not linear, but still monotonous. The fluid flow will be turbulent for velocities and pipe diameters above a threshold, leading to larger pressure drops than would be expected according to the Hagen–Poiseuille equation.

2.7.11 Bernoulli equation

Bernouli equation states, that

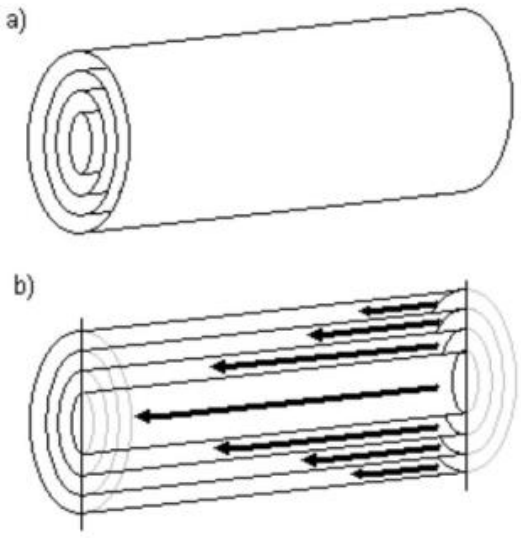

Figure 2.9: a) A tube showing the imaginary lamina. b) A cross section of the tube shows the lamina moving at different speeds. Those closest to the edge of the tube are moving slowly while those near the center are moving quickly.

$$\frac{v^2}{2} + gz + \frac{p}{\rho} = constant$$

where v is speed, g is gravity acceleration, z elevation of the point above the level, p pressure and ρ fluid's density. It is valid on assumption, that the fluid is incompresible and friction forces are negligible.

Having constant total flow, the flow velocity must be higher in vessel with smaller diameter. From this equation could be derived, that in smaller diameter vessel the pressure is substantially larger. This is important e.g. when studying stenoses.

Chapter 3

Overview of mechanical circulatory support devices

Mechanical circulatory support devices are designed to provide temporary or permanent support of the circulation in patients with both reversible and irreversible heart failure.

Circulatory system disorders are first treated traditionally using medications. This includes hypertension and other common disorders. Only acute circulation failure (failure in a meaning of insufficiency), or chronical disease in final phase, which results in failure, are indication for mechanical circulatory support (MCS). The main indication of MCS is heart failure after cardiochirurgic surgery in order to allow recover the native heart or to bridge the time till transplanation in patients with terminal chronic heart failure. According to Kettner[20], in US around 6000 patients use MCS after surgeries and for BTT indication MCS is used for around 300-400 patients per year[1]. Benefits of using MCS are [25]:

- restoration of cardiac output and blood flow
- reduction of heart failure symptoms
- improved end-organ function
- molecular and cellular improvement in myocardium

All these help to restore normal circulation and also relieves the heart from strain, which could help to recover the heart eventually.

Such MCS, which would nahradit srdce bez vedlejsich ucinku zatim neexistuje. Thius thesis tryies to vysvetlit nektere adverse effects and soearch for better soůlutions. Reseni terminalni end-stage heart failure. Do ty doby se to da resit medakamentozne.

3.1 Indication

Ventricular assist device is usually implanted to patients, whose cardiac index drops bellow 2,0 $l \cdot min^{-1} \cdot m^{-2}$, or systolic pressure is below 90 mmHg even with

[1] In contrast, [1] state, that US market needs around 30,000 devices annually

appropriate drug therapy. However, here the complex health condition is to be taken in account, for some patient this value is still far suficient (mostly due to old age, or the when state changes little by little), for some other this would be already fatal (especially acute circulatory diseases). Thus, fundamental is the detection of initial multi-organ failure, which is doubtlessly an indication to use MCS [31].

Extracorporeal devices such as centrifugal pumps (e.g. ABIOMED) are usually applied for short-term support and paracorporeal systems such as Thoratec or Medos (for pediatric patients only) are suitable for midterm support up to about 6 months. Partially implantable devices (Novacor, HeartMate (overtook by Thoratec Corp.)) are used for long-term support or as a destination therapy for patients, which are ineligible for transplantation.[10].

During a long term support on LVAD, patients may sleep, rest or exercise slightly like walking or climbing stairs. During the support, patient's native heart may get better or worse. In these conditions, the parameters of human circulatory system may change dramatically and so does the need for blood flow [50].

Usually, usage length is divided into three categories:

- Short-term support, up to 1 month
- Mid-term support, from 1 to 6 months
- long-term support, from 6 months up to a few years

With length of support relates various treatment approaches, as listed below.

3.1.1 Bridge to recovery

Heart has real probability to recover from some diseases (e.g. myocarditis, some forms of dillated cardiomyopathy) during mid-term to long-term support. This recovery may be chronic state compensation or full recover. Acute ischemias, myosarditis or graft rejection also short-term supports suit the purpose[31]. [31] also show studies, that give recovery rate of about 50% of treated patients after 6-12 months. Generally, bridge to recovery therapy (BTR) allows to exlude the necessity of transplantation in some cases.

3.1.2 Bridge to transplant

Today's most common usage of VAD is as a bridge to transplant (BTT) [31]. Patients must meet some general conditions[2] for a transplantation to be eligible for BTT or be already on the transplantation waiting list. After the hemodynamic parameters stabilize, the patient is written on the waiting list (if not already there). [31] show studies, which estimates survival to transplantation between 60-80 % (E.g. Thoratec claims survival of 69%). They also state, that the transplantation results are at least same as without previous use of VAD, because the patients are usually in better condition when undergoing the transplantation. During waiting on transplant, patients supported by certain devices (NovaCor, HeartMate...) could be discharged from hospital to home treatment[10].

[2]These conditions are reported by [31] as cardiac index under 2 $l \cdot min^{-1} \cdot m^{-2}$, systolic pressure 90 mmHg, left ventricle systolic fraction under 25% and some others.

3.1.3 Bridge to decision

Bridge to decision (BTD or also similar bridge to bridge (BTB), is used, when the patient is in critical circulatory failure state and exact diagnosis is not known nor it is time to find out (e.g. resuscitation). From definition BTD devices are meant for short-term support and are cheaper. During a few weeks, as the patient's health state stabilizes, following therapy is applied.

3.1.4 Destination treatment

Patients disqualified from transplantation program due to high age, healt state or other problems, are left on mechanical support as final treatment. Such devices has to provide appropriate life quality during long-term support. Currently, as the the devices become smaller, safer, more reliable and more convenientm, the number of usage grows. Statistics show, that using most recent devices, one year survival rate is over 70% [31].

3.2 Classification of MCS

Mechanic circulatory support devices are in truly meaning devices, which help the heart, or in more detail ventricles, either left or right, to pump blood through circulatory. But it is common to call this way also methods, which helps circulation in any way, such as ECMO or IABP.

Continuing in classification used in [18](however, this classificatin is not commonly accredited), the mechanical circulatory devices could be divided to three main subgroups:

Heart replacement devices are completely substituting native heart with artificial one. Total artificial hearts fall in this category.

Circulation assist devices are other means of facilitating the circulation. Primary aim is to provide perfusion to organs, not just save or help the heart, although also this could be the case. Such devices are extracorporeal mebrane oxygenation, intra-aortic balloon pump devices and modern Tandem Heart or Impella, and other.

Heart assist devices are those used for directly promoting blood flow through or overbridging it around the heart. This could be further divided to left, right and both ventricular support. This includes especially ventricular assist devices (or VADs). As the VADs are topic of this thesis, there would be discussed in more detail in its own section.

3.2.1 Total artificial heart

Total artificial heart (TAH) has quite long history, having its first implantation back in 1969. It was used as an 3-day BTT ([20]). After some successfull implantations in 80ties, this aproach has been suspended until 2001, when AbioCor TAH launched. This system uses internal as well as external battery pack with wireless energy transmission.

The only TAH approved by FDA (Food and Drugs Administration is an American regulation authority. It decides (among others), whether any medical

Figure 3.1: AbioCor TAH. Image from http://www.rwjuh.edu/news/artificial_heart_alert.html

remedy shall be used in USA) is the CardioWest TAH and that is for destination therapy only, where the patient is not eligible (due to age or other complications) for a transplantation. Its disadvantage is that there is no way back, because native heart has been extracted. In addition, the system is quite bulky and therefore is suitable for patients with large frame only.

Another TAH was a Jarvik-7 TAH with about 70 implantations as a BTT, but it is no longer in use today[40].

3.2.2 Intra-aortic balloon pump

Intraaortic baloon pump (IABP), also known as Intraaortic balloon counterpulsation is longest used method to support failing heart. Its implantation is rather easy, quick and relatively cheap.[20]. This method was originally introduced by Moulopoulos back in 1962 and first implanation came 6 years later. The principle is to increase perfusion of coronary arteries during diastole and thus help heart to recover. This is achieved by introduction of a thin balloon to descendent aorta through groin artery. The balloon is inflated and deflated based on heart rhytm, which is obtained from EKG or from pressure waveform. During systole is deflated, allowing more or less normal flow, and during diastole it is inflated, which limits flow and in combination with Windkessel effect (2.4.1 on page 8) increases pressure in aorta between heart and this balloon, leading to better perfusion of coronary arteries. The IABP is especially used after shock states after cardiochirurgic operation, or acute myocardial infarction. In terminal stages of CHF its usage si limited. Figure 3.2 shows the augmentation of pressure waveform during support by IABP. Note the increase during diastole, caused by the inflantion of the baloon.

The device is comparably cheap and the insertion is fast and simple, making it most used mechanical circulatory support ever.

3.2.3 Extracorporeal membrane oxygenation

Extracorporeal membrane oxygenation (ECMO) provides temporary support to heart and lungs function by means of cardiopulmonary bypass. In application of short- to mid-term MCS it is notedly used as bridge-to-bridge therapy in

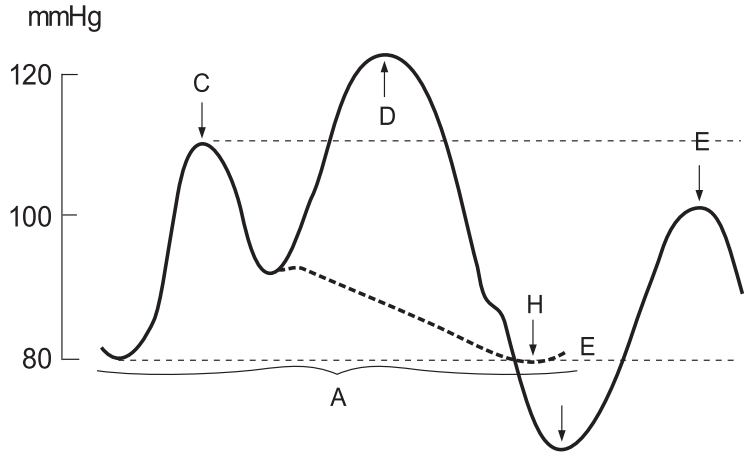

Figure 3.2: Augmentation of pressure in aorta before the balloon during IABP support. C is normal systolic pressure and D is the peak caused by IABP counterpulse.

acute heart or lungs failure, such as cardiogennic shock, myosardial infarction and postcardiotomy syndrome.[18]

ECMO consists of three main parts, which are oxygenator, heat exchanger and a blood pump. These parts, together with connecting tubes form closed system. Firstly, the blood flows from canulla in patient (usually in groin) through the pump, which propels it to oxygenator, where the blood is enriched by oxygen and disposed from carbon dioxide. Because blood loses heat to environment, it is needful to heat it in heat exchanger to appropriate level. Then the blood returns back to patient's body.

3.2.4 Other systems

Various number of other circulatory support systems exist. Here I list just a few of them.

Tandem heart Similarly to ECMO, the blood vessel access is made through groin artery and vein. The inlet canulla is led through femoral vein to left ventricle, where it sucks blood, which is then pumped by constant flow paracorporeal centrifugal pump to outlet in femoral artery. It is intented for short term support from a few hours up to two weeks ([40]), especially for postcardiotomy cardiogenic shock patients (those who have developed heart failure as a result of heart surgery or a heart attack) and as a bridge to a definitive therapy. Its main advantage is the percutaneous access, which enables relatively easy installation. This design was developed by Cardiac Assist Technologies Inc

Impella Impella from Abiomed Inc, pertinently system CardioHelpTM from Maquet company are used in paramedic applications. Impella is catheter-based cardiac assist device, which is inserted through femoral artery and through aortic valve directly to left ventricle. Here it sucks blood and expells it to aorta.

It serves as a partial circulatory support, with blood flow up to 2.5 liters per minute.

3.3 VAD

Ventricular assist devices (or VADs) are intented as direct support to ventricles.

Exctracorporeal (or paracorporeal) MCS are employed particularly in short- to mid-term support, either to bridge transplantation candidates or to support circulation after cardiochirugic surgery. Actual pump is placed outside the patient's body and its inlet and outlet are connected to body using canullae.

Pulsatile paracorporeal VADs are superior to ecmo or centrifugal pumps in a way of patient comfort, because they allow some extensive walks during on support, which eases patient's life ([35]).

First VADs were developedin 60s and 70s in pursuit for total artificial heart. They were designed to mimic own heart, i.e. filling during diastole and ejecting during systolic phase. Because of neture of such flow, those devices are called pulsatile flow (PF-VADs). Implantable PF-VADs spread as BTT in thousands since 1980. From 1970, they were implanted in around 10,000 patients[25].

VADs are further divided by placing to paracorporal (extracorporeal) and fully implanted. Paracorporal systems are placed outside patient's body and inlet and outlet are connected to vessels transcutaneously (through the skin) via canullae. Implanted systems, which is today prevailing group ([18]), are designed to be fully implanted, are reducing the inlet and outlet to just a power cord, while modern implantable devices employ transcutaneous energy transfer using coils, thus removing any hose piercing skin, which reduces the threat of infections and also is more convenient to patient.

Such a PF-VAD device si for example LionHeart VAD, which is specially intented for destination therapy. Its most advatage is, that it is fully implantable, including emergency battery pack. Energy transfer occurs wireless transcutaneously using a coil on both sides. This minimizes the threat of infection[27, 20].

Also, other fully implantable devices has been developed. Although also totally implantable PF-VAD exists, most of fully implantable VAD nowadays are CF-VAD (constant flow VAD), such as Thoratec Heartmate II, because of their reduced size and weight, power consumption and other issues..

3.3.1 Market share

As stated in expert report produced by Aoris for HeartWare (an Australian medical devices company) [1], market size incerased five folds since 1970. Old age and previous heart attack being the main risk factors, the annual incidence is about 1.5 million cases anually. As discussed in section 1.1 on page 2 there is about 1 million patients classified Class IV CHF worldiwide, however, as not all of the patients would benefit from the VAD or because other clinical reasons, the market in US requires about 30,000 LVADs per year and around 90,000 to 300,000 worldwide [1].

The market is further divided. About 3,500 patients in US are elegible for heart transplant, but only 2000-2400 do actually receive one. The remainder, as well as some patient who have to wait several months for a transplant, are candidates for bridge to transplant use of LVAD. [1]. As of 2004, there were six

devices approved for BTT Class IV use in Europe and three in US. In 2002, the US market for BTT LVADs was about 1000 devices annually, making it worth US$125-150 million ([1]). Worldwide the market is estimated at about 4000 implantations per year.

Use of VAD as a destination therapy is estimated at US$2 - 8 billion worldwide. In 2004, destination therapy represented most of then market and it was predicted to increase rapidly ([1]). The market size is predicted to be stable between 2004 and 2008.

However, entries stated by [1] are to be taken with reserve – *the need for* and *actually implanted* devices shall not be confused. Intermacs report[41] summarizes use of MCS in 90 hospitals in US and registers only around 1500 patients since 1996.

3.3.2 Usage by placing

Ventricular assist device is meant to assist ventricle to pump blood. As they are two ventricles in heart, we divide the support to left, right and both.

LVAD Left ventricular assist device (LVAD) is most frequently used (or as a part of Bi-VAD) support, while the left ventricle has much more work to pump blood through whole systemic circuit, so it is more susceptible to failure. According to [41], LVAD only is used in around 80% of implants. Usually, as inlet is selected own left ventricle and outlet is in aortic arch.

RVAD Right VAD (RVAD) does support right ventricle only. Its use is quite rare nowadays, as [41] registers only around 1% of implantations to be RVAD.

Bi-VAD Biventricular support () is usually formed using two devices working at same time. This situation emerges, when the heart is failing as a whole and not only left ventricle (as is usuall). [41] claims, that this treatment is used in 13% of cases.

3.3.3 Usage by product

For various indication there are used different VAD types.

> Device selection depends not only on specific patient characteristics and the pathology of the patient's heart failure, but also on device characteristics, device availability, and the experience of the surgical team. (From [9])

The device is selected based on individual patient's needs. Table 3.1 summarizes its use in clinical practise.

3.3.4 Connection of inlet and outlet

Originally, the inlet canulla for LVAD was inserted into left atria[11], nowadays the inlet is usually from ventricle through heart's apex as seen in figure 3.3. Reinhartz et al.[35] report, that left atrial cannulation proved a risk factor for neurological complication.

	After surgery	BTT	BTR	DT
ECMO	X			
Abiomed BVS 5000	X			
Bio-Medicus centrifugal pump	X			
Thoratec VAD	X	X		
HeartMate VAD		X	X	
Novacor LVAD		X	X	
Jarvik 2000		X		
MicroMed DeBakey VAD		X		
BerlinHeart EXCOR			X	
LionHeart LVD2000				X
CardioWest TAH				X
Abiocor TAH				X

Table 3.1: Most frequent used VAD models by indication as of around 2001 (from [20])

When the canullation is done through ventricle's apex, the VAD could work either in series with native heart or in parallel to it. In many patients especially early weeks after operation, the blood flow through aortic valve is minimal and nearly all of the blood is flowing through the VAD. Then the pump is working *in series* with native heart. As the heart recovers, it begins to contribute to cardiac output by pumping blood through aortic valve. In this case it is said to be connected *in parallel* to the VAD[25]. Native flow then merges with the VAD outlet, which arises some concerns in these patients.

3.3.5 Generations

PF-VAD are often reffered to as first generation pumps. Second, third and fourth generation were all designed using rotating element and producing contiuous flow ejection.

Second generation devices are CF that "use a magnetic coupling between the housing and the rotating element positioned with blood-washed bearings." [25]. These include Berlin Heart INCOR VAD or Thoratec HeartMate II.

Third generation are CF-VADS with no mechanical contacts between the impeller and drive mechanism. Thanks this improvement it was possible to eliminate bearing wearing as well as heat production there.

Fourth generation, including both impeller and centrifugal designs, makes use of magnetically suspended impellers. Such pumps are still in clinical trials, for example Levacor, DuraHeart amd VentrAssist ([25])

3.3.6 Pulsatile VAD

First generation VAD are paracorporeal systems like Thoratec VAD and are suitable for midterm support up to about 6 months [10].

PF-VADS (Pulsatile flow VAD) are used since 1970, having been implanted in thousands of patients ([25]) and some of them are still in use today, owing to wide clinical experience and recognition. They had been designed to mimic the native heart fucntion, which made them large, bulky, noisy and owing to

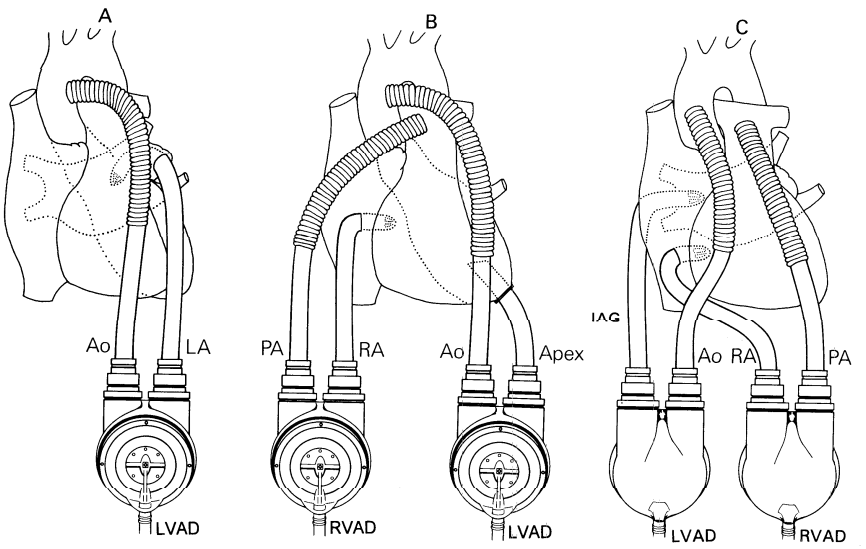

Figure 3.3: Schematics of the Thoratec PVAD placement in human body. Image from [43].

a number of moving parts also with quite poor reliability, because of bearing wearing down [25].

All of the PF-VADs have similar design. It consists of a flexible membrane or a pusher plate and valves to keep the flow unidirectional. Some of the devices are powered directly through a pipe by a gas, which creates pressure on the blood sac (Thoratec VAD), some others have motor of its own, which operates the pusher plate (e.g. Novacor). However, gas transfer line must lead also to those powered electrically to equalize pressure in motor chamber[25].

The blood-contacting surfaces are usually porous to encourage formation and adherence of pseudoneointima (new layer mimicking the inner-most layer covering blood vessel's wall) to minimize threat of thrombosis. Once this layer is formed, anticoagulation medication could be greatly reduced or even withdrawn [25].

It seems, that PF-VADs are overcome, however, they are still used and implanted. It takes long time from development, through clinical trials to approval and major usage.

3.3.6.1 Filling and ejection phase

During the filling phase, the inflow is supported by pressure gradient created by negative pressure provided to VAD chamber, which could be as low as -10 to -40 mmHg. For Thoratec LVAD device, the ejection drive pressure is usually set to 230 to 245 mmHg to assure the VAD was emptied completely during the allocated ejection time of $250 - 300$ ms[11, 42]. The filling and ejection course are shown in figure 3.4.

Thoratec itself recomends high driving pressure and systolic to completely empty the VAD:

> At low beat rates there is an increased risk of thrombus formation in the VAD. Therefore it is recommended that the device be operated at rates above 40 bpm and with complete filling and ejection of the VAD blood pump in the volume mode (auto mode on TLC-II). [...] When using the Dual Drive Console, do not lower the LVAD drive pressure below 225 mmHg or the RVAD drive pressure below 135 mmHg. Lower drive pressure may result in incomplete VAD ejection, which can lead to blood stasis and possible thromboembolism. It is recommended that the pneumatic drive pressure be set at least 100 mmHg above the systolic blood pressure (LVAD: 230 to 245 mmHg; RVAD: 140 to 160 mmHg) to completely empty the VAD with a systolic ejection time of 300 msec.
>
> (From [43])

The filling duration is substantially longer than the ejection phase, because it is harder to fill the VAD than to empty it. Two approaches are used to improve filling, firstly to lengthen the time allocated for filling and secondly to increase pressure gradient in inlet canulla.

Total VAD net outflow is determinde by its effective stroke volume and frequency rate. When the VAD has time to fill completely (with Thoratec VAD 65 ml), it would produce net outflow of 3.9 l/min at a rate of 60 bpm. Maximum flow is achieved, when the VAD fills and empties completely with no lost time between phases[11]. That means, that using FFFE (see section below) mode, the total net outflow is the highest possible.

[11] conclude, that optimal filling to ejection ratio is at 35 % ejection (at higher VAD rates with default conditions)

3.3.6.2 Modes

The VAD could be operated in three different control modes [11]:

- Fixed rate (FR), asynchronous to native heart rate
- Full-to-empty, (also known as Full-fill-full-eject [FFFE] or auto mode), also asynchrnonous
- Synchronous R-wave counterpulsation

Full fill, full eject This mode is recommended by manufacturer ([42]) for long-term support and is most widely used.

This simple, yet very powerful mode has fixed stroke volume and variable rate, which could renspond to the blood flow needs of the body and at the same time provides continuous washing of all blood-contacting surfaces to minimize the threat of thrombosis[11]. As stated in section 3.3.6.1, it also produces maximal total net flow among other modes.

A Hall-effect switch is used to tell, when the pump is full so the ejection could start. After ejection, which length is specified by the preset time (around 300 ms), the control switches to filling phase again. The duration of this phase is a function of preset filling pressure (vacuum) and pressure in inlet point (ventricle, atria). [11] also states, that at a constant maximal stroke volume of 65 ml, the VAD rate and thus the total outflow would respond to fairly wide range of

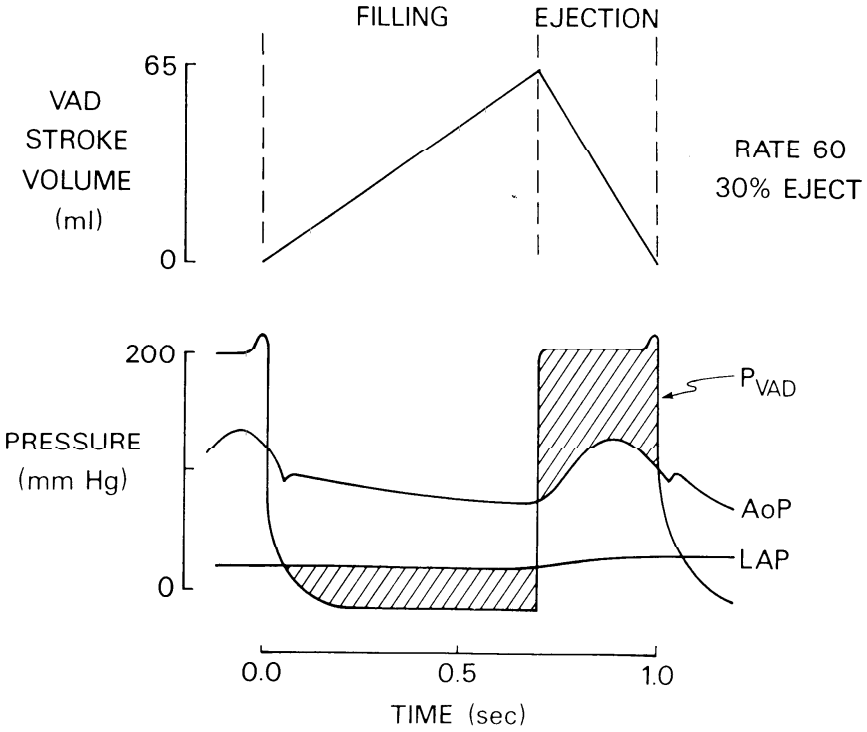

Figure 3.4: Schematics of VAD volume during filling and ejection, flow rate and pressure while cannulated from atrium. Pvad is provided pressure to the VAD, AoP aortic pressure, LAP left atrial pressure. Negative flow indicates inflow during filling and positive flow means ejection outflow. The flow and pressure is idealized here. Image from ([43])

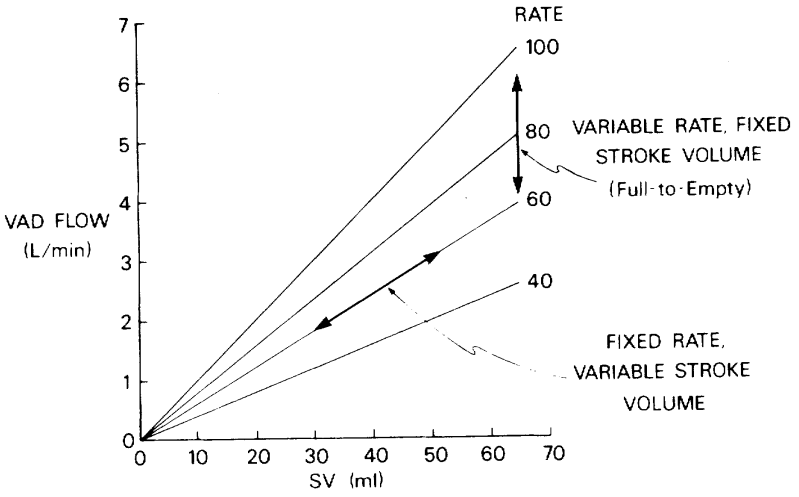

Figure 3.5: Schematics of variations of VAD output when in Fixed rate and FFFE (auto) mode with maximal stroke volume 65 ml. The arrows are showing means of autoregulation. (From [11])

blood flow demands as illustrated in figure Figure 3.5 on page 29. When the pump failes to fill in given time (specified as filling time for the fixed rate on console), the control initiates ejection as in fixed rate. As the pumping is not synchronized to native heart rate, the arterial pressure is charecterized by an incosistent amplitude and shape.

Fixed rate Only rate and fractional duration of the ejection are specified. Thoratec corp. [43] recommends using ejection time of ~300 ms, which should be set by ejection length fraction parameter. When changing pump rate, also ejection length should be adjusted, so the ejection time is again around 300 ms.

This mode is particularly useful when initiating support or for weaning patient from the support or any other case, where the flow is to be non maximal. VAD flow could be directly modified by changing the rate and fraction for ejection[11], so that the pump is not filled at full. Also, increase of the filling pressure (so that the filling gradient is lowered) would retard the inflow, which would result in incomplete filling and thus lower net outflow. However, since the outflow is directly dependent on filling, in is very sensitive to changes in inlet pressure in atria or ventricles.

This mode is also used as back-up mode, when other driving signals are lost.

Comparison to FFFE mode is shown in figure 3.5. FFFE mode works in highest possible flows, which could be even augmented, when the filling rate improves (that is increased venous pressure, which is usually during exercise or other strain). To the contrary, using FR one could adjust the flow rate to be submaximal, but the autoregulation is also kept – by increased venous pressure the filling is improved, which leads to larger stroke volume.

Synchronous R-wave counterpulsation mode is synchronized with R wave (the peak value, signalizing the systole) from ECG. This time point signalizes the control to end ejection. Then filling phase follows, which coincides with own heart systole and ejection occurs at own heart's diastole. In other words, when the native heart fills, the pump ejects and when native heart ejects, the VAD fills. When the canullation is done from the ventricle (as is common), filling in systole phase is advantageous because of the higher pressure gradient between ventricle (and filling pressure in the pump (around zero or even negative). VAD filling during ejection is also beneficial, because introduction of additional outlet lowers the pressure against which the heart must work, thus reducing wall tension, which could theoretically improve recovery of failing heart [11]. In addition, as the diastolic pressure is increased, which can improve blood flow through coronary arteries. More nutritions may also help the myocard to recover.

However, it may be harder to control filling and ejection, as the EKG signal may be potentially erroneous. Also, sometimes a complete stroke volume could not be achieved, leading to not complete washing of blood-contacting surfaces, which could increase the threat of thromboembolism.

This control mode is least employed.

3.3.6.3 Devices

There is number a number of devices, but since the medical remedies are strictly under control of state's administration, only approved devices may be used.

Thoratec PVAD and IVAD Thoratec has a number of PF-VAD devices on the market in Europe, Canada and USA, with very similar design. These are:

- Thoratec PVAD is over 20 years in clinical use, which makes it the oldest, yet widely used device even today. It is because the medical professionals got used to it and they have extensive experience. More than 4000 patients have been supported using this device [44]. It has been approved in US as BTT since 1995 and as BTR since 1998.
- Thoratec IVAD is an implantable variation of PVAD. It has been implanted to more than 500 patients. Approved in US since 2004 as BTT.
- Thoratec XVE also known as Heartmate I, boasts that no systemic anticoagulation is needed. It has been received by around 4500 patients worldwide. In USA, it has been approved since 2001 as BTT and as DT since 2003.

All these three pumps are in principle having very similar design, which was originally developed at the Pennsylvania State University College of Medicine [11]. The PVAD consist of a smooth seamless pumping sac made of segmented polyurethane (Biomer) enclosed in a rigid case. The pump is connected to pneumatic drive console, which provides high positive pressure for ejection and low or negative pressure for filling phase. In the pump there is inbuilt a Hall switch to indicate full fill state. All pumps have fixed maximal stroke volume, which is 65 ml with PVAD. The design is illustrated in figure 3.6.

When the PVAD is connected to atria, a 30 mm long canulla with internal diameter of 11mm is used as VAD inlet. As an outlet, there is a 18 cm long

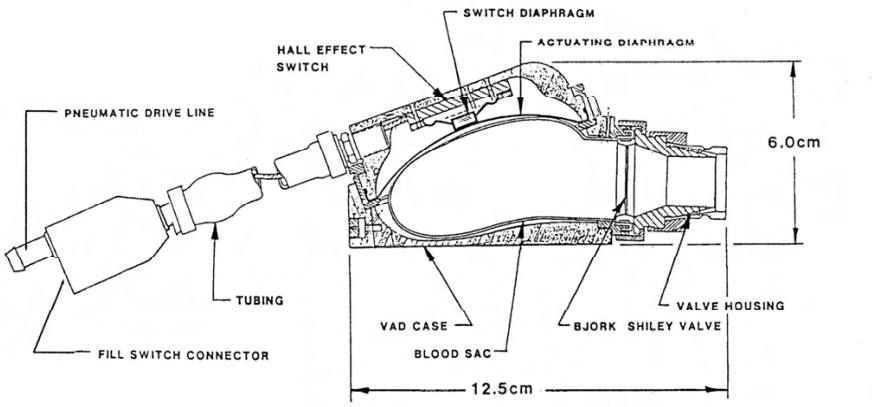

Figure 3.6: Schematics of Thoratec PVAD

tube with internal diameter of 17mm. The canullae are brought through the skin under the rib cage and connected to the VAD in paracorporeal position[11].

Berlin Heart Although it has been used since 1994 in Europe, it is still not as well known and widely used as Thoratec, Berlin Heart has its PF-VAD system on Europe market called EXCOR. Unlike Thoratec, they are manufacturing also different stroke volume – Thoratec PVAD stroke volume is 65 ml for both LVAD and RVAD, whereas Berlin Heart EXCOR is employing 80ml for an LVAD and 60 for RVAD (when in Bi-VAD) for adult patients weighting more than 50kg[3] and has various sizes for small patients.

The design and principles are very similar to Thoratec devices.

Medos Another German company, Medos, is manufacturing very similar system. It has been used since 1994. Similarly to Berlin Heart, it also employs pumps with different stroke volume depending in patient size.

Novacor Novacor left ventricular system, produced by World Heart, has been discontinued by manufacturer in 2008 and is no longer implanted. It has been used since 1984 and it was employed in more than 1,800 patients in North America, Europe and Japan.

Novacor, being implantable VAD, used a bit differrent technique. It contained electromagnet, which took care of pressing the sac, so there was no need of pneumatic driving pressure console. Percutaneous cannulation provided power and compensated pressure difference.

3.3.7 Constant flow VAD

Constant flow VAD (CS-VAD) uses some kind of rotating impeller to propel fluid through.

Important to say, that although the CF-VADs are designed to provide constant flow in constant conditions, in reality it is not the case. Currently, most of

[3] http://www.berlinheart.de/englisch/medpro/EXCOR/kanuelen/Finder

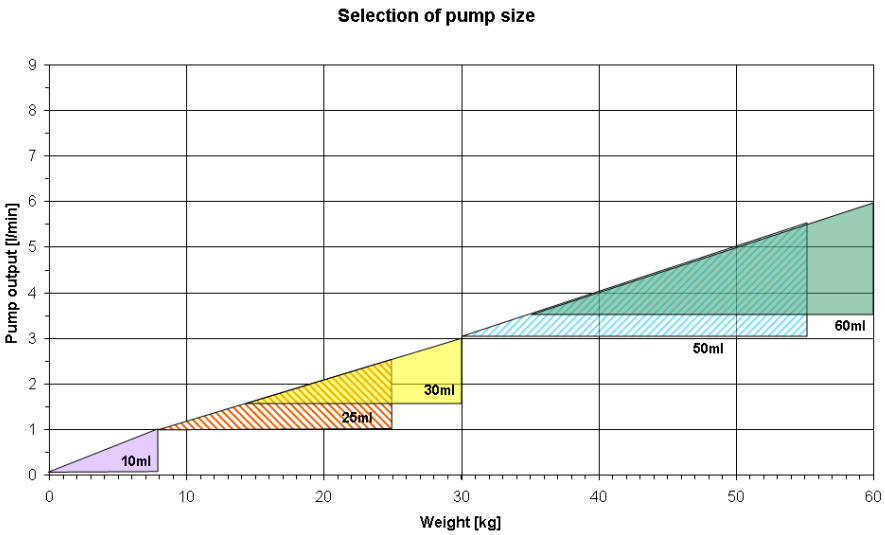

Figure 3.7: Berlin Heart EXCOR Pediatric size guideline: for different body size and intended flow output, different stroke volumes are recommended (From www.berlinheart.de)

Figure 3.8: Berlin Heart EXCOR VAD visualization with mobile driving system. (Modified from www.berlinheart.de)

the LVADs are cannulated into ventricles. The CS-VADs are usually sensitive to pressure gradient across the pump (especially *preload* pressure). Native heart, even impaired, does provide some systolic pressure, which creates the preload of the pump. The higher preload the higher pump output. Thus, even the CS-VAD is generating pulsatile flow, which is based on augmentation of native heart systole.

Basically, as of current, two designs are employed. First of it, the *axial flow* devices works as an Archimedes screw, rotating at approximately 10.000 rpm. They are usually designed to pump 5-6 l/m at 100mmHg pressure.

Other design, *centrifugal flow* has much lower rotational speed, which is typically 2000 to 3000 rpm. Because of this lower speed, the bearing is believed to have lifespan longer than 2 years ([25]) . These have been employed for short-term support during cardiopulmonary bypass and are relatively atraumatic to the blood in this aplication[25]

> In centrifugal pumps, the fluid enters through the inlet tube into the center of the pump, where an impeller that resembles a spinning top moves the fluid towards the outside of the pump, where it is collected and expelled through the outflow tube. Hydraulic levitation of the impeller occurs at a certain rotational speed, usually 1500–2000 rpm, and can achieve a wide range of flow rates at a fairly constant pressure. Impeller position, shape, and size are very important, as they affect the magnitude of the vortex force on the blood. Eliminating stagnant areas, typically at the bottom of the impeller, is important for reducing thrombogenicity and is sometimes accomplished with secondary channels. (From [25])

For both pump design types, the research efforts are done to project the propeller to inflict less damage to the blood and to optimalize shear stress so no coagulation would occur.

As the scope of this thesis lies in PF-VADs, I would not discuss further details and issues of CF-VADs here.

3.3.7.1 Devices

Many constant-flow devices emerged recently, many of them are still in development or clinical trials stage. This list is by no means complete.

Thoratec Heartmate II This CF-VAD has been implanted as DT or BTT in more than 4000 patients worldwide, with 79 % success over 18 months [44], which shows 10 % improvement over Thoratec XVE LVAS system.

Recently (as of February 2010), this system has been approved by FDA also for destination therapy in the USA, while for BTT it has been approved since 2008 there.

CentriMag This system produced by Levitronix company (distributed by Thoratec) is employing short-term constant flow extracorporeal support up to one month and is approved as an RVAD support. It uses centrifugal pump and the propeller is magnetically propelled and levitating, using no bearings.

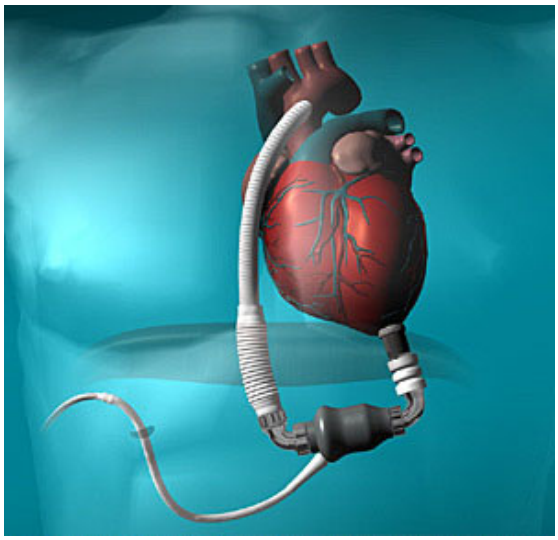

Figure 3.9: Thoratec HeartMate II LVAS. Notice short inlet cannulla (on right side) for apex cannullation and longer outlet cannulla. Image courtesy Thoratec Corporation, Inc.

Jarvik 2000 Jarvik 2000 is an axial pump wih a size about a "C" battery and weighting no more than 100g. It is implanted directly to apex using no inlet cannulla, where it is able to generate flow of about 5 liters per minute using 8 ,000 – 12,000 rpm.

In USA, the Jarvik 2000 system is undergoing clinical investigation, whereas in Europe it's approved for BTT and DT therapy.

Other Many other devices exists and many more are emerging. At random, MicroMed DeBakey introduced HeartAssist 5, which claims to be fifth generation VAD, BerlinHeart is offering its INCOR, HeartWare is pushing forward with their HVAD and others are also not asleep. Mostly, the VADs are authorize by CE Mark for usage in Europe, but they struggle to get to the US market, starting clinical trials there.

3.3.8 Adverse effects and complications

As nearly all medical remedies, the VADs and MCS in general suffers from a number of adverse effects.

3.3.8.1 Hemolysis

Damage to red blood cell which causes its rupture and destruction is called hemolysis. This could be easily measured. However, damage caused by extensive shear stress does not necessarily destroy the cell instantenously. That is called sub-lethal blood damage. Such damage affects function of the red blood cell.

> Exposure to shear can induce a stiffening of the cell membrane, causing more difficulty in deforming while passing through capillaries

> [33, 34]. In reality, many of the red blood cells in VAD patients have been chronically exposed to the high-shear environment of the pump, which has been shown to shorten their normal lifetime [33]. (From [25])

3.3.8.2 Embolism

Embolism on membrane or on valves is quite common threat. Thus, anticoagulation medicaments, which decreases the ability of blood to clot, have to be taken.

> In general, integrating a blood-contacting device with the human body increases the risk of thrombus formation and stroke. This is particularly true with VADs, as they often attach to the aorta proximal to the arteries that supply blood to the brain.(From [25])

Embolism may result in stroke, pulmonary or other non-cerebral organ infarction, leg ischemia, or other vascular obstruction. Continuous anticoagulation with heparin or warfarin is recommended[43].

Nonetheless, it is worth mention, that patients of similar age and disease, who do not receive any MCS, are also susceptible to thromboembolitic events. Short after implantation, there is recommendation not to use any anticoagulant drugs ([10]), as it could induce bleeding and anticoagulation therapy is employed afterwards. [10] also reports, that thromboembolic events occured in 28% of patients with Novacor LVAD and 15% with Thoratec patients (However, the number of patients was quite small - 144 patients with Thoratec and 85 with Novacor).

Hemodynamically significant stenoses Hemodynamically significant (HS) stenose is a arterial stenose with diameter lowered by more than 50% ([30]). Due to obstructed diameter, aside from higher flow resistance, also flow is much higher here, which results in turbulent flow and this may increase the risk of blood clotting (high shear rate), creating thromboembolisms. Such stenoses are often monitored.

In theory, when increasing flow thourgh stenosis, which was not HS, to certain level, due to higher speed a turbulent flow would occur, which classifies the stenosis to be HS. This theory needs to be proven though.

3.3.8.3 Native heart and VAD interaction

Implanting pulsatile VAD could also lead to potentially dangerous interaction with own heart's contraction. If the device works in fill-eject modes, own heart's filling rate is significantly reduced, which results in small stroke volume (VAD is taking care of the rest). Interaction would not be so important. However, in case of fixed-rate mode, the VAD fills until the signal to eject is received. Imagine, that the venous return and filling pressure is adequate engough to fill VAD quickly, thus leaving time for own's heart filling. In the worst case the heart frequency is so high (or VAD frequency so low), that it manages to fill completely while the VAD is full. Now, let both pumps eject their load at same time. We get flow peak about twice as high as normal conditions! This extreme peak hypertension would definitely cause some circulation disorders. The peak

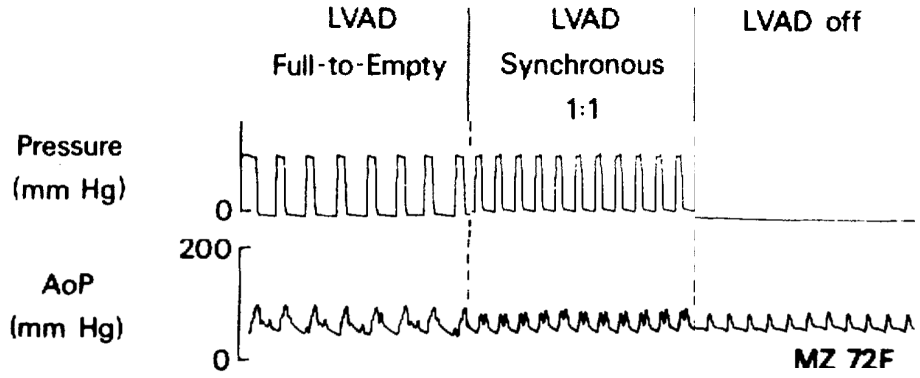

Figure 3.10: Interaction of VAD on aortic pressure when operating in asynchronous (FFFE - Full-to-Empty) and synchronous (R-wave sync) modes in 72-year woman. Note, that the synchronous mode has overall lower pressure because the pump has not been fully filled. Image modified from [11].

could be even more dangerous considering, that circulation with hypertension had years to adapt itself and now we are inducing it all of a sudden. Figure 3.10 is showing the interaction when in asynchronous full-empty mode and synchronous mode.

There is even possibility of rupture of (rather artherosclerotic) vessel during extreme pressure peaks.

Also, problems could arise on even still problematic stenoses. As mentioned in section 2.2.0.1 on page 5, clots may form at stenoses due to limited flow. When the flow rises dramatically over normal bounds, such clots could be torn off and cause embolia at other part of the body.

3.3.8.4 Infection

Although not direct adverse effect, still one of main complications (as summarized by [10], it varies from 12 to 48%). Prior to implantation patients are usually not in perfect shape condition and in addition the body is weakened by extensive operation. Although big efforts are made, the infection may be introduced by operation itself. Also, paracorporeal systems offers infection a way into organism through their connector sites, by which the canulae/wires enters the body. When fully implantable systems are used, the threat is lowered.

Also, some biocompatible materials are associated with increased risk of infection. For instance, the inner surface of Thoratec XVE, the Thoralon is associated with higher threat of infection, since the pathogens are encouraged to bind to it similarly as the material, which gives birth to pseudoneointima[15].

There are also concerns, that for increased infection could be responsible insufficient perfusion, but this has not been proved.

3.3.8.5 Bleeding

As well as infection, the bleeding is not adverse effect in truly meaning, but a common complication. [10] defines it as a loss of more than 1,500 $ml \cdot m^{-2}$ of

blood volume in 24 hours reports bleeding complication in around 22% patients (citing other authors, who report 20-45%, depending on definition), making it one of most frequent complications. Bleeding occurs either as an early complication because of operation technique or as a late complication at connector sites. [10] also report, that meticulous hemostasis during operation is one of the most important factors. Because bleeding may also result from anticoagulation treatment, they do not recommend employing it till 24 hours after operation.

3.3.8.6 Liver failure

[10] reported quite high incidence of liver failure (17%). From patients who suffered this problem, only 33% was succesfuly bridged to transplantation (as compared to 66% without liver failure). They also show, that patients, which are supported by BiVAD are more susceptible to liver failure, than those supported by LVAD only.

Possibly, liver failure may be caused by uncoordinated perfusion, which does not fit physiological needs.

3.3.8.7 Pulsatility issues

Pulsatility is not energetically favourable. But it is starting to prove, that constant blood flow is unable to perfuse tissues as effectively[45, 3].

It is a concern, that using constant-flow pump with weak native heart, the flow would lose its pulsatile character, which could lead to hypoperfusion[18], which is associated to a number of complications, such as organ failure or infection. I have not found any proves of this theory so far though.

Some studies are however showing the contrary. For example, [6] observed difference between extracorporeal pulsatile and non-pulsatile pig's lung reperfusion and in contrary to hypothesis, found no significant difference. Adtional research into this issue should be concluded.

3.3.8.8 Other complications

Program of mechanical circulatory support still has many caveats. Apart from complications, which were already mentioned, there is a number of other issues. For instance failure of the MCS[20] plays role, especially in long-term support, being the cause of death in nearly 3 % ([41])

As a primary cause of death, Intermacs[41] report multi-organ (overall 7 %), right heart (3.7 %) and renal (2.6 %) failure.

Intermacs report also states, that one month survival is about 91 %, which decreases to 50 % in 24 months survival. Transplanted or recovered patients are censored though, overall it was 275 deaths out of 1361 patients in total, which is death rate of only 20 %. However, these data are for aggregate VAD support and could not be distinguished, which type was implanted.

Chapter 4

Body size issues

Pediatric issues Selecting appropriate MCS is a questionable subject. As stated in section 3.3.3 on page 24, it depends not only on patient size, indication, but also on availiability of device and experience of medical team.

Most of current VADs availiable are designed for adult patients and options for pediatric patients are limited.

For fully implanted device is that even a physical problem to fit an adult device and cannullation into undersized patient. Therefore, paracorporeal devices are often employed.

Apart from cannulation, also hemodynamics issues arise, as the circulatory system of small patient is used to smaller flows. That is not such problem with CF-VADs, where we can limit the revolutions and thus lowering the overall flow.

Nowadays, although the CF-VADs are slowly conquering the market, first generation PF-VADs are still in use. Either because of limited availiability of CF-VAD, or because of higher experience with PF-VADs and/or lower trust in CF, as there are concerns about limited perfusion. Also, approvals of devices by administration have to be taken into account. For instance, in Northern America some of the CF-VADs were approved recently (see section 3.3.7.1 on page 33).

Device selection The current options for children who require mechanical circulatory support are limited. As of 2002: "Device selection for long-term support is much more complicated and often is subjective and based on the surgeons' experience and bias. For smaller patients (BSA 1.5 m^2), the Thoratec device and eventually a continuous flow pump are the only options. For the larger patient, all devices are potential options."[9]

> Patient size is 1 determinant in selecting a mechanical circulatory support device. The current pulsatile ventricular assist devices (VADs) were designed primarily for average-sized adults. The flexibility of the Thoratec VAD, however, has encouraged physicians to use it in a significant number of intermediate-sized older children and adolescents. (From [35])

As of 2003, "There are currently no other pulsatile devices available in the United States for this patient group. Alternatives include ECMO and centrifu-

gal pumps [...] The Thoratec Heartmate appears to be too large for smaller children."[34]

Paracorporeal pulsatile devices may be an option for longer term support in patients of intermediate size (approximately 20 kg or more, BSA of 0.8 m2 or more, children approximately 7 years or older). The Thoratec ventricular assist device (VAD) is one of the most frequently used pulsatile devices in this size and age group[35].

However, some of PF-VADs (such as Thoratec PVAD) are often manufactured in one size only and thus the stroke volume and total flow (like CI but together with VAD) could not be limited (at least in most used automatic mode). Also devices with smaller stroke volumes exist (Berlin Heart, Medos - see section 3.3.6.3 on page 30), but they are not approved everywhere (i.e. not in Northern America).

Some medical professionals do realize that it could increase chance of adverse effects and theorize, that small patients should have smaller stroke volume. The adult-sized PF-VADs are recommended for patients with BSA higher than 1.5 m^2.

In the last few years, most centers used the fixed rate mode with partial stroke volumes and high pump rates in children, which intuitively seems to be the correct physiologic choice for maintaining normal systolic and pulse pressures. When keeping high drive pressures, it ensures complete emptying of the pump, which is thought to reduce stasis and therefore thromboembolic events. This might be reflected in the lower incidence of neurologic events in the patients later in the series. [34]

Appropriate range Husein et al. (2008) were observing effect of adult-sized VAD on 22 pediatric patients and found that:

> "Optimal hemodynamics were defined as a cardiac index of 2.7 $l{\cdot}m^{-2}$, VAD rate of 80 beats per minute and fill/empty being 100%, meaning complete filling and emptying.
>
> *[...]*
>
> For patients with no VADRC *(VAD related complications)*, their mean ratios from ideal for blood pump size, pump rate and fill/empty ratios were 0.98, 0.92, and 1.00, respectively. For patients with VADRC, their mean ratios for blood pump size, pump rate and fill/empty ratios were 0.72, 0.72, and 0.78, respectively." (From [19])

From this it seems, that blood pump size is really responsible for needless adverse issues. But because they have investigated just 22 patients, their results could not be taken as a prove. But it provides promising direction, though.

Study results [35] conducted a retrospective study in 58 children and adolescents from 7 to 17 years old (mean age 13.8), who has been supported by Thoratec VAD in 27 centers worldwide as of December 1999 and mean patient's body surface area was 1.5 m^2 (ranging from 0.7 to 2.1m^2). They state, that 60% patients survived to transplantation and 10% to recovery of their native heart. They conclude, that patient age and size were not significantly associated with increased risk of death or adverse events. Leading complication was neurologic events.

However, they also report, that observed rate of neurological events (27%) were considerably higher than 5 - 15% reported for the Thoratec device. Even though the size of the patient were not significant, it appears, that young patients are more threatened by neurological events during support..

Excellent after-transplantion survival rate (97%) showed good patients' condition after support.

"However, although during the initial uses of the Thoratec VAD in children, rather low VAD rates between 50 and 70 minutes were used, more recently there appeared to be a tendency toward faster rates (80–90 min) and partial stroke volumes. Of the seven most recent patients in the current study, only one experienced a small, fully reversible thromboembolic stroke."[34]

Reinhartz et al. (2003) [34] also state:

> It has also been hypothesized that hemorrhagic strokes may be caused by high peak systolic blood pressure from high stroke volumes in oversized devices. In our patient group, only one of three patients with intracerebral bleeding was reported to be consistently hypertensive (systolic blood pressure 140 mm Hg). However, just short periods of hypertension may suffice to cause an event, and these periods may even go undetected. We therefore cannot definitively prove (or discard) this hypothesis given the limited data in this study.
>
> We recommend careful anticoagulation and application of higher pump rates with partial filling but complete emptying to minimize neurologic events. (From [34])

Next part of the thesis would try to prove such statement.

Chapter 5

Model

5.1 Objective

The design of a model is strongly affected by the experiment objective. I described the issues and background in detail in preceding chapters, so in short; I try to prove, that fixed stroke volume of the pump could be dangerous to patients of different sizes and especially that increased stroke volume could induce hypertension.

The model should also allow to characterize the vascular system by parameters, which should be similar to physiological for easy tuning.

Therefore it is sufficient to observe just very generalized macroscopic circulation.

5.2 Pulsatile models

After initial bibliographic search I made sure, that there have been already implemented handful of pulsatile models. However most of them were not revealed completely in the articles (missing parts and parameters), were too simple or too complex or do not fit my objective in other way.

Some models employ waterfall strategy, that means with no circulatory loop. That is not quite providential for the case, because although not directly in the objective, I would also like to study the venous return and to enhance this model in the future.

Bovendeerd et al ([16]) investigated dependence of intramyacardial pressure on ventricular loading and contractility and developed a lumped electrical analogy model with simplified systemic circulation and circulation through coronary arteries. However, their model emphasize coronary flow and ventricular contractility, but systemic circulation is quite simplified, using one inertance, resitance and compliance for arteries. However their description of the heart contractility and VAD is too complicated and I believe, that some parameters are missing. This model shows similarities to that proposed by [8], which could be regarded as extension of Bovendeerd's model, although they are not citing each other. [8] added second compliance to the models of arteries and veins, making the pressure and flow wafeforms more similar to that observed in big arteries, and inertance in peripherals, which damps oscillations, as the cappilaries really do.

One of most legendary models, the Gyuton's model of circulatory system, from 1972 was kind of milestone in physiology, while it suggested new ways, how to investigate complex physiology interactions using mathematical models powered by computers. This model was originally implented in Fortran language. Subsequently, it has been converted to other languages including MATLAB/Simulink and Modelica ([24]). This model incorporates a number of regulations, however, it is not pulsatile. It works just with mean arterial (resp. venous) pressure, which does not exactly suit my case. Nonetheless, efforts have been made to convert this complex model to pulsatile ([49]). For my goal, this model was unnecessarily complex, creating and validating such comlicated model with all regulations would be something like philosopher's stone for VAD simulation.

Some models also incorporated baroreceptor control [2]. The model proposed by [2] makes use of electrical analogies. Their design of VAD pump is quite similar to mine, with grounded capacitor with voltage source in series, which mimics pressure input.

Also, models of the pulsatile blood pump were developed. For instance, Yu et al. ([51]) developed a model of Novacor LVAS pump and validated it on physical mock circulatory model.

[16] as well as others employed just left side circulation for their study.

[12] studied arterial properties and proposed equations describing one-dimensional model of bifurcations, viscoelasticity and pressure-wave propagation.

5.3 Modelica language

Modelica is a modern acausal modeling environment developed by Modelica Association. Modelica is an object oriented declarative acausal multi-domain modelling language.

> Modelica is primarily a modeling language that allows specification of mathematical models of complex natural or man-made systems, e.g., for the purpose of computer simulation of dynamic systems where behavior evolves as a function of time. Modelica is also an object-oriented equation-based programming language, oriented toward computational applications with high complexity requiring high performance. (From [13])

5.3.1 Acausal (declarative) modeling

Declarative programming expresses the logic of computation, as opposed to imperative programming, which merely describes the sequence of actions to be done.

One way of studying physical systems is to build convenient abstractions of them called models. An acausal model is composed of

- variables
- relations between variables

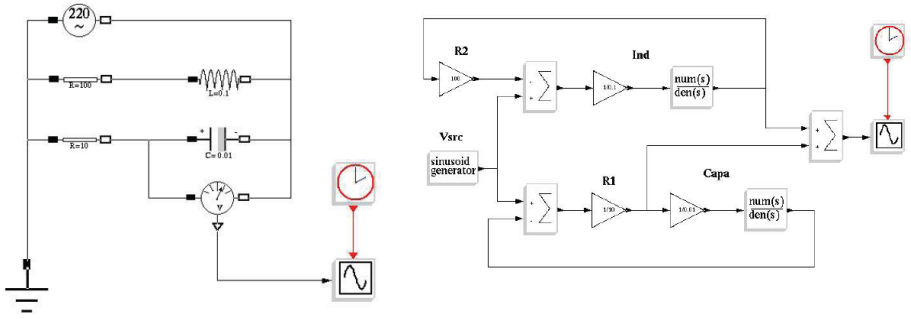

Figure 5.1: Acausal (left) vs. causal model (right). Note, that acausal modelling uses logical object connection, rather than way of computation. (From [14])

The variables in a model are functions of time to observable quantities (they implicitly expose changes inside models). The relations in a model act as constraints between the values variables take at each instant. Models interact through constraints between some of their variables. A simulation thus consists of extracting information from a model at one or more time instants.

Causal models, quite the contrary, are composed of

- Inputs
- Outputs
- Variables
- State variables
- Relations between inputs and (state) variables constraining the value of outputs and variables
- Relations between inputs and (state) variables constraining the value of the derivatives of state variables

Inputs of causal models handle data coming from the environment and outputs handle data to be exported to the environment. (State) variables of causal models are used to compute observable quantities. The key point is: data flow is explicit, i.e., it is possible to simulate a causal model using value propagation first and then integration. (Freely after [14])

Advantages of Modelica over some other current modeling environments (such as Matlab/simulink) are discussed also in [24]. They state, that acausal model better describes the basis of modelled reality and simulation models are much better readable and are less susceptible to mistakes.

Acauasal models represent relatively independent block in its domain and they could have both acausal and causal[1] connectors to other blocks combined together. So even in modelica you are able to model causally, if you want to.

[1]Causal input and output is used in Modelica quite often for input signals, for sensor readouts, which should not alter measured quantity. In my model I use causal connectors for instance in model compliantPumpFR for measuring volume in variableCompliance to limit inflow when it reaches maximum and to limit outflow when the vessel is empty.

> Traditional object-oriented programming languages like Simula, C++, Java, and Smalltalk, as well as procedural languages such as Fortran or C, support programming with operations on stored data. The stored data of the program include variable values and object data. The number of objects often changes dynamically. The Smalltalk view of object-orientation emphasizes sending messages between (dynamically) created objects.
>
> The Modelica view on object-orientation is different since the Modelica language emphasizes *structured* mathematical modeling. Object-orientation is viewed as a structuring concept that is used to handle the complexity of large system descriptions. A Modelica model is primarily a declarative mathematical description, which simplifies further analysis. Dynamic system properties are expressed in a declarative way through equations.
>
> The concept of *declarative* programming is inspired by mathematics, where it is common to state or declare what *holds*, rather than giving a detailed stepwise *algorithm* on *how* to achieve the desired goal as is required when using procedural languages. This relieves the programmer from the burden of keeping track of such details. Furthermore, the code becomes more concise and easier to change without introducing errors.
>
> [...]
>
> - Object-orientation is primarily used as a structuring concept, emphasizing the declarative structure and reuse of mathematical models. Our three ways of structuring are hierarchies, component-connections, and inheritance.
> - Dynamic model properties are expressed in a declarative way through equations.
> - An object is a collection of instance variables and equations that share a set of data. (From [13])

It also has its drawbacks, though. One of the greatest is, that we are used to *think* in procedural way of programming and puzzled by line of code, which simply holds all the time (just unline all the other programming languages we have been working in). Sometimes it really looks strange and we cannot avoid the feeling, that "that would be done in good old MATLAB in a minute", but one gets used to it eventually.

5.4 Used model

Used model is showed in figure 5.2. It is a lumped parameter model, consisting of blocks, which describe real physical entities, except that it is all summed up to form a single flow.

Unlike original model by conlon et al., as main units were selected pressure (in $N \cdot cm^{-2}$, that is hPa) and flow (in $cm^3 \cdot s^{-1}$ that is milliliter per second)

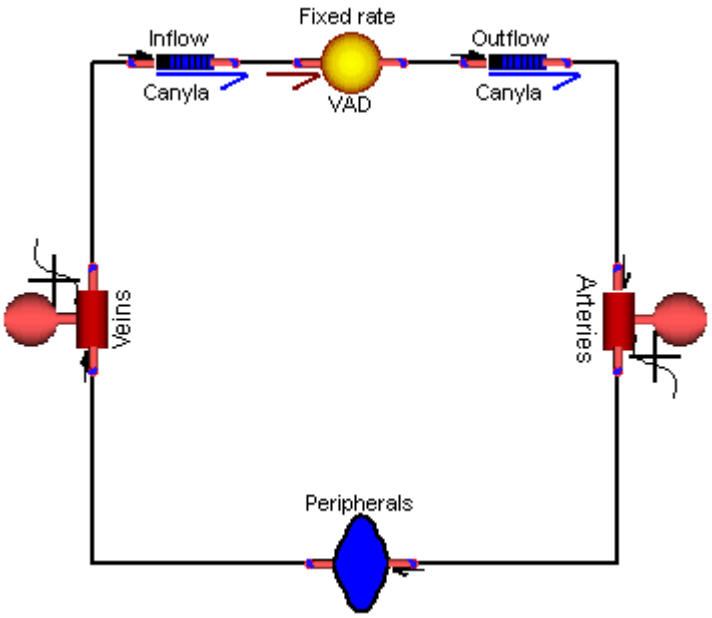

Figure 5.2: Used model

5.4.1 Model base

Model used in this work has been derived from the model proposed by [8]. One of the greatest advantages of this model was, that it included Matlab source codes for direct simulation. That helped debugging while converting model to Modelica environment.

Citing from their abstract:

> A mathematical lumped parameter model of the human circulatory system (HCS) has been developed to complement in vitro testing of ventricular assist devices. Components included in this model represent the major parts of the systemic HCS loop, with all component parameters based on physiological data available in the literature. (From [8])

They presented two variations - one, linear, provided only one compliance element in model of arteries and veins. This configuration is able to draw just basic pulses, more advanced configuration includes also second compliance, resistance and inertance in the model of vessels. To my model I chose the dual compliance configuration.

Also, they presented three different aortic compliance approximations - linear, exponential and polynomial of third order (figure 5.5 on page 52). Because the difference in output has not been so distinct, I decided to adopt the simplest linear approximation for potentially speeding the simulation up and more important, to make the parametrization clear.

5.4.2 Alterations

The base model from Conlon et al. consisted from 13 diferential equations and several function to express non-linear compliances and resistances. Its drawback however was, that authors did not work directly with pressure and flow units, but with volume ($[cm^3]$) and fluid momentum ($[N.s.cm^{-2}]$). So there had to be done some transformation to pressure ($[N.cm^{-2}]$) and flow ($[cm^3.s^{-1}]$), which meant completely rewriting the model.

Also, they used quite atypical model of VAD pump design, which has not been based on any current design. That was a piston force pumping against compliant vessel. Pressure arised in the compliant volume then propelled blood through aortic valve. I haven not discovered a way, how to set exact eject stroke volume and / or ejection pressure.

So, I had to change this block for a design more resembling currently used pulsatile VADs, such as Thoratec PVAD or Berlin Heart. This design consists of a compliant vessel with different (ejection and filling) pressure applied. Design of Thoratec VAD is described minutely in section 3.3.6 on page 25 and further implementation details are discussed below.

I have a strong suspicion, that in original code, the vena cava collapsing has been done completely wrong. By design, it should have been collapsed, if the pressure difference was smaller than 0.4 hPa which is around 30 mmHg. Putting aside, that this asuption solely is arguable (in veins should not be such high pressure, physiologically there should be 2 to 5 mmHg), the implementation declares, that if over this level, the resistance is much *higher* which is in direct contradiction to collapsing. The only phenomena, which could be simulated this way would be transition to turbulent flow, which apparently has larger resistance, but in veins that shall not be the case. Thus, the behavior has been changed to collapse at pressure 0 and also the resistance have been augmented 10 times.

5.4.2.1 Numerical simulation issues

Because of the numerical problems during simulation, the model was a bit simplified. This contains removing inertia from canullae, since they were not affecting the resulting flow much, but were inducing small oscillations and a very high peak on aortic valve closing, which in opposite led to opening of mitral valve eventually. It caused a situation, when during this short and high peak, both mitral and aortic valves were open and blood flew through pump, which was in diastole. Such behaviour does not give a true picture of what is happening, thus they were removed. Advanced modelling [2] of inertia effect would be needed to incorporate them back.

5.4.3 Assumptions and simplification

Each model has some simplifications. Since living organism is usually very complex environment, large simplifications were needed. I employed these simplifications:

[2] At least damped, so it would not generate peaks due to numericals discontinuities. E.g. as sawtooth transition, which should not be so sharp in reality. This apeared exactly in veins and thus it forced inertia in inlet canulla to shoot very high and thin peaks, which forced to open the valves at a time, when they should not.

- No gravity
- Blood is homogenous and incompressible
- Blood flow is laminar
- Vessels are impermeable
- Simplification of pulse wave propagation
- Constant and instant vessel's compliance
- Disregarding breathing effect
- Disregarding atria
- Disregarding own heart
- Left side circulation only
- No regulation
- Simpliest stable circulation

All of them are discussed and justified individually below.

5.4.3.1 No gravity

Elevation of organs above each other does not play any role. That is most similar to when the patient is lying.

5.4.3.2 Blood is homogenous and incompressible

My model treats fluid like electrical charge - as a homogenic fluid with no compressibility. This simplification is justified by the modeling objective - to study macroscopic flow and pressure. Then the own compressibility of blood is insignificantly small compared to any compliance element present within vessels.

However, Modelica's Fluid Library makes use of various fluid mediums with different compressibility and density of defined substances, which could be distributed throughout the system. Theoretically, the model could be extended later to use defined blood medium to study flow of particles (such as medicaments) through vascular system.

5.4.3.3 Blood flow is laminar

When we study the flow of any liquid through some system, one should be aware if it is laminar (and the resistance is linear) or turbulent. Modelling turbulent flow is extremely difficult, compared to laminar simplification. We could tell from Reynolds number which case occurs. Laminar and turbulent flow and its occurence are discussed in section 2.7.9 on page 15.

But since we use more abstract parameters as resistance (as against to diameter), we could partially incorporate this effect[3]. Because we study just the

[3]For instance the resistance in outflow canulla is set higher than would be appropriate for its length and diameter. This mimics the turbulent flow effect.

overall circulation, it is enough to tweak the parameters so the turbulent effects would be partly compensated. However, with the turbulent flow the resitance would be non-linear and dependent on velocity, which I do not reflect. In case we do not use this simplification, the model would be disproportionate complicated. Also, other simplifications have much bigger impact than this one.

5.4.3.4 Vessels are impermeable

In vivo, all vessels are partly permeable, especially capillaries, so they can transfer the gases, nutrients and liquid to the cells. At the beginning of the capillary some liquid is dissolved to tissue and at the end some is resorbed back. In normal pressure conditions the dissolved volume equals to the resorbed, or the edema would develop[36]. In short time simulation the effect could not be so strong though. Anyways, I assume there is no edema development. In general I asume, that all the vessels form a detached system with no leakage or inflow.

5.4.3.5 Simplification of pulse wave propagation

Blood in arteries is in constant pressure, just like if a rubber tube filled with water. Now, when we open the tap and let the water flow through the tube, it lurks. The pulse travels not only through the liquid, but also through the expansion of tube's walls. I completely disregard the fact, that the blood flows through flexible tube, which is able to carry the pressure wave. Instead I introduce just a few compliant vessels, which could change their volume in dependence on pressure and thus simulate the Windkessel effect (further discussed in section 2.4.1 on page 8). But again, considering given objective and that the Windkessel effect is quite good approximation[22], this simplification is valid.

5.4.3.6 Constant and instant vessel's compliance

I assume instant and constant vessel reaction, which is in fact not real. Arterial wall is visco-elastic structure and sharp change in volume would generate bigger pressure as if the change was slower[46]. This effect would introduce sharper pressure peaks in the model. On the other hand, parameters of model are already adjusted to changes of similar speed, which means this effect is compensated.

In fact, the relation between volume and pressure is a non-linear function. I use linearized version instead, with just two parameters - compliance (slope) and zero pressure volume (see figure 5.5 on page 52). The effect is not so important for overall result though. I used this linearization mainly to simplify the parametrization.

5.4.3.7 Disregarding breathing effect

In order to breath in, some suction have to arise in thoracic cavity, which creates pressure gradient between lungs and atmospherical pressure, consequently creating air flow in the lungs. Normal intrathoracic pressure varies during normal breathing cycle from about - 2 mmHg to - 6 mmHg[36] – it decreases while breathing in and increase while breathing out and this cycle repeats (see 5.3). However we are interested in significant pressure changes, rather than those

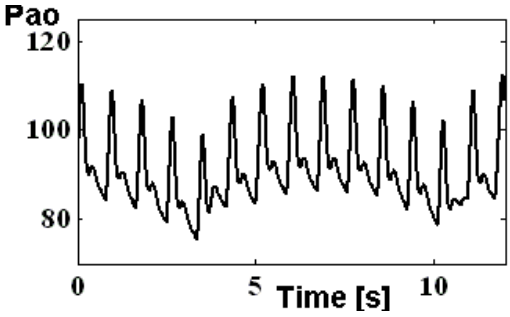

Figure 5.3: Effects of breathing on aortic pressure (in mmHg) as modelled by [32]

small pulsations, which relatively do not affect aortic pressure (when we project the pressure on straigth line or filter this lower frequency).

Also, output of extracorporeal pump (or any implanted with hard shell) should not be affected by this phenomena. One may discuss changes in the vein pressure, and how it could affect filling, but I consider this as negligible.

5.4.3.8 Disregarding atria

Atria would affect filling only of the pump slightly and veins pressure (there are no valves between veins and atria), which is not relevant. Also, considering quite big inflow canulla resistance, they would not have big effect.

5.4.3.9 Disregarding own heart

I assume not only zero aortic valve flow, but also zero ventricle contribution to pump filling. That would be for two reasons, firstly, we assume, that the native heart was impaired and not capable of pumping enough, which was indication for treatment with VAD. If the heart is powerfull enough to generate flow though aortic valve, it is a signal, that own heart is recovering[25] and it is an indication for weaning off the VAD and that is not our scope. Secondly, the interaction would make the aortic waveforms more complex, which I want to avoid.

As the pump in model works in fixed rate mode now, with enough time to fill, that it waits fully filled for an ejection, the native heart would just contribute to even faster filling and, when the VAD is full, to eject through aortic valve to possibly contribute to VADs ejection. That could in all cases just increase the aortic pressure. Therefore, by disregarding ventricle, the objective would not be easier to prove, thus such simplification is valid for current scope.

For future usage, the heart could be easilly added. Its enough to create a model of a ventricle and connect it in series to the inflow canulla (disabling the aortic valve in model) to simulate initial phase of treatment (with zero aortic valve flow). Enabling the heart's aortic valve and connecting it to aorta (parallel to VAD pump) we could simulate stronger heart with VAD as a support and observe the interaction.

5.4.3.10 Left side circulation only

This major simplification is only justifiable by the goal of this thesis, ita est observing *aortic* flow and pressure patterns, because mostly we use just left VAD (left ventricle is much more stressed so it fails more easily) and such support is better and more often described. Yet, the venous return (that is pressure and flow in vena cava) is quite similar to physiological. Venous return is also important for model to run and for pump filling, however when we assume, that the pump is going to fill anyways, than we could in extreme case even disregard venous return and work with open-loop simulator.

The simplification I am doing is virtually considering right circulation as one block. Imagine, that this block is placed just between the veins and the inlet canulla (as the ventricles are also disregarded). Then, as the pulmonary and systemic circulation are quite similar and assuming no edema, this block has same input and output. Therefore, when not interested in observing inner circulation, it is legal to not even use that block. Or in other words, I am replacing flow from pulmonary arteries with flow in vena cava. But the pulsations here are already damped and I expect the pressures in pulmonary veins and in venae cavae to be similar. So in given scope the simplification is justified.

5.4.3.11 No regulation

Apart from hydraulics only, the circulation is not regulated. Human circulatory is regulated by a number of mechanisms, which keep together homeostasis. They were further discussed in section 2.6 on page 9. Some of the mechanism could help the body to adapt circulatory system to artificial pump, but this is not the objective of this thesis. Instead I want to show, how the *unadapted* circulation would react to installation of a new pump.

Future work would be to add at least baroreceptor regulation for vasoconstrictions, which could help the body to acclimatise to device by changing (peripheral) resistance. Model of baroreceptor regulation is addressed by Sun or Ursino [38, 47].

5.4.3.12 Simpliest stable circulation

I do not consider the subject standing or moving any way. Also, I disregard all transitionally phenomena. The appropriate patient would be lying on its back with basal metabolism only (so sleeping perhaps).

Delay in which the pulse travels all over systemic circulation is not realistic as well. All delays are disregraded. This is valid only when studying stable circulation, which is the case.

5.4.4 Basic components – lumped properties of vascular vessels

Vascular system could be characterized by a serioparallel combination of three main components – resistance, compliance and inertia. This approach is equivalent to electrical analogies method, used in most of the models (at random [52, 50, 28] and many others), but with an advantage, that it is referred directly to pressure and flows fo fluid and not to abstract voltage and electrical flow.

Figure 5.4: Basic block components - from left to right resistance, compliance and inertia

Thus, the model is closer to reality (hereby I do not state, that it necessarily describes reality better, but the abstraction is closer).

Most of the blocks are made of these basic components. They resemble basic electrical components resistor, capacitor and inductor, but they work with different physical quantities - instead of voltage and current they use pressure and flow.

5.4.4.1 Flow resistance

Resistance is caused by friction of vessel's walls and in individual fluid's layers. Resistance R in a smooth long tube with laminar flow could be idealized as

$$\begin{aligned} R &= \frac{8\mu}{\pi r^4} \cdot L \\ R &= \frac{128\mu}{\pi d^4} \cdot L \end{aligned}$$

where $\mu$is fluid's viscosity, L length of the tube, r its radius and d its diameter. This implicates, that resistance changes with fourth power of diameter, or in other words, by changing vessel's diameter slightly, one would greatly affect its resistance. Bear in mind though, that this is just a macroscale simplification, because blood does not have exact properties as water and especially in very small vessels (capillaries) performs differently.

Similarly to resistor in electrical analogies method, the resistance R specifies the pressure drop Δp across the segment as a function of flow rate q:

$$\Delta p = R \cdot q$$

5.4.4.2 Compliance

As blood vessels are flexible cylindrical tubes, they allow to accumulate any amount of the liquid within. Difference between inflow and outflow generates flow into (or from) the volume. The more volume means larger diameter, thus larger grith, thus higher wall tension, thus also higher pressure inside. This relationship is quite nonlinear[8](as seen in figure 5.5), but it could be approximated by first order polynom as

$$\begin{aligned} volume &= \int q_{in} + q_{out}\, dt \\ stressedVolume &= max(volume - zeroPressureVolume, 0) \\ p &= stressedVolume/compliance \end{aligned}$$

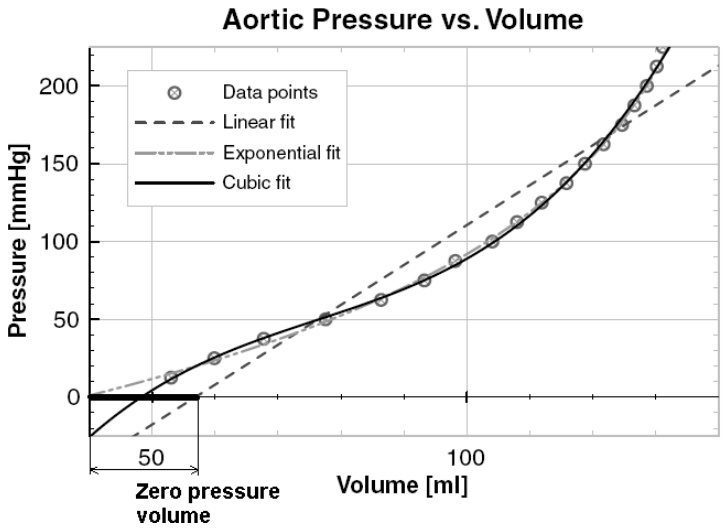

Figure 5.5: Human aortic Volume–pressure relationship, as measured by King et al.(1946). The linear approximation works with zero pressure volume and slope. Image modified from [8]

where q is the flow (positive inflow and negative outflow), p is the pressure, *volume* is the current volume of a vessel and *zero pressure volume* is the volume, in which the filling is same as empty vessel's inner diameter, thus there is no wall tension and thus zero pressure (see figure 5.5).

Parameter *compliance* states, how much the vessel is flexible, and is related to *stiffness*:

$$compliance = \frac{1}{stiffness}$$

. Note, that this basic block does not have volume limiting[4] - volume could be infinitely large or even negative. When entering real model inputs, the values mostly stays in senseful bounds, but anyways we have to check from time to time during simulation if the volumes stay in bounds.

Because the compliance is the only component, which is able to accumulate a volume, there has to be assigned some initial volume. This is discussed in section 5.4.7.1 on page 60.

5.4.4.3 Inertia

The fluid inertia is particularly important in vessel's with small diameter and dramatically changing flow speed. It arises from the fact, that moving volume of mass has some kinetic energy (Newton's Second law). In a long smooth tube, the inertia I is expressed as

$$I = \frac{\rho \cdot L}{A}$$

where ρ is fluid's density, L length of the tube and A is the cross-section area.

[4] Volume limiting component is introduced later in section

Figure 5.6: From left to right: Pressure sensor provides transformation from hPa ($N \cdot cm^{-2}$) to $mmHg$, PressureFlowConnector provides connection of pressures and flows between components.

The pressure drop Δp is then a function of flow q as:

$$\Delta p = I \cdot \frac{dq}{dt}$$

Like a coil it acts as if trying to prevent changes in flow. This behaviour could be dangerous, especially when flipping the direction of flow. Because the equations are solved numerically, some non-continuites (especially when the turning point is very sharp) could result in unrealistic high peaks[5].

5.4.4.4 Pressure sensor

Because all computations for pressure are done in units of hPa ($N \cdot cm^{-2}$) , it is needed to convert it to $mmHg$, which is widely used among medical professionals for historical reason. This component does not inluence the output in any way, it only computes $pressureMmHg$ as

$$pressureMmHg = p \cdot \frac{10^4}{133}$$

5.4.4.5 PressureFlow connector

Normally, signal is one-dimensional. But in modelica one could define any number of dimensions. Here I make use of just two - pressure and flow. Using this connector, the components are coupled together.

When two or more PressureFlowConnectors are connected together by a line, their pressures are considered equal at all cases, but the flows are all summed to zero (equal inflow and outflow), according to Kirchhof laws.

5.4.5 Major components

For better abstraction and variability, the whole model consists of larger blocks, which incorporate basic components. These larger blocks are then connected to form circulatory system. Using such design, model could be easily extended – for example, inserting second pump would mimic native heart interaction or duplicating all components, reconnecting them in appropriate way and setting suitable parameters would extend the model with pulmonary circulation.

Most of parameters are adopted from [8] and are listed in section 5.4.7 on page 60.

[5] As mentioned in section 5.4.2.1, that was happening in InflowCanylla for instance, where the pulsations of vena cava resembles saw signal, resulting in great pressure peaks. Therefore the inertance was removed from this component.

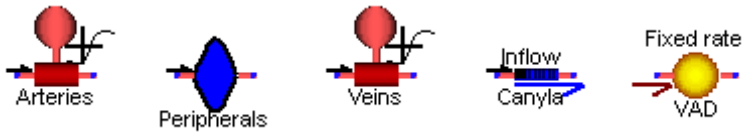

Figure 5.7: Major components - from left to right arteries, peripherals, veins, canulla and the pump

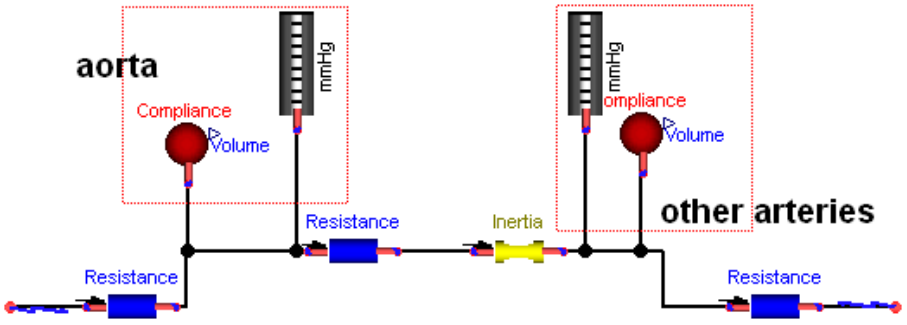

Figure 5.8: Model of arteries formed from basic components. Inlet on left side, outlet on right one.

5.4.5.1 Arteries

Arteries block model in together all arteries, from large ones to small arterioles. In many mock circulatory systems, the arteries are modelled using only one compliance[8]. As could be seen in figure 5.8, in this model it is divided into two segments. The left compliance mimics large artery – aorta, whose compliance is of special significance and the right compliance models summed compliance of the other arteries. Between them is some aortic resistance and inertia. The resistance of peripheral arteries are summed in Peripherals block.

Aortic resistance damps oscillations, which would emerge there. Its value has been taken from [8]:

> The required flow resistance of 0.0011 N s cm^{-5} is substantially larger than the resistance which would be computed based on Eq. (2) (with an aortic diameter of 2.5 cm, and length of 20 cm the expected flow resistance would be $2.09 \times 10^{-6} N \cdot s \cdot cm^{-5}$). The higher resistance in the aorta was chosen so that the performance of the simulations was acceptable. The larger value may reflect effects of unsteady flow, changing flow geometry and losses from the stretching and relaxing of the vessel walls and is consistent with the literature. (From [8])

They also state, that the flow in aorta is likely to be turbulent (as pointed out in section 2.7.9 on page 15), which could justify increased resistance. In addition, one could think of it not only as aorta, but large arteries as a whole. It is impossible to declare borderline between arteries which are modelled by first compliance and those included in the second exactly.

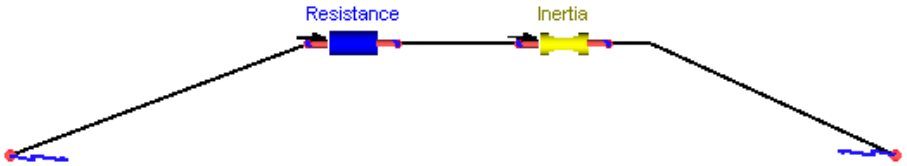

Figure 5.9: Model of peripherals formed from basic components. Inlet on left side, outlet on right one.

As of inertia, it has been computed by Conlon et al. from aortic diameter and length (2.5cm and 20cm) and they claim it generally agrees with the values in literature

Conlon et al.[8] use non-linear function of pressure-volume relationship in aortic compliance, but as the parameters should be varied later, I chose simple linear approximation, thus the block for arterial compliance is same as any other compliance (compare on figure 5.5). This could be easily switched though.

Notice also pressure sensors – the left one – aorticPressure is observed in following parts of this thesis. It roughly agrees to arterial pressure as measured *in vivo* in large arteries, such as brachial artery.

Resistances at the left and right ends does not play any role - their resistance is set as low as 10^{-12} and they are present for numerical stability issues only.

5.4.5.2 Peripherals

Peripherals block models microarterioles, capillaries and microvenules and represents all of the microcirculation. The capillaries have very small diameter, but as there are many of them, extremely large total cross-sectional area[36]. Thus they have significant resistance and inerti, while any compliance is neglected [8]. As peripheral resistance and inertance are not directly mentioned in literature, Conlon et al. based their values based on compilations of data availiable.

5.4.5.3 Veins

Veins block is very similar to arteries block. It also incorporates dual compliances, one represents veins and the other vena cava, which volume-pressure relationship is non-linear. Inbetween, there is a resistance, which is able to collapse on low (negative) pressure and thus many folds increase its resistance. For normal circulation it does not have any particular reason, but VAD could induce suction to the system, which makes it particularly important.

The non-linear compliance of vena-cava is also adopted from Conlon et al.[8].

They also set the veins pressure at nominal volume to 20 mmHg, which is higher than values in literature (around 5 to 15 mmHg). It is because the VAD is filled solely from pressure gradient. As I have changed the pump design so it is able to apply suction, this could be refined. However, to stick to original design and values as close as possible, the values were kept.

The second, vena cava, compliance demonstrates some important non-linearities.

> A piecewise linear curve (with three segments) was used to model the nonlinear vena cava compliance. Below a critical volume of 500 cm^3

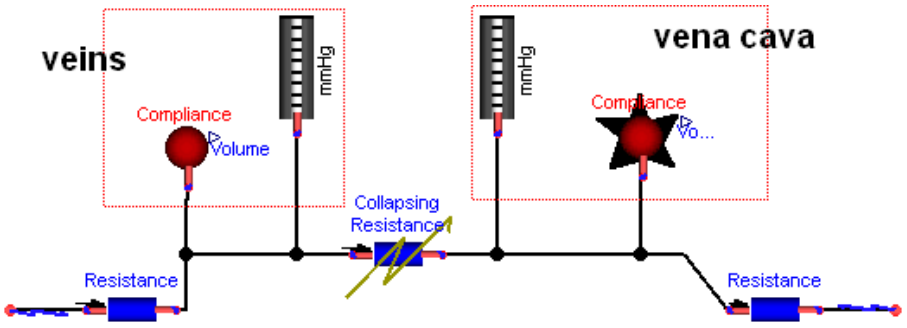

Figure 5.10: Model of veins formed from basic components. Inlet on left side, outlet on right one.

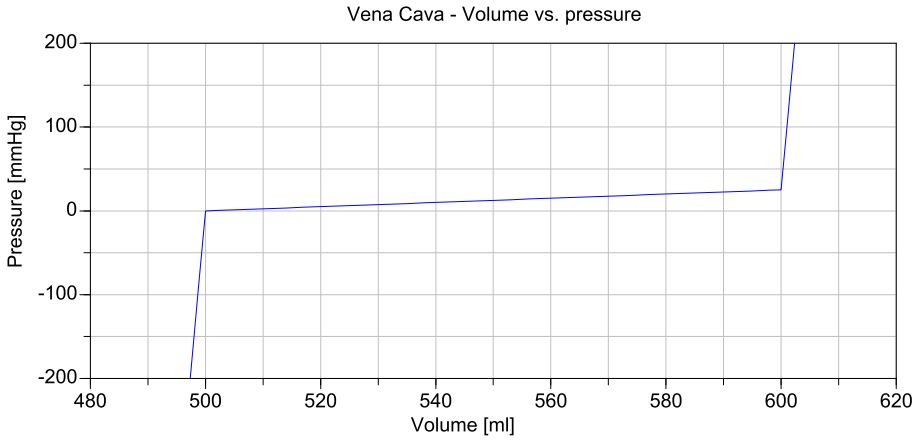

Figure 5.11: Nonlinear volume and pressure relationship, consisting of three parts, employed in model of vena cava. Each of the parts has linear compliance then.

> the vessel is deemed to have collapsed. The pressure at this critical volume was set to 0 N cm^{-2} (0 mm Hg). In the nominal range of volumes from 500 cm^3 to 600 cm^3 the vena cava compliance was set to 500 $cm^5N{-}1$ while at volumes below 500 cm^3 and above 600 cm^3 the compliance was 0.1 cm^5 N^{-1}. The pressure at the nominal vena cava volume of 600 cm^3 is 0.2 N cm^{-2} (15 mm Hg) which is (again) slightly higher than that commonly found in the literature. (From [8])

Similarly to arteries, outmost resistors are for numerical stability only and its values are not important for simulation.

5.4.5.4 Pump

Model of VAD by Conlon et al. did not suit my objective, so I developed a brand new one, based on design of Thoratec PVAD device working in fixed rate mode (see section 3.3.6.2 on page 27 for modes details). The base is a sac with limited

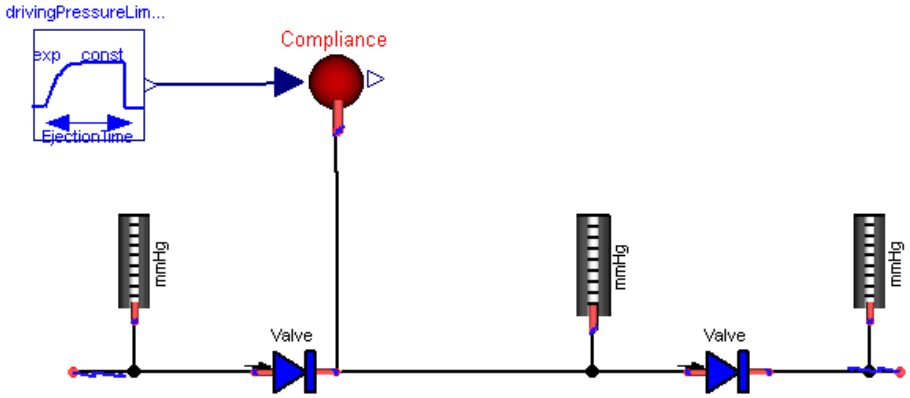

Figure 5.12: Model of VAD. Inlet on left side, outlet on right one.

Figure 5.13: Components of VAD pump – from right left to right driving pressure, variableCompliance and valve

volume and with pressure applied to it. Because the diaphragma is thin and flexible, I assume, that provided pressure equals pressure in sac inlet and outlet. This provided pressure matches that applied by pneumatic driving console.

One simplification made here is having compliance with both inlet and outlet unified to single pipe. It is an abstraction, that the valves are very close to actual sac, which is justifiable.

In addition, the pump is computing actual outflow from outlet (aortic) valve. Summed outflow for whole period must equal stroke volume. If it is lower, then the pump was either not fully filled or fully emptied. Contrariwise, when the actual stroke volume is larger than the maxVolume set to the pump, it means there is a parasite flow. This is undesirable behavior, induced probably by inertias as both valves have to be open at the same time. Thus, actual stroke volume has to be monitored during simulation.

Driving pressure Driving pressure mimics pneumatic driving as in Thoratec device. The pressure generated in real pneumatic console switches from filling to ejection and vice versa in a more or less ideal step function. However, as the inlet tube is of small diameter, it has significant resistance, which would delay the pressure rise during ejection. Some consoles do even provide a possibility to modify this resistance. Originally, I have not included this in the model and the aortic pressure waveforms looked quite distorted with very sharp rise. Therefore, I induce exponential rise in form of

$$pressure = 1 - \exp(-\frac{(time - T_0)}{alpha}$$

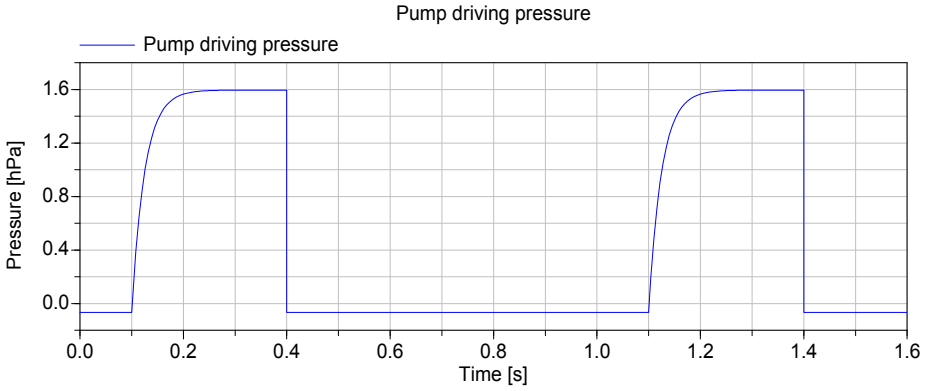

Figure 5.14: Driving pressure externally provided to variable compliance. Rate 60 bpm (1 Hz), systole fraction 0.3, filling pressure 120 mmHg (1.596 hPa) and filling pressure –5 mmHg (hPa), alpha 0.025

and then scale it to fit filling and ejection pressure. Here T_0 is time of starting current systole and alpha is a term controlling the exponential slope. Alpha was arbitrarily set to 0.025 to generate pretty output. Driving pressure course is shown in figure 5.14.

As noted above, the pump is working in fixed rate driving pressure.

Variable compliance Pumping sac originally developed from compliance element, which compliance parameter changed over time with ejection. That design is more similar to native heart, but the VAD works with provided external pressure. Assuming the pressure in blood sac is same as provided pressure, I can directly change inner pressure by the provided one.

One issue, which must be carefully addressed is the volume limiting. In physical component, the volume could not be negative or larger than its maximal vessel's volume. For numerical reasons, this is not easily done in Modelica, but after initial struggles we[6] came with an elegant solution. The pressure function is divided into three parts - normal, empty and full. Introducing extreme stiffness to outmost states, the inner pressure could be expresses as

$$\begin{aligned} p &= provided\,pressure + \\ &+ \begin{cases} (volume - maxVolume) * superStiffness & if\ volume > maxVolume \\ 0 & otherwise \\ (volume - minVolume) * superStiffness & if\ volume < minVolume \end{cases} \end{aligned}$$

volume relation to flow is the same as in compliance element

$$q = \frac{d\,volume}{dt}$$

where maxVolume and minVolume (usually 0) are parameters, superStiffness is analogy of very low compliance and it has been set to 10^3, so even small change in volume generates extreme pressure.

[6] I would like to thank to MUDr. Ing. Pavol Privitzer for pointing this out

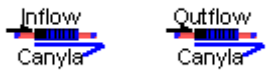

Figure 5.15: Inflow and outflow canullae icon

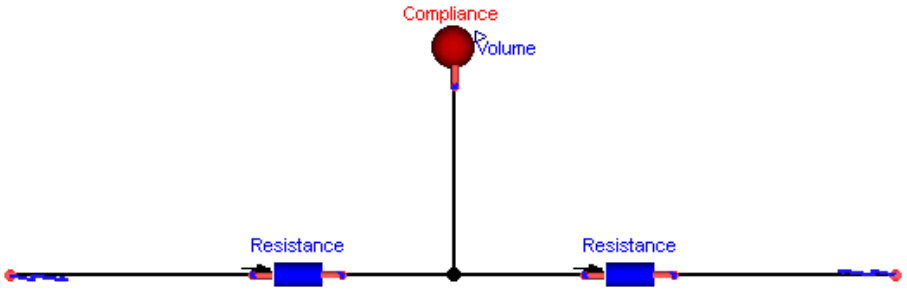

Figure 5.16: Inflow and outflow canullae model.

Valves Valves are another component, which induces nonlinearities and discontinuities. There have been chosen with special care.

They provide some small resistance when opened and large resistance, when closed. Closing depends on flow directing. The values of resistances were taken from [8].

They are based on diode in Modelica.Electrical.Analog.Ideal.IdealDiode library.

$$
\begin{aligned}
off &= s < 0 \\
p &= \begin{cases} s & if\ off\ is\ true \\ s \cdot closedResistance & if\ off\ is\ false \end{cases} \\
q &= \begin{cases} \frac{s}{openResistance} & if\ off\ is\ true \\ s & if\ off\ is\ false \end{cases}
\end{aligned}
$$

This introduce variable s which means the pressure when the valve is closed and the flow when the valve is closed. Variable *off* is a boolean, which indicates, if the valve is open or closed.

Also simpler designs have been tested, but in the end for numerical concerns, this design has been adopted.

5.4.5.5 Canullae

The pump is connected to body using two cannullae. Inlet cannulla is leading blood from ventricle (or vena cava in this model) to the paracorporeal pump, whereas the outlet cannulla connects the output of the pump with aorta.

They are modelled as a thin, flexible tubes with resistance and compliance. Original model of Conlon et al.[8] was also employing inertance, but for isues

during simulation were later removed. The inertance removal is further discussed in section 5.4.9.1 on page 66.

The values are simulating cannulla with internal diameter of 2.0 cm with the length of 10 (inlet) and 15 cm (outlet). Apart from the length, the cannullae are the same. The resistance of the outlet cannulla could not be easily calculated though, because of the complex (semi-turbulent or turbulent) characteristics of the flow. Thus, the resistance is quite higher and adjusted so the model has appropriate response.

To the contrary of Conlon, the resistance here is divided to two - before and after the compliance. This is to describe the reality in more detail and to add numerical security – e.g. when connected directly to other component such as compliance, then there would be infinite flow due to zero resistance.

5.4.6 Model implementation

Discussed model has been implemented in Modelica language, version 3.1. As the relations and equations are known and modelica is a language of high abstraction, the implementation is was easy. In fact, it is nearly a matter of just rewriting equations into appropriate blocks. As already mentioned above, I chosed abstraction of major blocks, which consists of basic blocks. All blocks are connected using the PressureFlowConnector. Some blocks (arteries and cannullae) use inheritance to inherit global icons.

The implementation details reveal enclosed documentation, which is enclosed on CD (Appendix A on page 91)

5.4.7 Default parameter values

Parameters of components were originally adopted from model of Conlon et al.[8], which are more or less based on physiological values. After inducing different pump though, the systolic pressure was too high and so were the flow, so the values had to be adjusted to fit the waveforms in physiological bounds (see figure 5.20 on page 65). Thanks to this tuning, the pressure wave looks more like physiological in new conditions.

Used paramters for default model are listed in table 5.1 on the next page as well as the original value. Dot notation is used to depict membership.

5.4.7.1 Initial volume

As already mentioned above, compliance blocks do need some volume in the beginning. The way how the initial volume is distributed over whole model affects only settle time, but total amount of initial volume is very important - it makes pressure in compliances altogether. If all the blood flew away, there would be no pressure in vessels. Therefore, I asume constant distribution among compliances and instead of using four parameters I introduce new parameter *Total blood volume* which distributes volume among systemic compliances in given ratio:

Block.parameter	Old	Current	Unit
Total blood volume*	3424	3493	ml
pump.inletValve.openResistance	8E-4	8E-4	$N \cdot s \cdot cm^{-5}$
pump.inletValve.closeResistance	800	800	$N \cdot s \cdot cm^{-5}$
pump.drivingPressure.ejectionPressure	N/A	220	$mmHg$
pump.drivingPressure.fillingPressure	N/A	-5	$mmHg$
pump.drivingPressure.systoleFraction	N/A	0.3	-
pump.drivingPressure.rate	N/A	60	bpm
pump.drivingPressure.alpha	N/A	0.025	-
pump.variableCompliance.superStiffness	N/A	1000	$cm^{-5} \cdot N$
pump.variableCompliance.maxVolume*	N/A	65	ml
pump.variableCompliance.minVolume	N/A	0	ml
pump.outletValve.openResistance	8E-4	8E-4	$N \cdot s \cdot cm^{-5}$
pump.outletValve.closeResistance	800	800	$N \cdot s \cdot cm^{-5}$
outflowCannulla.compliance	0.79	0.79	$cm^5 \cdot N^{-1}$
outflowCannulla.zeroPressureVolume	46	46	ml
outflowCannulla.resistance	0.0011	0.002	$N \cdot s \cdot cm^{-5}$
arteries.aorta.compliance*	29.3	50	$cm^5 \cdot N^{-1}$
arteries.aorta.zeroPressureVolume*	57	57	ml
arteries.inertance*	3.4E-5	3.4E-5	$N \cdot s^2 \cdot cm^{-1}$
arteries.resistance*	1.1E-3	0.8E-3	$N \cdot s \cdot cm^{-5}$
arteries.arteries.compliance*	101	110	$cm^5 \cdot N^{-1}$
arteries.artereis.zeroPressureVolume*	468	468	ml
peripherals.inertance*	0.0275	0.0275	$N \cdot s^2 \cdot cm^{-1}$
peripherals.resistance*	0.013	0.013	$N \cdot s \cdot cm^{-5}$
veins.veins.compliance*	2500	2500	$cm^5 \cdot N^{-1}$
veins.veins.zeroPressureVolume*	1333	1234	ml
veins.collapsingResistance.openResistance*	1.3E-4	1.1E-4	$N \cdot s \cdot cm^{-5}$
veins.collapsingResistance.closeResistance	6.7E-3	6.7E-3	$N \cdot s \cdot cm^{-5}$
veins.venaCava.compliance*	500	300	$cm^5 \cdot N^{-1}$
veins.venaCava.zeroPressureVolume*	500	500	ml
veins.venaCava.maxFill*	600	600	ml
veins.venaCava.complianceMaxFill*	0.1	1	$cm^5 \cdot N^{-1}$
inflowCannulla.compliance	1.19	1.19	$cm^5 \cdot N^{-1}$
inflowCannulla.zeroPressureVolume	31	31	ml
inflowCannulla.resistance	1.3E-5	1.2E-3	$N \cdot s \cdot cm^{-5}$

Table 5.1: Default model parameters. *Current* is the value currently used as default value, *Old* is that used by Conlon et al[8], which are rounded for lucidity. Parameters marked with * are expected to change in different patients.

$$
\begin{aligned}
Aortic\,volume &= 100 \cdot \frac{total\,blood\,volume}{reference\,blood\,volume} \\
Arterial\,volume &= 600 \cdot \frac{total\,blood\,volume}{reference\,blood\,volume} \\
Venous\,volume &= 2000 \cdot \frac{total\,blood\,volume}{reference\,blood\,volume} \\
Vena\,cava\,volume &= 600 \cdot \frac{total\,blood\,volume}{reference\,blood\,volume}
\end{aligned}
$$

$Reference\,blood\,volume$ is defined as sum of all default vascular volumes plus default initial volume of inflow and outflow canullae which have constant volume. The pump is not counted in, because it is empty at the begining. So, altogether, that is:

$$reference\,blood\,volume = 100 + 600 + 2000 + 600 + 133 + 60 = 3493$$

As the initial volumes are just estimation of actual volume, that would develop transitional state, until the volumes pour into their place and pressures get stable.

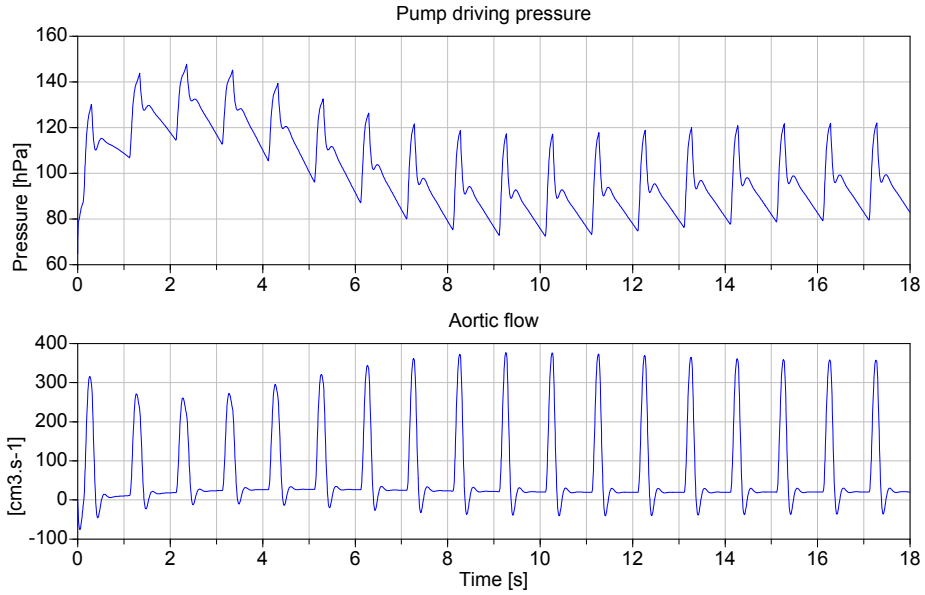

Figure 5.17: Aortic pressure (top) and flow (bottom) waveform during transients

5.4.8 Model results

As already mentioned, the subject of observation are the aortic pressure and flow waveforms. Using values listed in table 5.1 on page 61, model generates waveforms as shown in figures 5.17.The values observed are pressure on aortic compliance and flow trhough aortic resistance.

After the transients performance, once the volumes in compliances and flows on inertances stabilize, we could observe more realistic pressure and flow patterns as in figure 5.18.

As could be seen there, both aortic pressure and flow waveforms are similar to those of natural published in literature ([36, 46]).

One difference though is the sharp decrease from the first peak in the pressure waveforms. To explain that, one must perceive, that what I model here is not natural heart, but mechanical device. In natural ventricle, the pressure inside ventricle is continuous. The aortic valve closes once the pressure inside is lower than the aortic one. On the contrary, the pressure in VAD is changed rapidly (either when it is empty or when it switches to filling) from maximum to minimum, which induce such discontinuity.

In figure 5.20 is output of model, when employing parameters originaly used by Conlon et al.[8] (see table 5.1 on page 61). As one could see, the pressure is too high and also the flow peak is terrible, thus the parameters have been tweaked to adjust the waveforms to more physiological shape.

5.4.9 Caveats and known issues

Beware, that the order of elements should not be swapped. For instance, in ouflow canulla, originally there came compliance firstm then resistance and finally inertia element. This configuration was creating a lot of state events, which

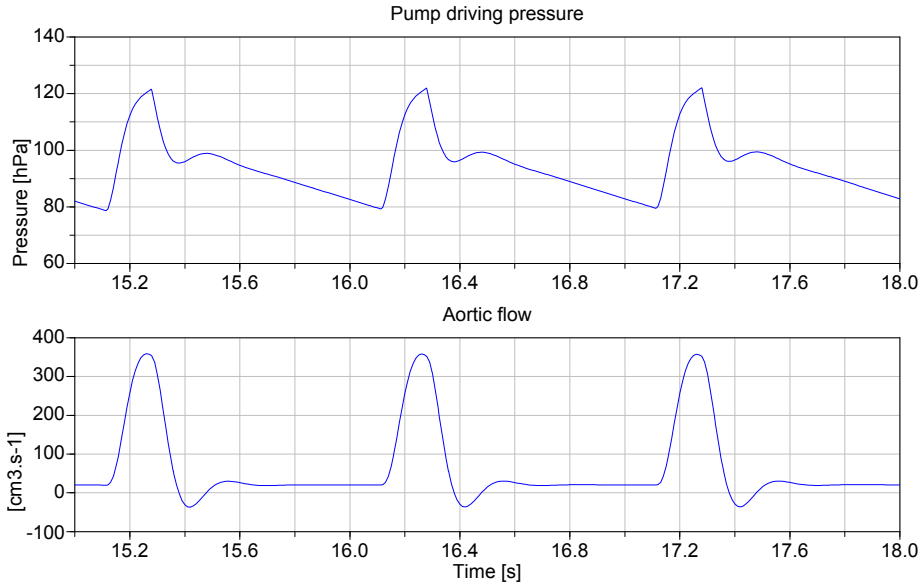

Figure 5.18: Aortic pressure (top) and flow (bottom) waveforms after transients

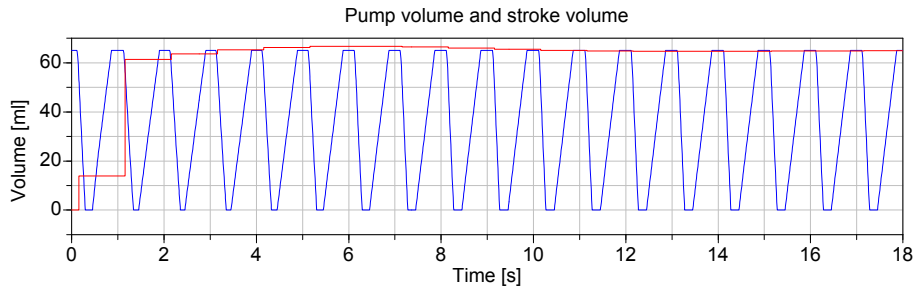

Figure 5.19: Volume of the pump (top) and stroke volume

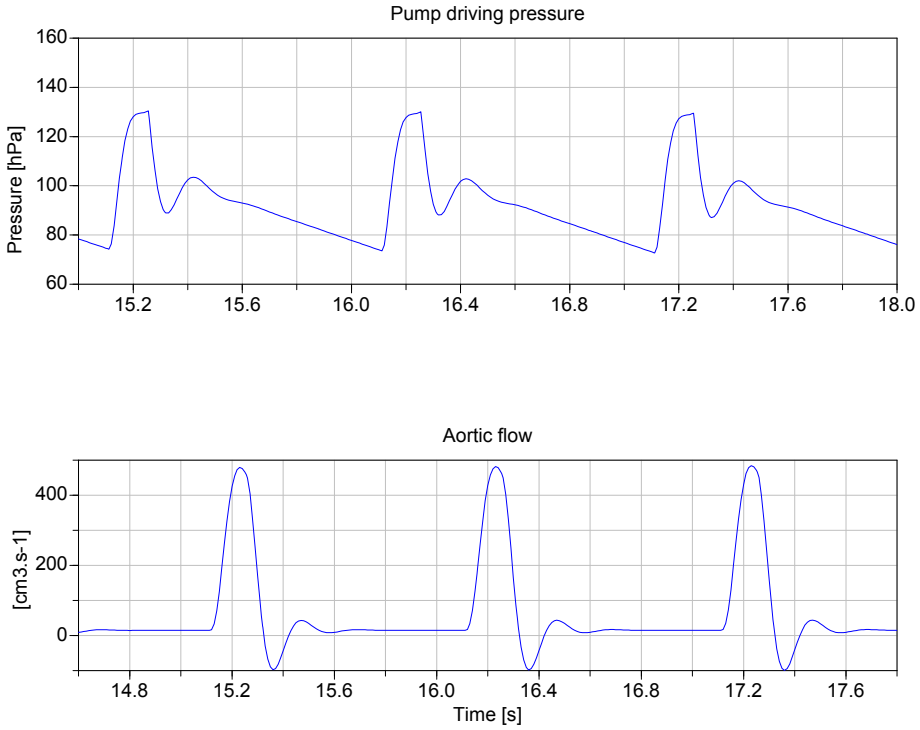

Figure 5.20: Model with parameters used by Conlon et al. (See table 5.1 on page 61 for comparison)

slows down the simulation extremely.

5.4.9.1 Hybrid modelling

Although this model is simple compared to other circulatory models, for Modelica it is not as simple. Having in together more than 200 equations, of which more than half are non-trivial (more elements than just x=1), both time-continuous (e.g. pressure course) and discrete variables[7] (ejection signal, current stroke volume) and discrete events (volume of the pump, valves), it makes the simulation particularly complex.

Proprietary Modelica environment Dymola has quite advanced simulation optimization and thus is able to simulate it rather quick (around 1s), whereas open-source implementation of OpenModelica takes more than 13s to perform the same simulation.

Events One decent problem while simulating the model was the time needed for simulation. Originally, in simulation time of 20s and using 800 intervals, the computation time could arise up to 5s or even more. This depends on individual parameters, which generates hard-to-solve singularities, especially when using *'if'* statements.

In Modelica, each use of a "if" could be a problem in large models. [13] warns, that each use of such would create an event, which is compared to actual state. E.g. let us have

$$i = if\ x > 0\ then\ x\ else\ 0;$$

The variable x is monitored and once it crosses zero, an event is generated. That holds the simulation, until all state changes are computed (e.g. i = 0 from now on. But this can lead to a series of other changes.).

On the other hand, approximation by polynomial or exponential functions is also not favorable, while it leads to numerical errors, where e.g. resitivity is higher than all bounds. Step approximation function with fixed maximum and minimum may have been better solution, but this leads to very hard computation with unstable jacobians and in effect the time needed is even a few folds higher. For example, I used step approximation of a valve function similar to

$$resistance = if\ (pressure > 0)\ then\ openResistance\ else\ closedResistance;$$

which could be approximated by *tanh* function as

$$resistance = closedResistance * (\tanh(-10 * pressure) + 1) + openResistance;$$

The result was quite same, but a large number of warnings about residuals in Jacobian matrix were issued and the overall time was considerably longer. Thus, I do not recommend continuous time approximation of step function.

Oscillations Problem with many state events is not making so much trouble when the simulation variables change slowly. But when comes to oscillations, it is really a disaster. As mentioned above, such situation was exactly when having inertias in cannullae, which caused troubles at valves.

[7] Combined continuous- and discrete-time system is called hybrid and is quite of an issue to model and simulate it [13].

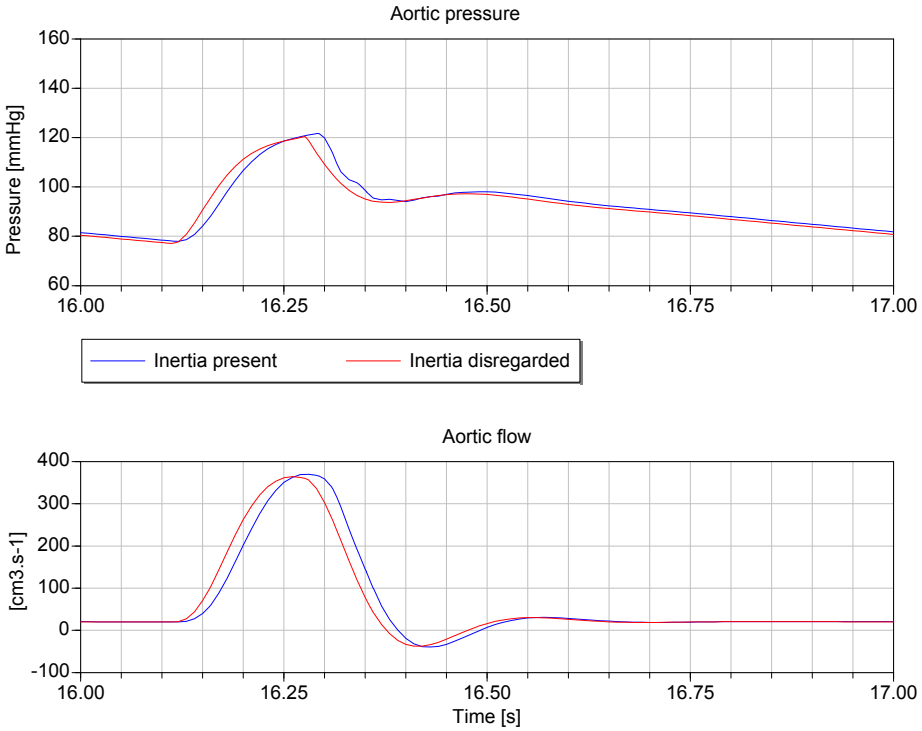

Figure 5.21: Aortic pressure and flow affected by the presence of inertia in cannullae

The effect of canullae inertia is shown in figure 5.21. Because the shape is quite similar, but the simulation takes twice as longer (and in rare cases i gets stuck), I decided to disregard it.

5.4.9.2 Too high veins pressure

The pressure in veins, adopted from Conlon et al. is inappropriate high. I wanted not to change parameters which were not needed to be changed, so I left it as it was.

In current experiments I use fixed rate mode, so the delayed filling caused by smaller pressure gradient would not affect the results much. But for future experiments, especially when VAD filling is important, I recommend adjusting parameters to lower the veins pressure from around 20 mmHg to realistic 5 mmHg.

5.4.9.3 Driving pressure

Driving pressure proved itself as of high importance and effect on aortic pressure. It is hard to simulate it though, because no exact data of driving pressure *inside* the pump exists, only the pressure in driving console is known.

For better simulation it would be necessary to include model of pneumatic hose and the VAD interaction.

5.4.9.4 Fixed rate

Current model of pump does work in fixed rate mode only. For lucidity, the rate was set to 60 bpm (1 Hz). This holds the VAD, which is usually full, for a period of time before ejection, which is not desirable. For future work, automatic mode (FFFE) should be implemented too.

5.4.10 Parameter consequences

To perform some experiments, one should conceive, what role does individual parameters play. Therefore I varied selected parameters and studied their response on aortic pressure.

Peripheral inertance has only small or none effect on pressure and volume peaks, larger number only extends time until it settles.

Arterial resistance affects pouring between aorta and arteries. Reduces dichrotic notch greatly, but increases overall peak. Also reduces flow peak, especially reflow.

Lowering of *aortic compliance* heightens pressure peak a little, it rather brings it a bit earlier. It broadens dichrotic notch dramatically.

Lowering *arterial inertance* results in lagging of the top of the pressure peak, and smoothens the dichrotic notch (nearly eliminating it). It also nearly clears the negative flow peak.

Lowering *arterial compliance* lags the pressure peak a little, heightening it a bit. It also brings the dichrotic notch up and raising the second peak. The pressure fall is steeper though.

Lowering *venous compliance* highens the the whole pressure peak. Own systolic peak is not highened as much as the diastolic. Also, the dichrotic notch and peak are exxagerated. Also, it lowers (and broadens) the flow peak a little.

Lowering borders of *vena cava* by 40% does not affect output during steady state at all. However, when also *zero pressure volumes* are lowered by the same ratio, peak gets higher, especially dichrotic notch and dichrotic peak. Also, diastolic end pressure is highered. Flow is also lowered. It has overall nearly same effect as lowering venous compliance, while as the volume is lowered to about 360 from 600, it just adds volume to veins.

Changing *compliance of vena cava* does not affect the result at all.

Varying with *venous resistance* also does not affect the results, unless its too much and it prevents the pump from filling.

Lowering *total blood volume* by 40% results in loss of pulse, as the volumes get below zero pressure volumes, which results in stop of circulation. So I lowered it by 20% only, which lowers total pressure and does not allow the pump to fill. To the contrary, when raising *total blood volume* by 20%, the pressure is overall higher by about 50%, the peak is rounder and so is dichrotic notch and dichrotic peak, which is also a bit delayed.

5.4.11 Validation

Regretably, the model could not be validated directly on patients for number of reasons.

Firstly, in given scope it is not possible to run such an experiments. Even though some patients could be still supported by pulsatile VADs in local medical centres (IKEM etc.), contacting them would be complicated. Also, to succesfully validate, one must change parameters of the pump (such as its volume, which would require changing pump) and larger changes which could threaten the patient. Therefore, only very limited asset would be possible. That is also ethically inadmissible.

In addition, some of the simplifications made are quite unrealistic (i.e. no regulation, no own heart etc.), which would ruin validation.

Animal test remains a possibility, as well as.some models have been validated just on mock circulatory loop (e.g. [51]). This should be also possible for this model. Expensive devices (including the VAD) and equipment would be needed for both though.

Rather than validation of the model one should try to review and validate objective, assumptions and equations of this model and to compare it to other physical models. Also the fact, that the response on changing various parameters is as expected and as physiological, does indicate the corectness.

Chapter 6

Experiment

The goal of this thesis shall also be to confirm, that patients with different sizes needs individual pump settings and especially that setting same stroke volume to small and large patient may be dangerous.

6.1 Objective

All patients have quite same physiological pressure waveform. But small patient patient would have substantially lower flow, using lower stroke volume (and usually even higher rate). This is discussed in section 2.3.0.3 on page 7. To create the same pressure curve with lower SV, some of the parameters of vascular bed must be different. Now, when we have patient, whose vascular bed is used to smaller flows, we introduce larger pump with larger stroke volume. The hypothesis is, that the pressure would rise accordingly and could inflict hypertension.

It would be enough to just increase or decrease stroke volumes in default middle patient though, but for demonstrational purpose it is more impressive to show how the *small* or *large* patient are affected.

6.1.1 Subsequentional goal

Simulating small body size of patient, we take the reduction of stroke volume as granted. By inducing this, we would have to change other parameters of vascular bed to obtain the pressure waveform as similar as possible. It is a challenge, which parameters would have to be changed.

In my theory, by studying pressure and flow waveforms, we could tell the parameters of a blackbox, the vascular bed. Hereby I propose this topic for extensive future work.

6.2 Experiment overview

Experiment is done on the model described in 5. According to objective, three subjects are prepared. The default parameters of model are considered as a middle patient, then small and large patients are prepared.

Patient	BSA* [m^2]	BMI* [-]	Height [m]	Weight [kg]	SV [ml]
Small	1	20	122	30	35
Normal	1.7	20	172	59	65
Large	2.4	25	202	102	100

Table 6.1: Definition of three patients of different size. Parameters marked with * has been set arbitrarily. SV means stroke volume.

From arbitrarily set BSA of different-sized patients unwinds stroke volume. Then the parameters of vascular bed are adjusted, so the pressure waveform is as similar as possible. Other parameters of pump are left untouched for demonstration purpose.

So, we have three patients with three pumps of different stroke volume and three vascular beds, adjusted to belonging pump.

Now is to observe, how the pressure waveform would change, when the pumps are switched. Particularly, when inappropriately *large* pump is inserted to *small* vascular bed and vice versa, when normal pump is inserted to vascular bed of very large patient.

6.3 Definition of patients

As the crucial parameter for chosing VAD is the BSA, patients are defined mainly using that. Additional parameter is the BMI, so I would have patients with realistic height and weight. I neglect the effect of different sex, assuming it is same for all three patients and refering to as males. Height and weight are derived from equations 2.2 on page 5 and 2.3 on page 5, stroke volume are based on equation 2.4 on page 7. The values are rounded. Hereby I define *small*, *normal* and *large* patient. Their sizes are summarized in table 6.1. It should be mentioned again, that as the patient's native heart is failing, his vascular bed could be already used to lower flow rates and pressures. Therefore, even the normal-sized patient could have parameters of vascular bed similar to substantially smaller patient.

For computation of the values, simple Modelica model PATIENT.MO has been created and is enclosed on CD.

6.4 Parameters

This section deals with different parameters for *small* and *large* body size. I base my values on data from Conlon et al.[8], which is the normal-sized patient. Thus here I discuss parameters of small and large patient.

Computing and proving the parameters exactly depending on body size would be sufficient enough for another thesis. In addition, they are dependent also on various other factors than size[33]. Therefore I just discuss, which way and how much they are *expected* to change and taking that as a basis for fine-tuning, I set them arbitrarily.

Parameters are generally divided into three groups:

- Fixed parameters

Parameter	Patient		
	Small	**Normal**	**Large**
Maximal stroke volume [ml]	35	65	100
Ejection pressure [mmHg]	220	220	220
Filling pressure [mmHg]	-5	-5	-5
Rate [bmp]	60	60	60
Systole fraction [-]	0.3	0.3	0.3
Alpha [-]	0.025	0.025	0.025

Table 6.2: Pump parameters

- Pump parameters
- Vascular bed parameters

Last two groups have three predefined set of parameters, corresponding to small patient, normal patient and large patient.

6.4.1 Fixed parameters

Some parameters were considered as fixed, as they are not expected to change from person to person. I assume, that same canullae are used in operations. Nonetheless, canullae are affecting the blood flow minimally (except for resistance, but this parameter is tuned anyway).

6.4.2 Pump parameters

To evaluate effect of different stroke volume, the pumps are considered equal, except for maximal stroke volume, in all three patients. This is quite unrealistic and would surely affect the pressure waveform so it could never be same in the three cases, but it is needed to prove, that just excessive stroke volume could lead to hypertension. Parametres are summarized in table 6.2.

6.4.3 Vascular vessel parameters

Vascular vessels are formed of compliances, resistances and inertias. The considerations made here are based on equations stated in section 5.4.4 on page 50.

6.4.3.1 Resistances

There are generally three resistances in this model – arterial, peripheral and venous. All of them are considered substantially larger, as the diameters are smaller. Also, I expect smaller patients to have smaller capillaries total cross-section, thus larger peripheral resistance. To the contary, resistance is also dependent on length, which is lowered in smaller patients.

6.4.3.2 Compliance

According to [33], who concluded study on arterial compliance on young children between 9-11 years, arterial compliance depends from 44% on body mass,

overall fitness, blood pressure and maturity. Also, Fergusson and Randall (1986) conclude, that "the quotient SV/PP was a good estimate of compliance"

As discussed in section 5.4.7.1 on page 60, initial volume is assigned using *Total blood volume* to all components at once. *Total blood volume* could be approximated as[4]

$$Total\,blood\,volume = (3.29 \cdot BSA - 1.229)$$

which for patient of BSA is 4.36 l. To meet the model's default, which is 3.493 l, it is scaled down by the quotient to

$$Total\,blood\,volume = (3.29 \cdot BSA - 1.229) \cdot \frac{3493}{4361}$$

Each compliance has also parameter zero-pressure volume and initial volume. Zero-pressure volume is in direct correlation with diameter or more precisely cross-section area A and length L;

$$Zero\,pressure\,volume \sim A \cdot L$$

but in fact, the zero-pressure volumes are based on that of normal normal patient's, which is scaled by the total blood volume ratio.

6.4.3.3 Inertia

As explained in 5.4.4.3 on page 52, inertia is also based on diameter and length. But as the relationship is not easily predictable, primarily I do not assume some big changes.

6.4.3.4 Values

After some adjusting to keep the pressure waveform similar to *normal patient*, the final parameters are shown in table 6.3 on the following page.

6.4.4 Comparison of patients of different size

How the fitting was successful could be seen in figure 6.1 on the next page and 6.2. The small patient has faster and sharper response (similarly the large patient has it slower and rounder) because of the shape of ejection driving pressure (see figure 5.14 on page 58). During ejection, the full volume is ejected much faster, still while fast rising. This could be managed by adjusting alpha and ejection pressure on pump, but for purposes of definiteness there have been made no changes to the pump except for stroke volume.

6.5 Results

Figure 6.3 on page 75 shows what happens, when we connect normal pump with stroke volume of 65 ml to small patient. There is clearly even more than stage-II hypertension. This figure proves, that it is be dangerous to support small patient with pump designed for adults in full-fill-full-eject mode.

Another possibility how to restrict excessive pressure is using higher beat rate. In accordance to Thoratec recommendations, the rate was set to 120 bmp

Parameter	Patient		
	Small	**Normal**	**Large**
total blood volume	1650	3493	5336
arteries.aorta.compliance	40	50	70
arteries.aorta.zeroPressureVolume	27	57	87
arteries.inertance		3.40E-05	
arteries.resistance	0.001	0.0008	0.0006
arteries.arteries.compliance	70	110	160
arteries.artereis.zeroPressureVolume	221	468	715
peripherals.inertance		0.0275	
peripherals.resistance	0.0255	0.013	0.0008
veins.veins.compliance		2500	
veins.veins.zeroPressureVolume	583	1234	1885
veins.collapsingResistance.openResistance	13E-05	11E-5	9.3E-5
veins.collapsingResistance.closeResistance		0.0067	
veins.venaCava.compliance		300	
veins.venaCava.zeroPressureVolume	236	500	764
veins.venaCava.maxFill	283	600	917
veins.venaCava.complianceMaxFill		1	

Table 6.3: Vascular vessels parameters for three different patient. Empty field means no change.

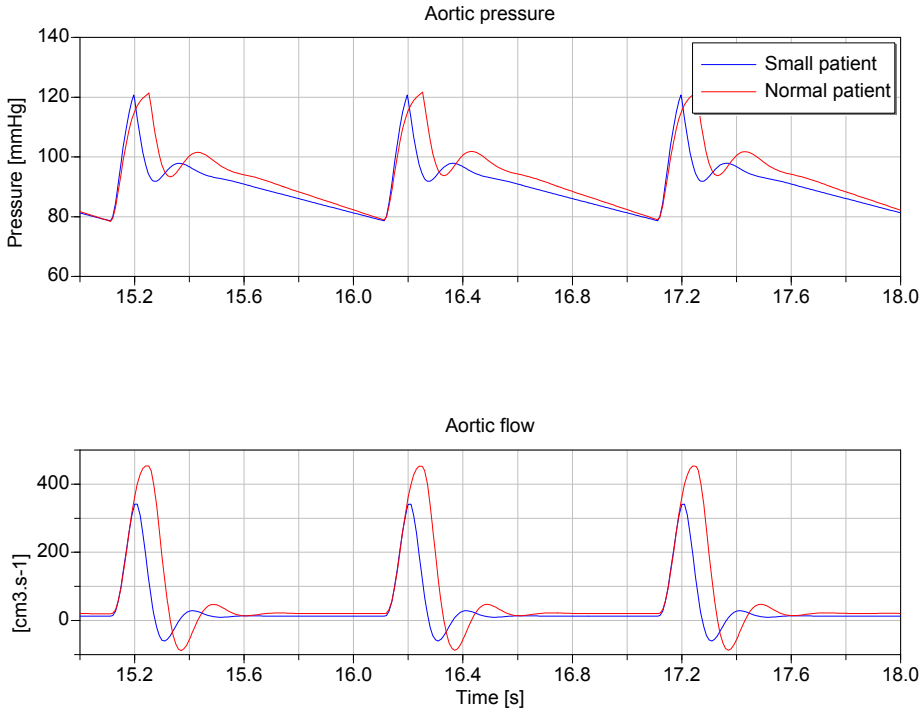

Figure 6.1: Aortic pressure and flow for normal and small patient. Note, that the small patient has much faster response.

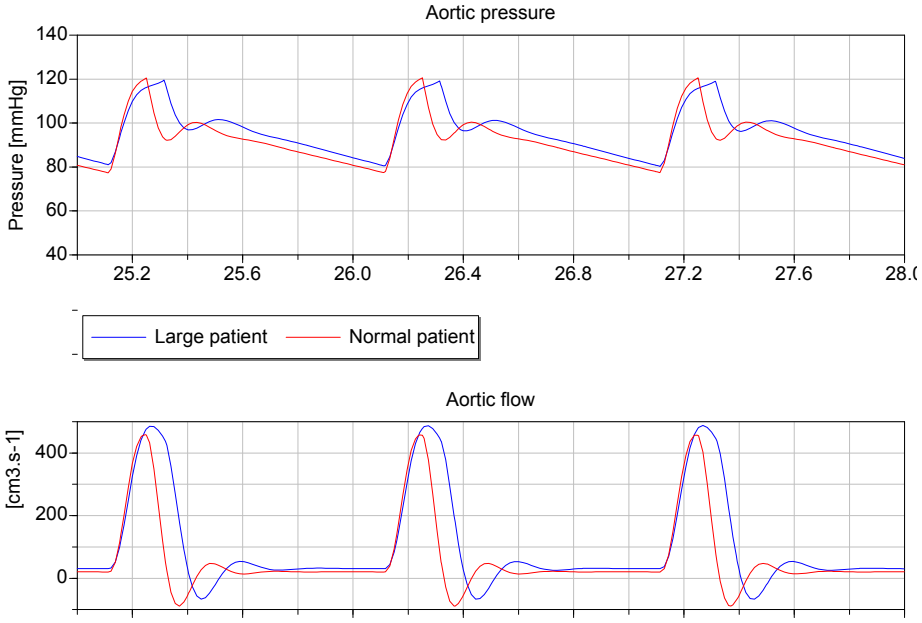

Figure 6.2: Aortic pressure and flow for normal and large patient. Note, that the large patient has slower response.

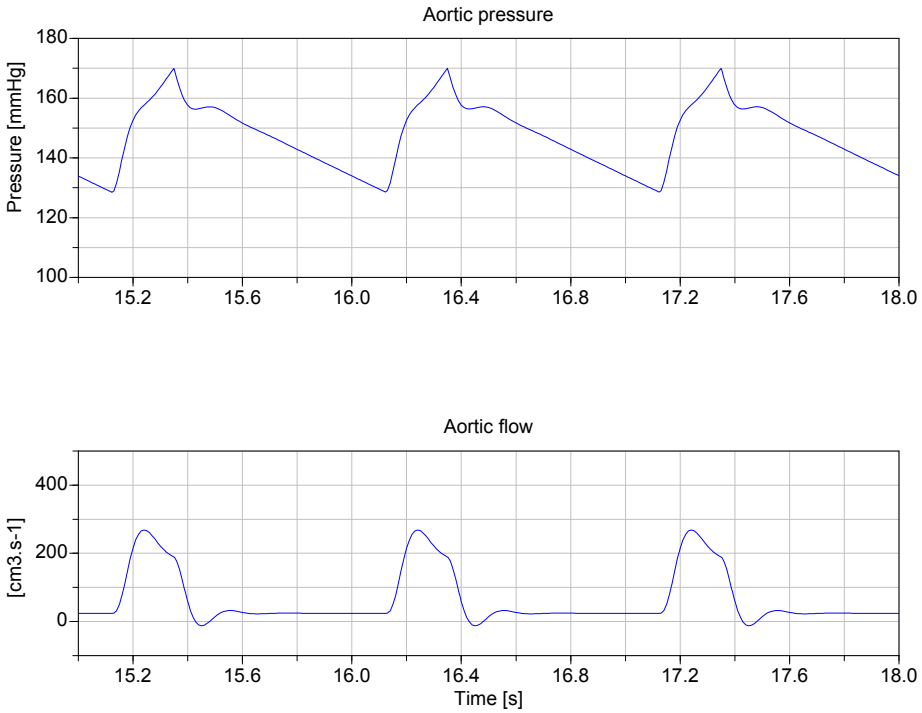

Figure 6.3: Aortic pressure and flow in small patient with normal-sized pump

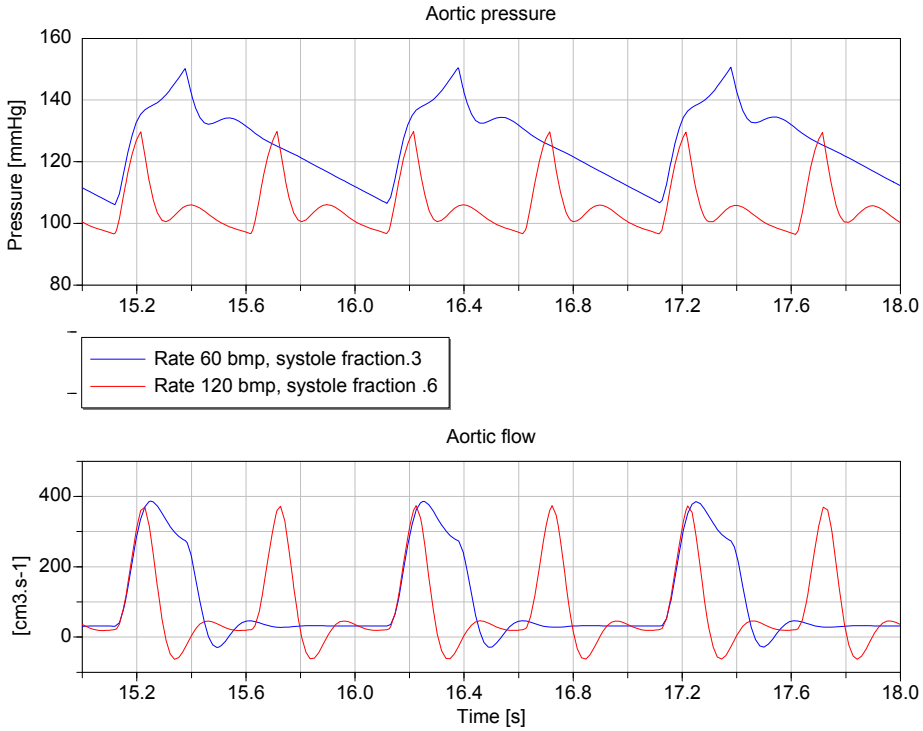

Figure 6.4: Aortic pressure and flow in normal patient with large (100 ml) pump using normal and double beat rate

and the systole fraction adjusted to 60 % so the ejection would last again 300 ms.

However, according to the model, it shows, that is not satisfactory enough, as the pressure does not have enough time to drop to adequate level and the pressure peak sends it to hypertension. This has been demonstrated on normal patient using large 100 ml pump. The results are shown in figures 6.4 and 6.5.

However, by adjusting peripheral resistance sligtly from 0.013 to 0.01 (as would probably happen due to vasodilatation initiated by baroreflex), the pressure return to adequate bounds. This could be seen in figure 6.6 on the following page. Stroke volume in the dual rate was kept at 40 ml. This shows, that increasing beat rate could help the patient. Notice, that the total pump outflow very similar ($2 \cdot 40 = 80$ compared to $1 \cdot 100 = 100$)

To demonstrate how the total outflow affects the result, I put a normal-sized pump to large patient. The pressure is clearly low, but not as much to reach hypotension. As the stroke volume is lower (100 to 65), but the frequency stays at the same rate (60), the total flow is also lower. Now, I increased the rate so the flow stays equal at 6 liters per minute[1] and systole fraction so the systole lasts again around 300 ms. The result is shown in figure 6.7. It shows, that although the diastolic pressure is slightly higher (but not reaching hypertension), the systolic pressure stays ideal at 120mmHg (provided, that the pump manages to full completely).

[1] $100 \cdot 60 = 65 \cdot 95 = 6000\,[ml \cdot s^{-1}]$

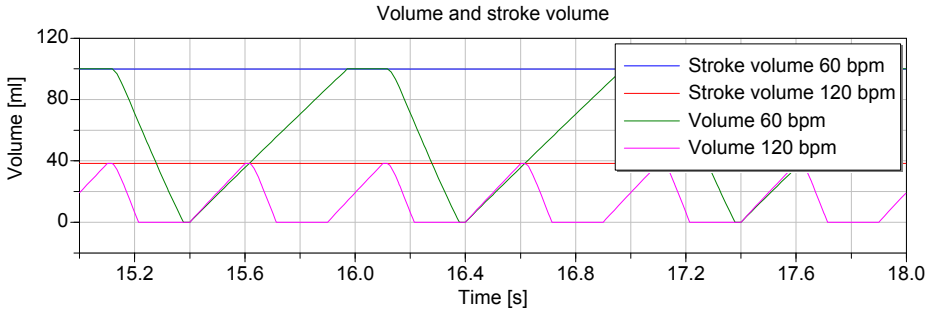

Figure 6.5: Pump volume and stroke volume in normal patient with large (100 ml) pump using normal and double beat rate

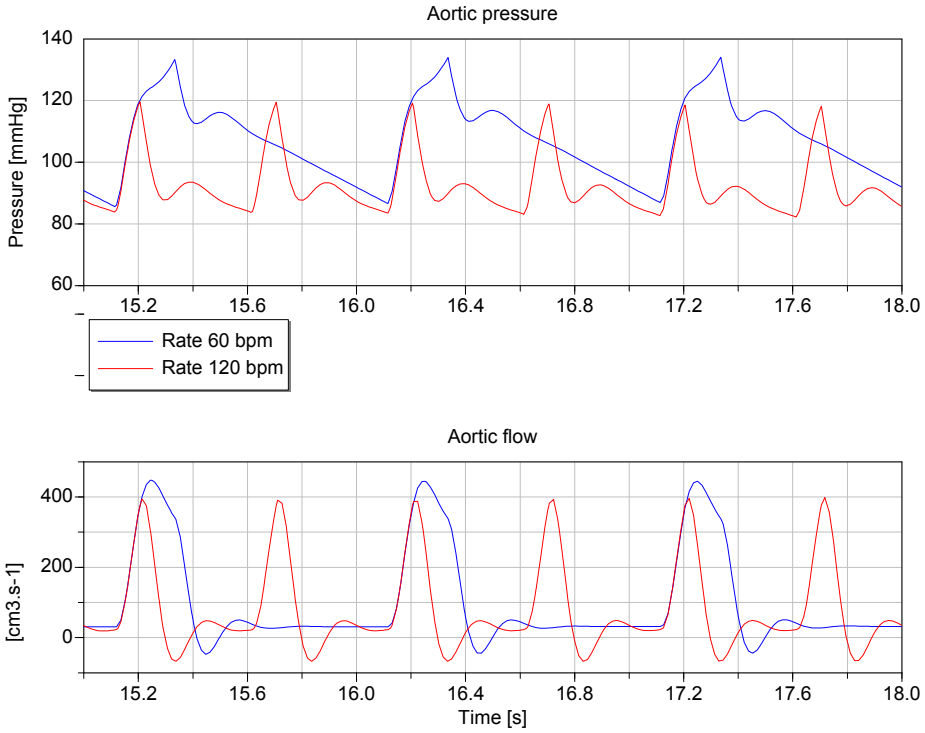

Figure 6.6: Aortic pressure and flow in normal patient with large (100 ml) pump using normal and double beat rate with adjusted peripheral resistance from 0.013 to 0.01

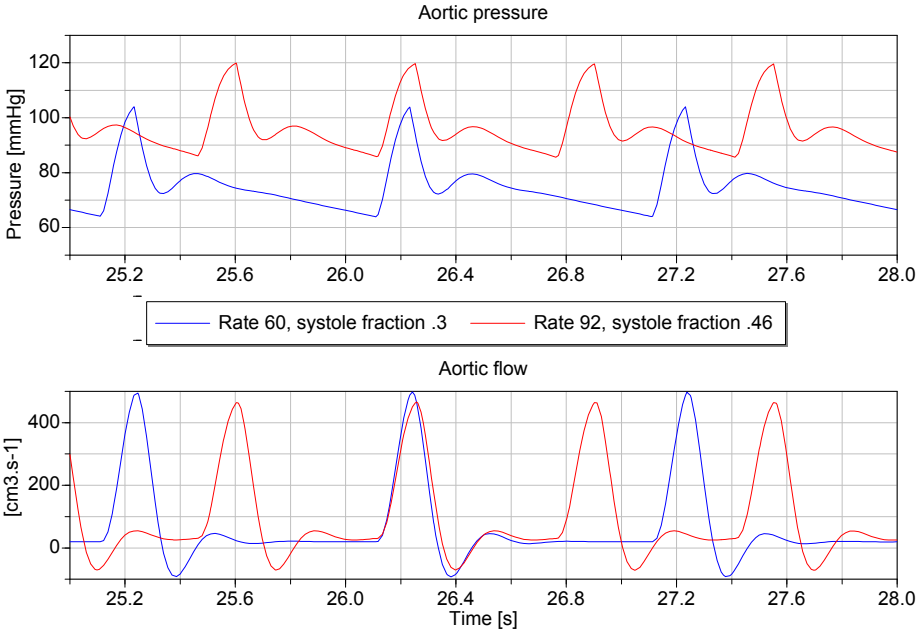

Figure 6.7: Pressure and flow waveforms in large patient with normal (65 ml) pump using normal (60) versus adjusted beat rate (92), when the cardiac output stays same as with large pump.

6.6 Discussion

Human body is very complex mechanism and such model could hardly describe it as a whole. However, modelling could help us in understanding the basic principles.

Results show, that increased stroke volume really causes hypertension. But higher stroke volumes are connected with higher outlow. Future work may show, which factor is more harmful for patients – if it is the extensive pressure or immoderate overall flow.

For purposes of simplicity and clarity, many issues were disregarded. Especially the effect of baroreflex should be taken into account in future simulations, as the effect of peripheral resistance is quite vital.

Also, when trying to demostrate, that the FFFE mode is harmful fo small patients, this mode should have better been actually implemented. Instead, FR mode has been used to observe same time period and not to be affected by variable period. But as could be seen from figure 6.4, even when the stroke volume is lower, the overall pressure was higher. This suggests, that employing higher rate leads to overall higher aortic pressure.

But in order to implement FFFE mode correctly, the length of filling phase is of particular interest. But as it depends mainly on venous pressure (in fact on difference between vena cava pressure and filling pressure of the pump), current model has to be adjusted in means of lowering venous pressure substantielly (this issue is discussed in section 5.4.9.2 on page 68). Due to higher venous pressure, in current simulation the pump has no problems with filling. However, that may

not be generalized, since the filling rate is of high importance.

In future simulations, there would also be advisable to include native ventricle. Modeling such would not be as problem - I propose using current design of the VAD pump and change driving pressure from exponential damped step to half-sine function, so it is similar to intra-ventricle pressure [36]. I tested this approach and it looks promising, however it is not within current scope.

Chapter 7

User interface application

7.1 Purpose

While the model was created in Dymola environment and could also been simulated in there, it is not good way of presentating it to users. First of all, Dymola is commercial application of Dassault Systemes (Formerly Dynasim AB) and user should not be bothered with need for commercial application.

There exist free open source implementation of modelica called OpenModelica [1], which is also able to simulate any modelica model, but the user interface is not meant for first-time users and also installing new application in order to just view the model is too inconvenient.

This user-friendly front-end interface (further referred to as an APPLICATION) should serve as learning and demonstrational aid for doctors and medical professionals. It would allow to observe simply how the blood circulation is affected when the parameters are changed, with accent on different body size.

7.2 Solution requirements

In order to present a model to the user, one should use some user-friendly application. This should be:

- Easy to install or no installation at all.
- Easy to access, so it should be deployable via internet
- Easy to use, that means the usage should be as simple as possible, but not simpler (as proposed by Einstein).

7.2.1 Requirements on application

Application should serve to perform the experiment described in chapter 6 on page 70easily and should also allow to modify selected parameters of pump and cardiovascular system and facilitate the simulation. Then, the simulated aortic pressure and flow waveform should be plotted.

[1] Produced by Open Source Modelica Consortium. http://www.openmodelica.org/

The experiment, which has to be demonstrated, is to show that (and how) different stroke volume would perform in different patients (represented by changed parameters). Therefore, three sets of the pump parameters (small, medium and large) and three sets of vascular system parameters (again small, medium and large) should be pre-saved in order to load it quickly. Chosen parameters are discussed in section 6.4 on page 71.

The simulated waveforms should be shown after transitionall effects, which takes place because of non-ideal initial conditions (so one must wait, till the flow stabilizes). These stabilization takes between 5-15 seconds, so it should be enough to show 3 second interval from 15 to 18 seconds.

Also, owing to changed parameters, the pump may sometimes not fill or empty completely. To remind, stroke colume is defined as

$$end\,Diastolic\,Volume - end\,Systolic\,Volume$$

And as the stroke volume of the pump is crucial for the objective of the simulation, the pump volume and/or the stroke volume should be also shown. Because the waveforms are not particularly important, it is just stroke volume, which should be ideally constant, I decided to show the full progress from $time = 0s$. to $time = 18s$, so there could be observed, if the transitional effects have already subsided.

7.3 Proposed system design

So I aim for easy to install and easy to use solution, downloadable from internet. In [21] they suggest using web-based solution, connecting Modelica and Silverlight [2]. Silverlight is a perfect deploy solution, that with just a small plugin one is able to get interactive rich internet content.

However, as of recent, its not possible to simple link modelica and silverlight together. To understand the connection, we must first look at modelica compilation and simulation sequence.

Firstly, modelica flattens the all the classes used in the model into one model. Then an OpenModelicaCompiler (OMC) is called, which produces a code in C language. This code is run afterwards with simulation parameters (such as start time, lenght and other input parameters) and this code then provides the time-variant calculations and integrations [13].

Although Silverlight is a .NET family product, due its web nature does not support importing C libraries like .NET. Standalone C# .NET application, or also WPF, would be capable of this, but those contradicts a little my easy to install and easy to access requirement. So in order to present models created in modelica using silvverlight, it is necessary to compile produced C code to C# .NET platform.

Other possible aproach is to have a web-service running on a server, which processes input parameters, simulates the model and respond simulated data. I consider this approach rather clumsy and inconvenient, firstly there si a need

[2] Microsoft Silverlight is a web application framework that provides functionalities similar to those in Adobe Flash, integrating multimedia, graphics, animations and interactivity into a single runtime environment. Initially released as a video streaming plugin, later versions brought additional interactivity features and support for CLI languages and development tools. (http://en.wikipedia.org/wiki/Silverlight)

of a server running the webservice, secondly, the computational demandingness is quite high for in detail simulation and instead of server, the client machine should solve it.

Team at *Laboratory of Biocybernetics and Computer Aided Teaching* by Charles University in Prague (further referred to as a *patf-biokyb*) [3] is currently developing such translato (further referred to as modelica.net translator). When the model is translated to C#, it could be quite easily coupled to silverlight, which offers nearly no-install (or just the silverlight plugin, in case the end-user does not have it laready installed), small donwload size and thus unlimited reach.

7.4 Application design and implementation

Application has been designed according to the requerements. The platform is Silverlight 2.0 with target .NET version 3.5. This becomes the standard nowadays and is already installed in all computers running Microsoft Windows 7 (by default) and big part of machines with Microsoft Windows XP (through automatic updates).

MainPage is the main class. It contains instances of all other classes below. It creates the general user interface.

Model is a single-instance design pattern container for the compiled model. It contains funtion computeCurves which performs the simulation and saves the results in lists of points. The computeCurves needs class ParamSet as input.

ParamSet is a class which contains variable parameters of the model (i.e. of the pump and vasculars)

SimpleGraph is a part of Bodylight.Controls project, developed by *patf-biokyb* (mentioned above), which offers a single line graph. I introduced small improvements to this component. This class is used several times, for plotting the pressure, flow and stroke volume patterns.

SliderControl is a graphic user interface class, which provides slider and a textbox linked together for easy parameters assignment.

7.4.1 Features

As seen in a screnshot in figure 7.1 on the following page, the application offers features such as:

- In pressure curve, the normal pressure is shown by orange lines, specifying the borderlines of hypertension and hypotension.
- Parameters could have additional information provided as a tooltip.

[3] Charles University in Prague
Faculty of Medicine
Institute of Pathological Physiology
Laboratory of Biocybernetics and Computer Aided Teaching
http://patf-biokyb.lf1.cuni.cz/

- Grey lines above pressure and flow graphs and above volume and stroke volume graph could be used for resizing the graphs size.
- Buttons *Small subject*, *Normal-sized* subject and *Large subject* below *VAD parameters setttings* would set pump parameters to pre-defined values. Similarly, buttons below Vascular system parameters settings would set values of vascular system.
- The button *Count* runs the simulation of the model and plots the waveforms.
- The graphs *Pressure curve* and *Flow curve* show aortic pressure waveform from the time, when the transitionall effect should be over. The graph below, *Volume and stroke volume* show the pump filling and current stroke volume for the whole simulation time, so one could see also the effect of transitionals.

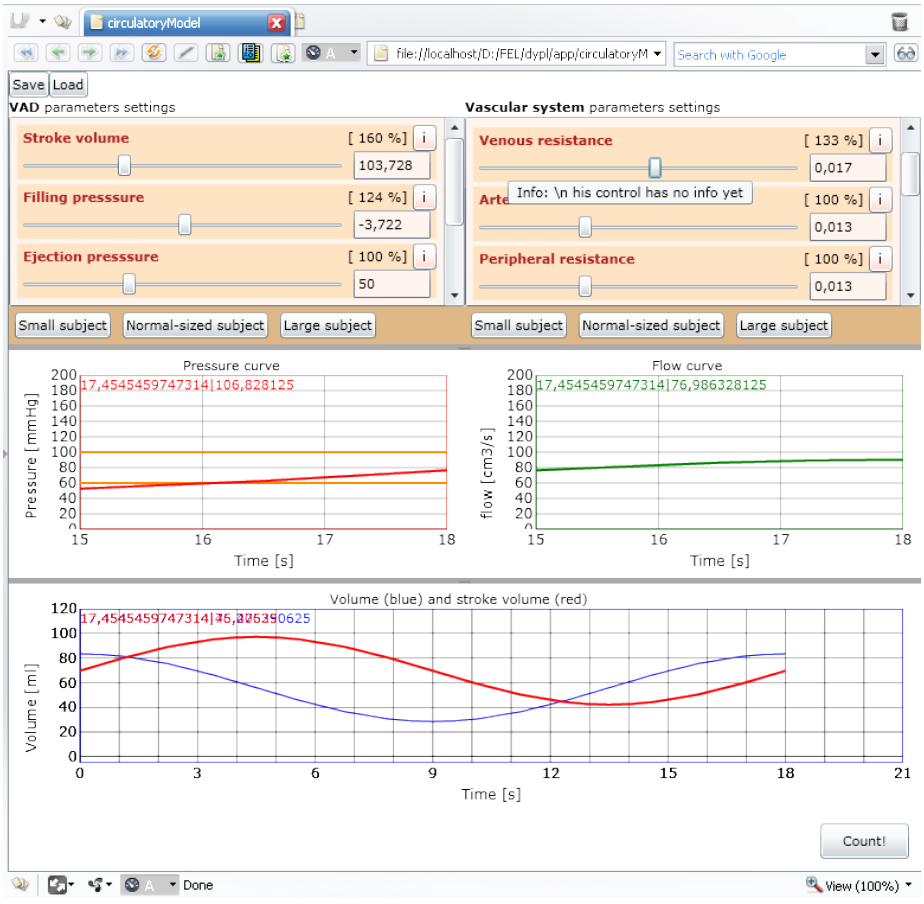

Figure 7.1: Screenshot of the application, as rendered in Opera browser in Windows XP OS. Notice the synthetic waveforms, since the model is still not linked.

7.4.2 Hardware and software requirements

System requirements are the same as requirements to run Silverlight plugin.

> "Silverlight is supported by all major browsers on both Mac OS X and Windows, and with Moonlight on Linux as well. Particular care is being taken to account for differences in platform and browser capabilities to ensure a consistent experience including experiences on Internet Explorer 6, 7 8, Firefox2 and 3, Safari 3 and 4, and now Google Chrome." (http://www.microsoft.com/silverlight/faq/#sys-req)

On system running Windows 7, Windows Vista or Windows XP Service Pack 2 it is at least Intel® Pentium® III 450MHz or faster processor (or equivalent) and 128MB of RAM (As defined by Microsoft. http://www.microsoft.com/silverlight/faq/#sys-req)

Silverlight plugin is about 6MB large, but is in most cases is already pre-installed. Currently, the size of application is 244KB, but as noted in 7.5, since the actual model is currently not included, its size may grow greatly.

7.4.3 Documentation

Auto-generated documentation is availiable on enclosed CD (See section A on page 91).

7.5 Problems

At the time of writing, as the modelica.net translator is still in development, it was not able to simulate the model properly. It is planned, that by the time of presentation, it should work pretty. However, all the components are prepared, so once the translated model is availiable, it would be enough to modify the function computeCurves(ParamSet paramSet) in class Model.

Chapter 8

Conclusion

Modelica is a developing method for multidisciplinary simulation and modelling. Using Modelica.net compiler the results could be presented in a user-friendly way for impressive demonstrations.

A simple model of human pulsatile circulatory hemodynamics based on paper by Conlon et al.[8] has been implemented in Modelica language and improved with pump of Thoratec PVAD design. This model was designed to make physical mock circulatories obsolete. Modelica implementation offers very simple extensions of the model for future uses.

When using pulsatile ventricular assist device support (such as Thoratec PVAD), stroke volume should be of concern in very small patients. Automatic mode (full fill, full eject) should not be employed in such cases[1]. This has already been known, but simulation experiment conducted in this paper proves it. Instead, fixed rate mode in combinations with reduced filling pressure[2] allows to not fill the chamber completely, therefore ejecting smaller stroke volume.

Extensive amount of future work arise. Firstly, is to design and implement various body autoregulation mechanisms into current model. Also other issues, which were neglected in this introductionary thesis could be easily added, such as pulmonary circulation or interaction with native ventricles.

Secondly, it would be to measure, compute or acquire from literature exact parameters of vascular bed in dependence on BSA, height, weight, age etc. and as a holy grail, to investigate a way, how to acquire vascular bed characteristic based solely on pressure and flow waveforms.

[1] Also devices with smaller stroke volume exists – for example Berlin Heart EXCOR, then the automatic mode would be appropriate

[2] Towards zero, since filling pressure is usually negative

Bibliography

[1] Aoris Nova. Heartware expert report. A letter to HeartWare Limited, 2004. 1, 3.3.1

[2] G. Avanzolini and A. Cappello. Computer simulation of the controlled cardiovascular system: application to cardiac assistance evaluation. In *Computers in Cardiology 1991, Proceedings*, pages 693 – 696, 1991. 5.2

[3] A. Baba et al. Microcirculation of the bulbar conjunctiva in the goat implanted with a total artificial heart: effects of pulsatile and nonpulsatile flow. *ASAIO journal*, 2004. 3.3.8.7

[4] J. J. Batzel, F. Kappel, D. Schneditz, and H. T. Tran. *Cardiovascular and Respiratory Systems. Modelling, Analysis and Control.* Society for Industrial and Applied Mathematics, Philadelphia, 2007. 2.2, 6.4.3.2

[5] J. Booth. A short history of blood pressure measurement. In *Proceedings of the Royal Society of Medicine*, 1977. 2, 2.7.2

[6] H. Brandes, J. Albes, A. Conzelmann, M. Wehrmann, and G. Ziemer. Comparison of pulsatile and nonpulsatile perfusion of the lung in an extracorporeal large animal model. *European Surgical Research*, 2002. 3.3.8.7

[7] Collective. Statistics. our guide to current statistics and the supplement to our heart & stroke facts. Technical report, American Heart Association, 2009. Availiable at `http://americanheart.org/presenter.jhtml?identifier=1200026`. 1.1

[8] M. J. Conlon, D. L. Russel, and T. Mussivand. Development of a mathematical model of the human circulatory system. *Annals of Biomedical Engineering*, 2006. (document), 5.2, 5.4.1, 5.4.4.2, 5.5, 5.4.5, 5.4.5.1, 5.4.5.1, 5.4.5.2, 5.4.5.3, 5.4.5.4, 5.4.5.5, 5.4.7, 5.1, 5.4.8, 6.4, 8

[9] D. H. Delgado et al. Mechanical circulatory assistance: State of art. *Circulation*, 2002. Availiable at `http://circ.ahajournals.org/cgi/content/full/circulationaha;106/16/2046`. 3.3.3, 4

[10] A. El-Banayosy, R. Korfer, L. Arusoglu, L. Kiznerand, M. Morshuis, H. Milting, G. T. O. Fey, and K. Minami. Device and patient management in a bridge-to-transplant setting. *Annals of Thoracic Surgery*, 2001. 3.1, 3.1.2, 3.3.6, 3.3.8.2, 3.3.8.4, 3.3.8.5, 3.3.8.6

[11] D. J. Farrar, P. J. Compton, J. H. Lawson, J. S. Hershon, and D. J. Hill. Control modes of a clinical ventricular assist device. *IEEE Engineering in Medicine and Biology Magazine*, 1986. 3.3.4, 3.3.6.1, 3.3.6.1, 3.3.6.2, 3.3.6.2, 3.5, 3.3.6.2, 3.3.6.2, 3.3.6.3, 3.10

[12] L. Formaggia and D. L. ans Alfio Quarteroni. One-dimensional models for blood flow in arteries. *Journal of Engineering Mathematics*, 2003. 5.2

[13] P. Fritzson. *Principles of Object-Oriented Modeling and Simulation with Modelica 2.1.* Wiley-IEEE Press, 2004. 5.3, 5.3.1, 5.4.9.1, 7, 7.3

[14] S. Furic. Hybrid acausal modeling using modelica. Presentation for LMS international, 2007. Accessible at http://www.afsec-cnrs.org/wp-content/uploads/2007/07/Modelica%20Presentation.pdf. 5.1, 5.3.1

[15] R. J. Gordon, B. Quagliarello, and F. D. Lowy. Ventricular assist device-related infections. July 2006. 3.3.8.4

[16] P. H. M. heerd, P. Borsje, T. Arts, and F. N. van De Vosse. Dependence of intramyocardial pressure and coronary flow on ventricular loading and contractility: A model study. *Annals of Biomedical Engineering*, 2006. 5.2

[17] M. B. Higginbotham, K. G. Morris, R. S. Williams, P. A. McHale, R. E. Coleman, and F. R. Cobb. Regulation of stroke volume during submaximal and maximal upright exercise in normal man. *Circulation research*, 1986. Availiable at http://circres.ahajournals.org/cgi/content/short/58/2/281. 2.3.0.2

[18] P. Hunka. Optimalizace nastavení veno-arteriální ecmo u cirkulačně selhávajících pacientu. Master's thesis, Czech Technical University, Prague, Czech Republic, 2010. 3.2, 3.2.3, 3.3, 3.3.8.7

[19] S. A. Husain et al. Ventricular assist device implantation in the pediatric population: Does pump size selection and associated hemodynamics impact outcomes? *ASAIO Journal*, 2008. 1, 4

[20] J. Kettner. Mechanické srdeční podpory a náhrady. *Kardiofórum*, 2004. 1.1, 3, 3.2.1, 3.2.2, 3.3, 3.1, 3.3.8.8

[21] J. Kofránek, M. Mateják, and P. Privitzer. Kreativní propojení objektových technologií pro tvorbu výukových biomedicínských modelů. In *Objekty 2009*, pages 1–21. Gaudeamus, Univerzita Hradec králové, Objekty 2009. 7.3

[22] D. N. Ku. Blood flow in arteries. *Annuals Review of Fluid Mechanics*, pages 399–434, 1997. 2.2.0.1, 2.4, 2.4.1, 2.6.0.2, 2.6.0.3, 2.6, 2.7.5, 2.7.9, 5.4.3.5

[23] D. Macků. Limity pulsatilních mechanických srdečních podpor. In *Matematika na vysokých školách, Herbertov*, 2009. 1, 2.3.0.2

[24] M. Mateják, J. Kofránek, and J. Rusz. Akauzální vzkříšení Guytonova diagramu. *Medsoft*, 2009. 5.2, 5.3.1

[25] K. May-Newman. Computational cardiovascular mechanics. 2010. 1.1, 2.2.0.1, 3, 3.3, 3.3.4, 3.3.5, 3.3.6, 3.3.7, 3.3.8.1, 3.3.8.2, 5.4.3.9

[26] Mayo Clinic. Secondary hypertension; Definition, May 2008. 2.7.4

[27] S. M. Mehta, W. E. Pae, G. Rosenberg, A. J. Snyder, W. J. Weiss, J. P. Lewis, D. J. Frank, J. J. Thompsonc, and W. S. Pierce. The lionheart lvd-2000: a completely implanted left ventricular assist device for chronic circulatory support. *Annals of Thoracic Surgery*, 2001. Accessible at http://ats.ctsnetjournals.org/cgi/content/full/71/3_suppl/S156. 3.3

[28] M. R. Mirzaee, O. Ghasemalizadeh, and B. Firoozabadi. Simulating of human cardiovascular system and blood vessel obstruction using lumped method. *Proceedings of World Academy of Science, Engineering and Technology*, 31, July 2008. 5.4.4

[29] B. J. E. Misgeld. *Automatic Control of the Heart-Lung Machine*. PhD thesis, Fakultät für Elektrotechnik und Informationstechnik Ruhr-Universität Bochum, 2006. 2.6.0.2

[30] National Kidney Foundation. Guidelines for vascular access. http://www.kidney.org/professionals/kdoqi/guidelines_updates/doqiupva_iv.html, March 2010. 3.3.8.2

[31] I. Netuka, J. Malý, and O. Szárszoi. Mechanické srdeční podpory v terapii terminálního srdečního selhání. *Cor Vasa*, 2008. 3.1, 3.1.1, 3.1.2, 2, 3.1.4

[32] D. Ramachandran, C. Luo, T. S. Ma, and J. W. C. Jr. Using a human cardiovascular-respiratory model to characterize cardiac tamponade and pulsus paradoxus. *Theoretical Biology and Medical Modelling*, page Availiable online at http://www.tbiomed.com/content/6/1/15, 2009. 5.3

[33] K. Reed, D. Warburton, R. Lewanczuk, M. Haykowsky, J. Scott, C. Whitney, J. McGavock, and H. McKay. Arterial compliance in young children: the role of aerobic fitness. *European Journal of Cardiovascular Prevention & Rehabilitation*, 2005. Abstract at http://www.ncbi.nlm.nih.gov/pubmed/16210937. 6.4, 6.4.3.2

[34] O. Reinhartz, J. G. Copeland, and D. J. Farrar. Thoratec ventricular assist devices in children with less than 1.3 m2 of body surface area. *ASAIO Journal*, 2003. 4, 4

[35] O. Reinhartz, F. M. Keith, A. El-Banayosy, L. R. McBride, R. C. Robbins, J. G. Copeland, and D. J. Farrar. Multicenter experience with the thoratec ventricular assist device in children and adolescents. *The Journal of Heart and Lung Transplantation*, 2001. (document), 1, 3.3, 3.3.4, 4, 4

[36] S. Silbernagl and A. Despopoulos. *Atlas fyziologie člověka*. Avicenum, Praha, 1984. 2.6, 2.6.0.2, 2.7.1, 5.4.3.4, 5.4.3.7, 5.4.5.2, 5.4.8, 6.6

[37] P. Stein and H. Sabbah. Turbulent blood flow in the ascending aorta of humans with normal and diseased aortic valves. *Circulation Research*, 1976. 2.7.9

[38] Y. Sun, M. Beshara, R. J. Lucariello, and S. A. Chiaramida. A comprehensive model for reight-left heart interaction under the influence of pericadium and baroreflex. *American Physiological Society*, 1997. 5.4.3.11

[39] R. M. Suri, R. C. Daly, J. A. Dearani, and C. G. McGregor. Successful use of thoratec biventricular support in a small child awaiting cardiac transplantation. *The Annals of Thoracic Surgery*, 2005. (document), 1

[40] Texas Heart Institute. Heart assist devices. http://www.texasheartinstitute.org/Research/Devices/, March 2010. 3.2.1, 3.2.4

[41] The Data Collection and Analysis Center University of Alabama at Birmingham. Quarterly statistical report. implant dates march 1, 2006 to december 31, 2009. Technical report, INTERMACS, Interagency Registry for Mechanically Assisted Circulatory Support, March 2010. Accessible at http://www.uab.edu/ctsresearch/intermacs/statisticalsummaries.htm. 3.3.1, 3.3.2, 3.3.8.8

[42] Thoratec Corporation Inc. *Dual Drive Console Instructions for Use*. Manual downloaded from http://www.thoratec.com/medical-professionals/resource-library/index.aspx on 18.2.2010. 3.3.6.1, 3.3.6.2

[43] Thoratec Corporation Inc. *Thoratec Ventricular Assist Device (VAD) System Instructions for Use*. Manual downloaded from http://www.thoratec.com/medical-professionals/resource-library/index.aspx on 18.2.2010. 3.3, 3.3.6.1, 3.4, 3.3.6.2, 3.3.8.2

[44] Thoratec Corporation Inc. Clinical outcomes. Published at company's website, http://www.thoratec.com/vad-trials-outcomes/clinical-outcomes/index.aspxasofApril2010, 2010. 3.3.6.3, 3.3.7.1

[45] R. Tominaga, W. Smith, A. Massiello, H. Harasaki, and L. A. R. Golding. Chronic nonpulsatile blood flow. iii. effects of pump flow rate on oxygen transport and utilization in chronic nonpulsatile biventricular bypass. *Journal of Thoracic and Cardiovascular Surgery*, 1996. Accessible at http://jtcs.ctsnetjournals.org/cgi/content/full/111/4/863. 3.3.8.7

[46] S. Trojan et al. *Fyziologie. Učebnice pro lékařské fakulty. 1. část.* Avicenum, 1987. 2.2, 2.3.0.3, 2.4.1, 2.1, 2.7.6, 5.4.3.6, 5.4.8

[47] M. Ursino. A mathematical model of the carotid baroregulation in pulsating conditions. *IEEE Transactions on Biomedical Engineering*, 1999. 2.6, 5.4.3.11

[48] U.S. Department of Health and Human Services. Reference card from the seventh report of the joint national committee on prevention, detection, evaluation, and treatment of high blood pressure. NHLBI publications, 2003. Accessible at http://www.nhlbi.nih.gov/guidelines/hypertension/jnc7card.htm. 2.1

[49] C. Welp, J. Werner, D. Böhringer, and M. Hexamer. Investigation of cardiac and cardio-therapeutical phenomena using pulsatile circulatory model. *Biomed. Technik*, 2004. 5.2

[50] Y. Wu, P. E. Allaire, G. Tao, and D. Olsen. Modeling, estimation, and control of human circulatory system with a left ventricular assist device. *IEEE Transactions on Control Systems Technology*, 2007. 1.1, 3.1, 5.4.4

[51] Y.-C. Yu, J. F. Antaki, and J. R. M. S. P. J. Miller. Mathematical model of pulsatile blood pump for lvas control. In *Proceedings of the American Control Conference*, pages 3709–3713, Albuquerque, New Mexico, 1997. 5.2, 5.4.11

[52] Y.-C. Yu and X. Zhang. A simple cardiovascular system model for ventricular assist device development. In *Bioengineering Conference, 2009 IEEE 35th Annual Northeast*, 2009. 5.4.4

Appendix A

Enclosed CD content

The enclosed CD contains this text, Modelica model source and documentation and application source codes and documentation. The folder structure is as follows:

app Contains the developed application binaries, documentation and sources

- **bin** compiled demonstration of application. Entry point TestPage.html.
- **doc** contains documentation of silverlight application generated by Doxygen[1]. Entry point index.html.
- **src** contains source code of silverlight application.

mod Contains the developed circulatory model, its Modelica source and documentation

- **doc** contains HTML documentation of Modelica model. Entry point Conlon.html.
- **src** contains Modelica source of the model.

pac Simple Modelica model of different patient sizes. Based on weight and height (or BMI and BSA), it computes the other parameters, including stroke volume and some additional.

txt contains pdf file with this thesis

[1] Doxygen is a documentation system for C++, C, Java, Objective-C, Python, IDL (Corba and Microsoft flavors), Fortran, VHDL, PHP, C#, and to some extent D. Homepage http://www.stack.nl/~dimitri/doxygen/