DESIGN AND IMPLEMENTATION OF AN IN-VITRO CAROTID ARTERY FLOW CIRCUIT WITH PULSATILE FLOW CONDITIONS

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Abstract

In the study an *in-vitro* flow circuit with pulsatile flow conditions is designed and implemented. The flow circuit will be used to examine the effect of stent placement on flow characteristics with Echo Particle Image Velocimetry (echoPIV).

The design of the circuit is split in two phases. In the first phase, a simple flow circuit is designed to simulate the waveform in the carotid artery of older adults. The design includes a gear pump and a piston driven pump [ViVitro pump] that generate a pulsatile waveform, which is recorded with a mass flow meter. The mean volumetric flow profile is analysed by comparing it to the *in-vivo* common carotid artery (CCA) waveform. During the second phase, elements of the two-element windkessel model are added to regulate the pressure in the circuit. The arterial compliance and the peripheral resistance of the vessels are simulated with a compliance chamber and a resistance in series. The influence of the additional elements is analysed by comparing the resulting waveform with the modeled waveform of the simple circuit. The velocity flow profile of the CCA is taken into account by estimating the Reynolds and Womersley number in the circuit.

The analysis shows that the modeled waveform in the flow circuit resembles the waveform in the CCA, but the flow rate is higher due to the performance of the gear pump. Furthermore, the spread is relatively large at the early systole and early diastole because of the performance of the piston driven pump. The resulting pulse pressure in the circuit is 20 mmHg, with a systolic and diastolic pressure of 110 and 90 mmHg. The pulse pressure can be improved by changing the size of the compliance chamber. Moreover, the resistance and compliance visibly influence the pulsatile flow profile, but the resulting waveform largely resembles the *in-vivo* waveform. The Reynolds and Womersley number are 500 and 4.4 respectively, so the velocity profile is laminar.

To conclude, in the current flow circuit a straight-tube phantom of a carotid artery can be inserted. The elements of the designed circuit mimic the pulsatile flow conditions of the carotid artery in the body. With several adjustments, the *in-vitro* circuit can be used for reliable and reproducible experiments with echoPIV.

Contents

Acronyms

BPM beats per minute.

CAS carotid artery stenting.

CCA common carotid artery.

CO cardiac output.

ECA external carotid artery.

ECAA extracranial carotid artery aneurysm.

echoPIV echo particle image velocimetry.

ICA internal carotid artery.

MAP mean arterial pressure.

MCL mock circulatory loop.

SD standard deviation.

SV stroke volume.

UCA ultrasound contrast agent.

VFP velocity flow profile.

VFR volumetric flow rate.

1 Introduction

Patients with carotid artery disease have a high risk of brain damage. The carotid artery is more prone to narrowing due to atherosclerosis, called carotid artery stenosis, when people age, have a unhealthy lifestyle or have diabetes. The blood flow can be restricted due to a plaque in the blood vessel. Also a bulge can form in the wall of one of the carotid arteries due to weakening of the artery wall, called an extracranial carotid artery aneurysm (ECAA). [1] When symptoms of an aneurysm or stenosis are present, such as pain, numbness, tingling and weakness in the neck, the patient has to be treated. Both pathologies can lead to serious medical issues, such as strokes.

Carotid artery stenting (CAS) is a technique that is used to increase the blood flow by inserting a stent. Each patient needs to have a proper stent to create the best possible outcome of the CAS. However, the intervention can still be technically improved in stent delivery and design. The quality and functioning of a stent can be analysed by looking at the flow characteristics in the artery.

Echo Particle Image Velocimetry (echoPIV) is used to study the flow characteristics and in this case the effect of stent placement on the blood velocity. In echoPIV an ultrasound contrast agent (UCA) is used for ultrasound images as tracer particle. The imaging technique enables the measurement of velocity vectors in flow, for example in blood vessels. [2]

The study on the effect of stent placement is performed in an *in-vitro* model with a phantom of a carotid artery. An *in-vitro* model is preferred over an *in-vivo* study, because it is possible to change the parameters of the model in a controlled environment. Another advantage is that the UCA will remain longer in the circuit than in the body, so more experiments can be done with the same amount of microbubbles. The disadvantage is that the *in-vitro* model is a simplification of the real situation and assumptions must be made.

Experiments with echoPIV have already been done on an *in-vitro* model with steady flow conditions to examine the effect of stent placement on the flow characteristics. However, the waveform in the carotid artery is pulsatile. In order to obtain more reliable results from the study, the flow of the circuit must be pulsatile as this corresponds to the situation in the body.

The research question is: *How can an in-vitro flow circuit of a simplified carotid artery with pulsatile flow conditions be designed and implemented for measurements with echoPIV?*

In this report first some background information is described about the anatomy and physiology of the cardiovascular system, focusing on the carotid artery. Then a description of the designed flow circuit is given, which is used to create the desired pulsatile flow of the setup. Thereafter, the development of the circuit is mentioned including all necessary elements of the cardiovascular system. Eventually, the results are evaluated and discussed.

2 Background

The research project starts with an inventory to get a good understanding of what is required for the design of a flow circuit for a carotid artery phantom. In this section information is gathered about the anatomy and physiology of the human circulatory system, the fluid mechanics in a tube, the typical waveform in the carotid artery and several types of mock circulatory loop (MCL) systems.

2.1 Anatomy of the cardiovascular system

The flow circuit is a simplified model of the cardiovascular system. In this section the anatomy of the circulatory system and specifically the carotid artery are discussed.

2.1.1 Circulatory system

The cardiovascular system includes the heart, vessels and blood of the human body. It is divided into two blood circuits, the pulmonary circuit and the systemic circuit, see figure 1. In the pulmonary circuit deoxygenated blood flows to the lungs where the blood is oxygenated, and returns to the left atrium of the heart. In the systemic circuit the oxygenated blood is pumped through the left ventricle to the upper and lower body to supply blood to the organs. Blood then flows back to the heart through the systemic venous system. The cardiovascular system makes sure that nutrients, oxygen and hormones are transported to the cells throughout the body and metabolic wastes are removed.

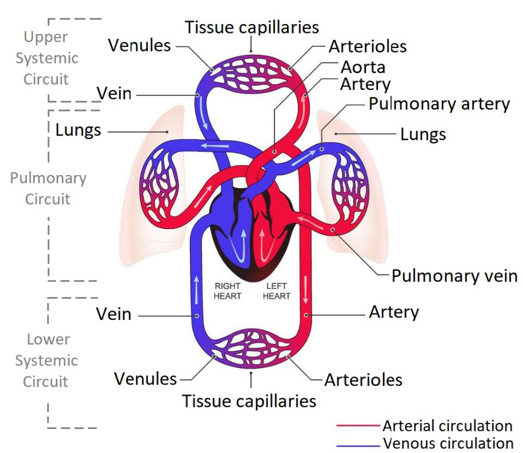


Figure 1: *the pulmonary and upper and lower systematic circuit of the cardiovascular system* [3]

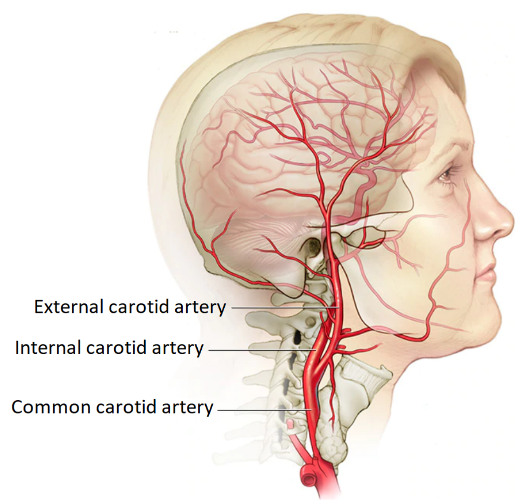


Figure 2: *anatomy of the carotid arteries including the internal carotid artery (ICA), external carotid artery (ECA) and common carotid artery (CCA)* [4]

2.1.2 Carotid artery

When the left ventricle of the heart contracts, blood is pumped into the aorta. When the blood reaches the aortic arch, the artery subdivides into three major branches. Two of these branches result in the right and left common carotid artery. [5]
The carotid arteries are two large blood vessels in the neck that carry oxygenated blood to the brain, neck and face. The common carotid artery (CCA) divides into the internal carotid artery (ICA) and the external carotid artery (ECA), see figure 2.

2.2 Physiology of the cardiovascular system

The flow in the cardiovascular system depends on several factors in the body. The physiological components must be distinguished to be able to create proper conditions in the flow circuit. Most important information about the cardiac cycle generated by the heart, the pressure of the blood and the regulaters that influence the blood pressure is reviewed in this section.

2.2.1 The cardiac cycle

The blood flow in the arteries varies in time due to the pulsatile driving pressure of the heart. The cardiac cycle of the heart consists of the systole and diastole. Diastole is the stage where the ventricle relaxes and fills with blood, while systole is the process of forcing the blood out of the ventricle.

2.2.2 Blood pressure

The blood pressure, expressed in millimeters of mercury (mmHg), is the force per unit area exerted on a vessel wall by the blood. [6] The arterial pressure is influenced by the amount of blood forced into the arteries and the compliance of the vessels. Compliance indicates the tendency for blood vessel volume to increase as the blood pressure increases. The walls of the large elastic arteries contain elastic fibers, formed of elastin. As compliance is inversely proportional to stiffness, high compliance means that the vessel wall stretches easily. The arterial compliance of young adults is approximately 2 mL/mmHg. The compliance of older people decreases, because stiffness of the wall increases due to molecular changes in the arterial wall. [7]

Every time the heart contracts, it simultaneously gives kinetic energy to the blood. The wall of the arteries dilate during systole as a result of the pressure and exerted energy. After systole the aortic valve closes, preventing blood to flow back into the left ventricle. During diastole the aortic pressure drops to its lowest value, called the diastolic pressure. Therefore, the dilated blood vessel narrows again. The systolic pressure and diastolic pressure are approximately 120 mmHg and 80 mmHg in healthy people, respectively. The difference between the systolic and diastolic pressures is called the pulse pressure. [6]

The mean arterial pressure (MAP) is the average pressure over one cycle in the aorta. The MAP is slightly less than the mean of the average systolic and diastolic pressures. This is caused by the shorter period of systole compared to diastole. The MAP of healthy people is approximately 93 mmHg, see figure 3. [6]

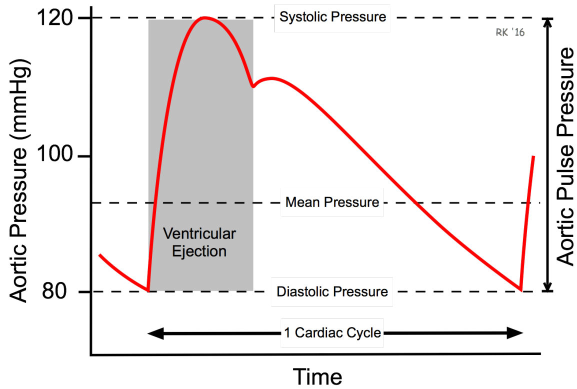


Figure 3: *the aortic pressure (mmHg) of one cardiac cycle of the heart* [5]

2.2.3 Pressure regulators

The pressure in the vessels is regulated to keep the cardiovascular system in homeostasis: to maintain the blood pressure high enough to provide adequate tissue perfusion without damaging the blood vessels. There are three main parameters that affect the pressure directly: the cardiac output, peripheral resistance and blood volume. [5]

- The cardiac output (CO) represents the amount of blood pumped by each ventricle in one minute. It is the product of the heart rate (HR) and stroke volume (SV). The SV is the amount of blood pumped by the left ventricle in one contraction.

- Resistance is the amount of friction the blood experiences when flowing through the vessels. The diameter of the vessel has the most influence on the resistance. The body has the ability to change the resistance to flow by constricting or dilating the arteries. Poiseuille's law states that the resistance is inversely proportional to the fourth power of the blood vessel radius. [8] The resistance also increases when the blood encounters abrupt changes in the vessel diameter or wall, as the flow switches from laminar to turbulent. The peripheral resistance is the resistance of the entire systemic vascular bed. It is mainly caused by the arterioles and can be calculated using formula 1. [8]

$$Resistance = \frac{Mean\_Arterial\_Pressure}{Cardiac\_Output} \tag{1}$$

- The blood volume is the volume of the red blood cells and the plasma in the circulatory system of the blood.

2.3 The waveform in the carotid artery

The heart generates a volumetric flow rate (VFR) waveform that propagates through the circulatory system and changes along the way. [9] Downstream, the peak of the pressure pulse slightly delays and its shape slightly changes. [10] Therefore, the waveform in the carotid arteries differs from the waveform in another artery.

As atherosclerosis is a progressive disease, mainly older adults are at risk of rupture of a plaque. The VFR waveform in the arteries of older adults differs significantly with the waveform of healthy young adults. [9] [11] This is caused by multiple reasons. For example, atherosclerosis chronically increases the pulse pressure because the arteries become less flexible. [5] Arterial stiffness results in a higher systolic pressure, because of reduced capacitance, and results in a lower diastolic pressure as there is less elastic recoil. [12]

The mean carotid waveform of older adults can be seen in figure 4. The early systole is represented by M0-P1 and the late systolic declaration with H1-H2. Feature points M2-P3 display the early diastole and the late diastole is defined from D1-D4. The cycle period is 949±149 ms and the average heart rate of older adults is 65 ± 10 BPM. [11]

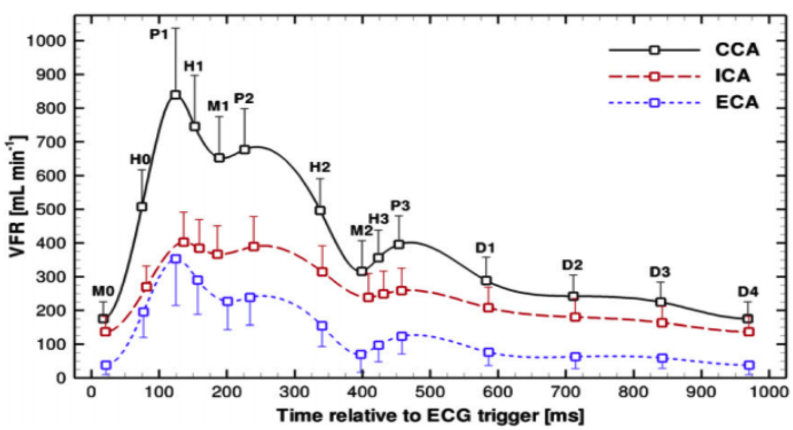


Figure 4: *mean carotid waveform of the common carotid artery (CCA), internal carotid artery (ICA) and external carotid artery (ECA) in older adults fitted by splines. Each feature point has a label and an error bar.* [11]

Flow within the carotid artery is driven by blood pressure. The mean flow rate in the CCA is 465 mL/min ± 52 (mean ± SD). [13] The flow in the region of the bifurcation reflects the complex vessel anatomy of this segment of the artery. The flow rates in the ICA and ECA are 265 mL/min ± 60 and 186 mL/min ± 51 respectively. [14] [15] As the diameter of the ECA is smaller, the peripheral resistance in the external carotid outflow is higher so more blood flows to the ICA. [16]

2.4 Fluid mechanics

Blood flows through the vessels and constantly deforms under applied forces, such as viscous and inertial forces. The velocity flow profile (VFP) of a fluid in motion is discussed by means of the Reynolds and Womersley number to understand the appearance of the profile. Also, the velocity profile in the carotid artery is specified.

2.4.1 Reynolds and Womersley number

For an incompressible fluid, such as blood, the fluid mechanics can be described by the Navier-Stokes equation. The Reynolds number and the Womersley number are two physical parameters that influence this equation. Both numbers are dimensionless and control the velocity profile of a fluid in a tube. The difference is that the Reynolds number controls the steady flow part of the equation and the Womersley number describes the pulsatile flow of the equation. They are influenced by the physiological conditions of the body and affect the hemodynamic parameters in the (possibly blocked) artery.

The Reynolds number (N_{RE}) is a dimensionless value that represents the ratio of convective inertial forces and viscous forces, to study fluids as they flow in a cylindrical tube. The number determines if the flow is laminar or turbulent. The flow is laminar when viscous forces are dominant, so the Reynolds number is low. The flow is turbulent when the inertial forces are dominant, so the Reynolds number is high. The velocity profiles of laminar and turbulent flow profiles can be seen in figure 5.

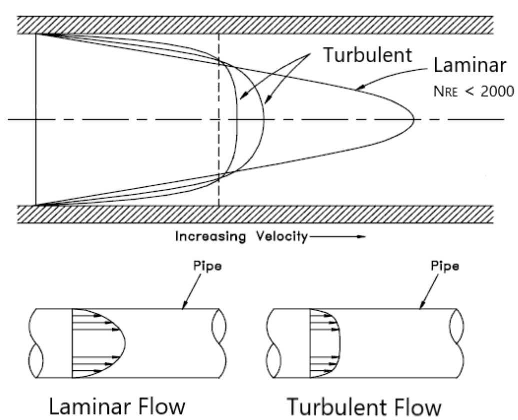


Figure 5: *The velocity flow profiles in a cylindrical tube of a laminar and turbulent flow profile, depending on the Reynolds number* [17]

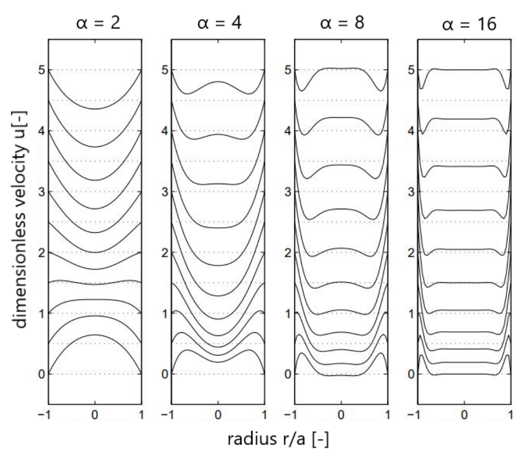


Figure 6: *The velocity profile in a cylindrical tube resulting from different values of the Womersley number (α = 2, 4, 8, 16)* [10]

The Womersley number (α) is a dimensionless value that describes the ratio of transient inertial forces and viscous forces. The number determines the velocity profile in a cylindrical tube under pulsatile flow conditions. The effect of the Womersley number on the velocity profile can be seen in figure 6. When the Womersley parameter is low, viscous forces tend to control the flow and the velocity profile is parabolic. Therefore, the centre-line velocity oscillates in phase with the driving pressure gradient. When the number is high (>10), the transient inertial forces are dominant and the velocity profile is flat. For the values of α in between, the viscosity dominates the flow in the boundary layer and the inertia dominates the flow in the core of the cylindrical tube. [10] [18]

2.4.2 Fluid mechanics in the carotid arteries

Reynolds number in the CCA is approximately 280, for a mean flow of 7.8 mL/s and a pulse frequency of 60 beats per minute (BPM). [19] The Womersley number in the carotid artery is approximately 4.4. The flow in the CCA is like a cylindrical tube as described above in section 2.4.1. However, the velocity flow profile in the ICA and ECA after the bifurcation differs from the flow in the CCA. They can be considered as two curved tubes. The velocity profile in curved tubes is influenced by centrifugal forces, which causes a secondary flow to be induced. The velocity flow profile in the carotid artery can be observed in figure 7.

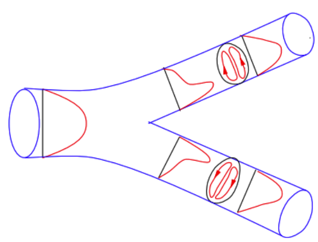


Figure 7: *velocity profile in the carotid artery with an asymmetric profile in the internal carotid artery (ICA) and external carotid artery (ECA)* [10]

2.5 Flow circuit

2.5.1 Mock circulatory loop

Mock circulatory loops (MCLs) are a widely used tool for *in-vitro* investigations to test and validate the hemodynamic performance in several devices. Hemodynamics describes the dynamics of blood flow. [20] Often the MCL consists of a setup with short connecting tubes, actuators, resistive and capacitive elements, with a small adjustable test section. [21] Such a flow circuit mimics a certain part of the cardiovascular system and visualizes wave phenomena of the circulation in these regions. Many different arrangements of mock circulatory loops exist.

2.5.2 Windkessel model

MCLs are often based on a windkessel model. The windkessel effect can be described by a basic two-elements to a more advanced four-element Windkessel model. The model is used to analyse the arterial blood pressure waveform in terms of interaction between the stroke volume, the compliance of the aorta and large elastic arteries, and the resistance of the smaller arteries and arterioles. Different kind of models are displayed in figure 8.

The two-element model consists of two parallel components: arterial compliance and the peripheral resistance. The arterial compliance means the artery stretches due to the pressure. This behaviour is modeled with a capacitance as it takes in more charge or fluid when more voltage or force is applied. The peripheral resistance is simulated with a resistance. Without the resistance the model would have an infinite current, which is not a meaningful model. This model predicts that in diastole, when the aortic valve is closed, pressure will decay exponentially with a characteristic decay time.

The three-element windkessel model adds another resistance. Therefore, the relation between the flow and the pressure during systole is taken into account. This resistance simulates the characteristic resistance or impedance of the aorta. [8] In large arteries the resistance is low and the characteristic impedance is a real value. [8]

The four-element windkessel model also includes the total arterial inertance, which is the summation of the inertances of the entire arterial system. [22] This element is represented by an inductor parallel to the second resistance, because the current in the coil cannot change instantaneously. The inertia was neglected in the previous models.

The windkessel effect decreases when people get older, because for example the arteries become less compliant. This results in an increased pulse pressure, as the systolic pressure is elevated.

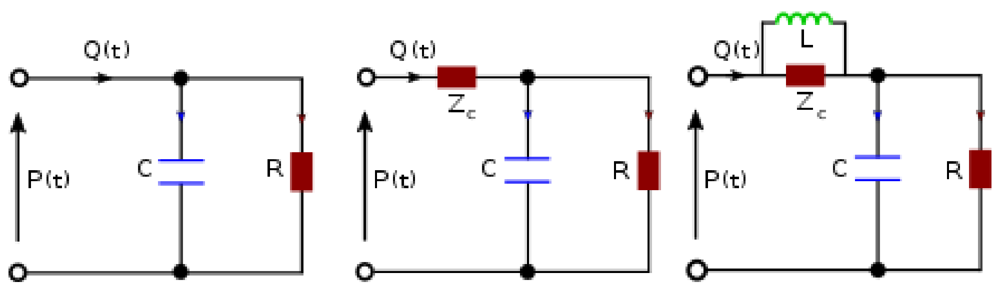


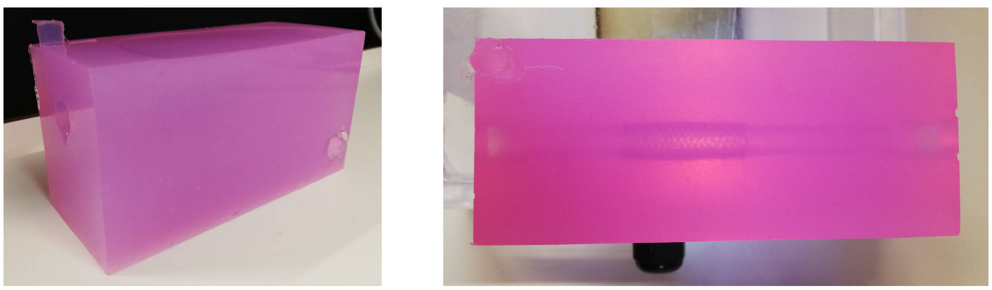
Figure 8: *various windkessel models displayed as an electrical circuit: two-element (left), three-element (middle), four-element (right) model with C: capacitance, R: peripheral resistance, Z_c: characteristic resistance, L: inductance. P(t) is the pressure and Q(t) is the charge through the circuit* [23]

3 Design

In this section the flow circuit for the carotid artery is designed. In order to make adequate design choices, the function of the circuit is discussed and the requirements are listed. A simple and an advanced flow circuit are designed and each element of the circuits is discussed. Eventually, the design is evaluated by reviewing the requirements.

3.1 Function definition

The main function of the flow circuit is to perform reliable and reproducable tests with echoPIV on the phantom. A phantom is a specially designed object, which mimics a part of the body. For this thesis the phantom simulates the carotid artery with an inserted stent. The phantom (110x44x56mm) has already been made in an earlier study and is molded with PVA, see figure 9. The physiological conditions in the phantom must correspond to the situation inside the body, such as the blood pressure and the waveform in the carotid arteries.



(a) Isometric projection

(b) Top view

Figure 9: *PVA phantom of straight tube with an inserted stent*

3.2 Requirements

In order to design an experimental setup with pulsatile flow conditions, the requirements need to be described. The requirements are based on the demands of the user and the background information of the physiological conditions.

Requirements

- The phantom should be insertable and removable from the flow circuit.
- Different kind of phantoms must be able to be connected to the flow circuit.
- The ultrasound transducer must be able to measure the posterior, medial and lateral side of the carotid artery in the phantom.
- The system must generate a pulsatile waveform.
- The waveform in the circuit must resemble the waveform of the CCA in older people.
  - The minimal flow rate must be approximately 3 ± 0.5 mL/s.
  - The systole must appear between 100 and 250 ms.
  - The diastole must appear between 450 and 550 ms.
  - The maximal flow rate of the systole must be approximately 14 ± 0.5 mL/s.
  - The maximal flow rate of the diastole must be approximately 7 ± 0.5 mL/s.
  - The average flow rate of the waveform must be 7.8 ± 0.5 mL/s.
- The velocity flow profile must mimic the profile in the CCA.
  - The velocity profile must be laminar, so the Reynolds number must be <2000.
  - The Womersley number must be <10 as the viscous forces must be dominant.
- The circuit must contain the possibility to add contrast material, such as micro bubbles.
- The flow circuit must resemble the systemic circuit of the cardiovascular system.
  - The system must operate with a heart rate between 60 and 70 BPM.
  - The pressure in the phantom must vary between 80 and 120 mmHg.
- The MCL must be watertight to avoid leakage.
- The flow in the setup must be consistent for minimally 10 minutes.

3.3 Design process

The design process of the setup is done in two phases. First, a simple MCL is designed to implement the waveform. In the second phase, the simple MCL is improved into a more advanced MCL by including elements of the windkessel model. In the advanced MCL several variables can be adjusted to set the physiological conditions in the phantom.

3.3.1 Simple flow circuit

In the first phase, a simple flow circuit is designed to be able to create the desired volumetric flow profile. In this section each components of the simple circuit is discussed. There are often several options to implement a component, so they are analysed and eventually the best approach is chosen. The flow circuit is displayed in figure 10.

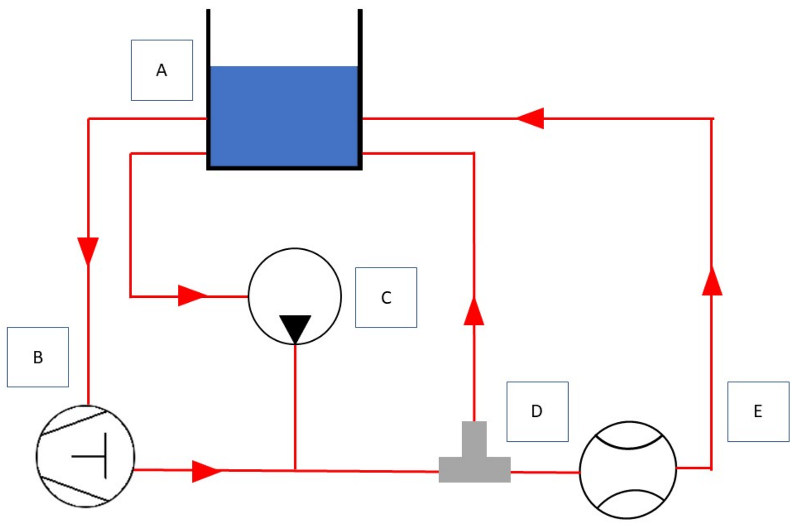


Figure 10: *schematic overview of the simple mock circulatory loop with A: fluid reservoir, B: ViVitro pump , C: gear pump, D: bypass device, E: mass flowmeter. The flow circulates counterclockwise* [24] [25]

The experimental setup consists of various elements coupled by both rigid and flexible tube connections. The tubes resembles the blood vessel of the cardiovascular circuit. The tube has an inner diameter of 6 mm, with a wall thickness of 1.3 mm. This diameter is chosen as it resembles the size of the carotid artery.

Element A: Fluid reservoir
The closed circulation of the MCL begins and ends at the open topped reservoir, where most of the fluid is stored. The reservoir replicates the large blood volume present in the venous system. The tank has two outlet tubes connected to the Vivitro pump (B) and the gear pump (C). Furthermore, the reservoir contains two inlet tubes linked with the bypass (D) and the mass flowmeter (E).

The flow from the inlet tubes is pulsatile. However, it is assumed that the flow towards the pump should be constant because otherwise the generated flow of the pumps will be disturbed. Therefore, the flow must be uncoupled. An option is to divide the reservoir into two parts with a separating wall, see figure 11. In this way, the level changes caused by the pulsatile flow do not disturb the upstream conditions in the second part of the reservoir. The inlet tube is located just beneath the water level in the first part of the reservoir to avoid air to enter the system and to prevent backflow due to pressure difference. The two-compartment design of the reservoir was chosen and constructed. However, during measurements it became clear that a one-compartment reservoir instead of a two-compartment reservoir is sufficient as well. The volume and the pressure of the fluid in the reservoir instantly damp the pulsatile flow conditions significantly as the velocity of the fluid is relatively low.

The circuit will be filled with 3 L of fluid, which circulates through the system. A blood mimicking fluid (BMF) is used as a flowing medium. The BMF is a glycerol-water mixture for a temperature range of 10-50 degrees. The mass fraction of glycerol is 0.392 and the viscosity of the fluid is $3.3 \cdot 10^{-6}\ \frac{m^2}{s}$. This corresponds to the viscosity of blood at normal hematocrit.

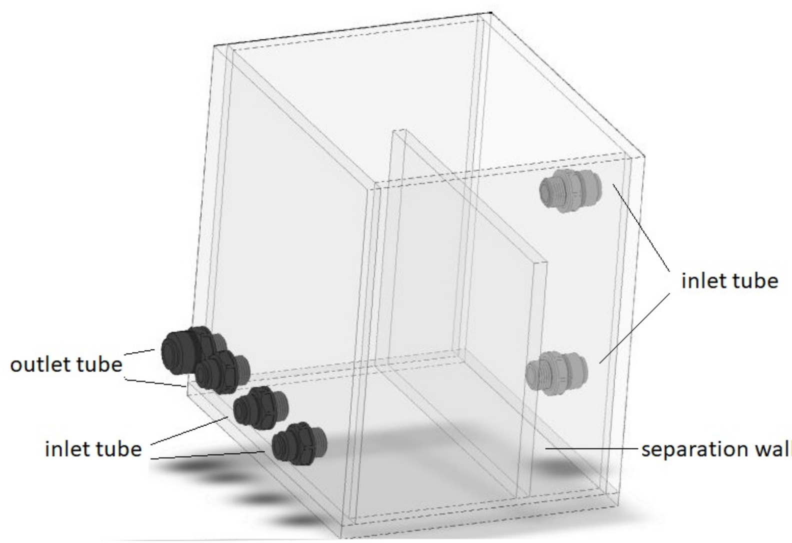


Figure 11: *isometric projection of fluid reservoir with two compartments divided by a separation wall. The outlet tubes go to the pumps. The inlet tubes at the right side are used when both compartments are functioning. The inlet tubes at the left side are used when only one compartment is operating.*

Element B: ViVitro pump
The cardiac cycle of the heart is generated by the ViVitro pump. This pulsatile pump induces a pulsatile output or time-varying physiological flow and is able to replicate the volumetric displacement and beat rate of the heart. It consists of three main parts: a controllable piston, a fluid chamber that represents the ventricle, and the mechanical valves. The cardiac cycle in the pump begins with the piston being pushed in forward direction, which causes the membrane in the fluid chamber to squeeze. When the outflow valve is opened and inflow valve closed, fluid is led into the system. Afterwards the piston is moved backwards to its initial position, and the inflow valve is opened allowing the fluid chamber to be filled for the next cardiac cycle. The piston position is controlled by the computer. The waveform generated by the piston position profile is discussed in section 4.1.

Figure 12: *ViVitro SuperPump with a controllable piston, a fluid chamber and mechanical valves inside. The waveform and amplitude can be set by the controller.* [24]

The inlet and output tube of the ViVitropump have a diameter of 15 mm, so a transition must be made to a tube with a different inner diameter. A flexible tube with an inner diameter of 14 mm is used. The advantage of a flexible tube, compared to a rigid tube, is that the ViVitro Pump can be handled more smoothly, because the in- and outlet tube will not break off and the pump can be moved slightly. For example, while draining the air from the pump. The tube can expand under pulsatile flow conditions, which corresponds to the aorta. The tube at the outlet of the pump goes to a rigid tube with an inner diameter of 6 mm and then to the rest of the circuit.

Element C: Gear pump
The Vivitro pump generates a waveform that goes to 0 mL/s after each cycle. However, the desired volumetric flow profile has a minimal flow of 3mL/s, based on the waveform of the carotid artery in older adults. In order to simulate the correct waveform in the phantom, another pump is implemented that generates a constant flow.

The flow of this pump and the ViVitro pump meet at their intersection and are combined in the rest of the MCL. The advantages and disadvantages of several pumps are discussed in appendix A.When the available pumps are compared, none of them meet all the requirements. The fuel gear pump [Modelgraft, F3007] is chosen to be implemented in the MCL as it is able to generate the desired minimal flow constantly. However, it appeared that the gear pump cannot operate at a low (<4.5V) input voltage for a long time. The operating time varies every measurement, ranging from two minutes to five minutes. The other pumps are not applicable.

The pulsatile flow, generated by the ViVitro pump, may induce a small amount of flow to the tube of the gear pump instead of all the fluid going towards the phantom. This is due to the stronger flow from the ViVitro pump compared to the gear pump. Two options are discussed to eliminate this flow.

- A valve can regulate the flow by opening or closing, so the flow to the gear pump can be prevented. On the other hand, when the valve is closed, due to the higher pressure of the ViVitro pump, the flow from the gear pump is blocked. Consequently, the pressure in the pump will increase and damage may occur.
- The gear pump can also be placed at a higher position than the ViVitro pump. Due to gravitational force, the fluid will flow downward and have a higher pressure at the intersection. This will minimize the flow to the gear pump sufficiently.

Considering the two options it is chosen to place the gear pump at a higher position. In addition, it is much more simple to implement this than a valve. The gear pump is adjusted to the outside of the reservoir.

Element D: Bypass device
The bypass can alter the direction of circulation. When the handle of the bypass device is rotated, the fluid flows directly to the reservoir instead of going through the flowmeter (F). This is convenient for experiments with echoPIV, because the user can decide when to do a measurement with the flowmeter very precisely. The data from the flowmeter can be analysed more easily since it contains less irrelevant information. Also, the pumps can continue to operate while no measurement is done to obtain consistent conditions in the MCL for all measurements.

Element E: Mass flowmeter
The pulsatile flow profile of the fluid is measured by a flowmeter. The flowmeter is a Digital Mass Flowmeter/Controller [Bronkhorst_V3.35, Cori-Flow]. The developer states that the flowmeter has a high accuracy for liquids of ± 0,2 % of rate. It measures the mass flow in one direction, so it cannot measure backflow simultaneously. The flowmeter is connected to a computer, which communicates with the flowmeter through flowDDE. The data from the flowmeter can be displayed real-time on FlowPlot on the computer. FlowPlot [Bronkhorst] is a software application with a signal monitoring program that visualizes the dynamic behaviour of meters and controllers.

3.3.2 Advanced flow circuit

In the second phase, the elements of the advanced flow circuit are designed. These elements have to correspond to the physiologic conditions in the systemic circuit of the body. They influence the blood pressure and the volumetric flow profile in the phantom of the flow circuit. In order to accomplish this, the components of a two-element windkessel model are included.

As discussed in section 2.5.2, the two-element Windkessel model consists of a capacitance and a resistance, which resemble the arterial compliance and the peripheral resistance. The implemented waveform is the volumetric flow profile of the common carotid artery and therefore does not pass the aorta. Therefore, the aortic characteristic impedance is disregarded, because the influence of the aorta is already taken into account by the waveform.

During the second design phase the simple flow circuit is extended. In figure 13 the advanced flow circuit is displayed highlighting all the elements.

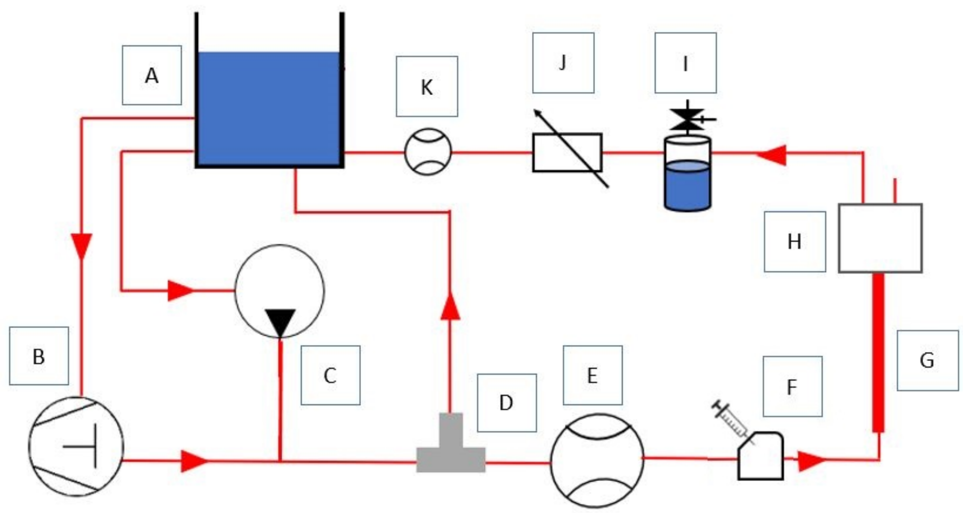


Figure 13: *schematic overview of the advanced MCL of the carotid artery with A: fluid reservoir, B: ViVitro pump, C: gear pump, D: bypass device, E: mass flowmeter, F: bubble injection device, G: straight tube, H: phantom container, I: compliance chamber with pressure meter, J: resistance device, K: flowmeter. The flow circulates counterclockwise.* [25]

Element F: Bubble injection device

An ultrasound contrast agent (UCA) must be injected in the circuit for measurements with echoPIV. Microbubbles are used as a tracer particle. The bubbles can be injected through the bubble injection device, which is placed in series after the mass flowmeter. The injection needle can be placed in a small pipe with a luer adapter, so the bubbles can be inserted calmly and smoothly. The injection may cause some disturbance in the flow and velocity profile of the fluid, which will be dealt with by the following element.

Element G: Straight tube
Steady and pulsatile flow conditions influence the velocity profile in the tube, as discussed in section 2.4. The velocity profile at the entrance of the phantom must be equal to the velocity flow profile in the CCA. Therefore, a straight tube [RS, Festo Air Hose Blue Polyurethane] of 75 cm is located before the phantom to make sure the flow field is known and fully developed in the phantom. The Reynolds number and Womersley number in the CCA are approximately 280 and 4.4 respectively. Also, the disturbance caused by the bubble injection will resolve because of the straight tube.
The rigid tube should have the same inner diameter as the phantom to ensure a proper connection. An inner diameter of 8 mm is chosen in the phantom, although the common carotid artery (CCA) has an inner diameter of approximately 6 mm. This diameter is necessary for inserting a stent in the phantom, because the tube does not expand like a vessel. Consequently, it is expected that the Reynolds and Womersley number are slightly larger than the *in-vivo* conditions due to a bigger inner diameter.

Element H: Phantom container
The circuit will be used for echoPIV measurements on the phantom. The phantom container determines that the phantom remains in the same position during measurements, so experiments can be executed accurately.
Fluid enters the phantom through a tube at the side of the CCA. On the other side of the container, fluid can exit the phantom through two tubes, the ICA and the ECA. It must be possible to insert different kinds of phantoms: a simplified phantom with a straight tube and a phantom with a bifurcation. The width of the container is therefore slightly larger than the width of the phantom to be able to use various phantoms.
Furthermore, the ultrasound transducer must be able to measure the posterior, medial and lateral side of the carotid artery in the phantom. In order to allow this, the top of the container should be entirely open while the sides should be partly open. The sides also give some support to the phantom to remain in the same position during the measurement. The bottom of the container is covered with a sheet of polyurethane, which absorbs ultrasound waves. Therefore, the reflection of ultrasound waves is minimized and they do not disturb the measurement.

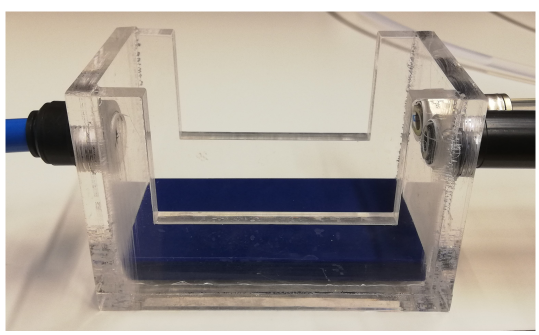


Figure 14: *phantom container with a sheet of polyurethane*

Element I: Compliance chamber
The tendency of the arteries and veins to stretch in response to pressure has a large effect on perfusion and blood pressure. The compliance of the arteries must also be included in the flow circuit. The arterial compliance is implemented as a capacitance in the windkessel model. A compliance chamber is designed to provide the expansion per increase in hydraulic pressure in the circuit.
The trapped-air compliance reservoir is filled with fluid and compressible air. At the bottom of the cylinder an in- and outlet tube for fluid are present. The pressure in the chamber is measured with a pressure meter [Welch Alleyn, C0297] in [mmHg]. It is connected to the top of the compliance chamber. The pressure can be regulated with a hand pump by pushing more air into the chamber or by releasing air.

The size of the compliance chamber can be established using equation 2 for the compliance [mL/mmHg]. ΔV is the change in volume [mL], and ΔP is the pulse pressure [mmHg].

$$C = \frac{\Delta V}{\Delta P} \tag{2}$$

The systolic pressure is 120 mmHg and the diastolic pressure is 80 mmHg at the aorta. Therefore, the pressure difference must be approximately 40 mmHg, because the carotid artery is adjoining the ascending aorta. The compliance of older people is approximately 1.5 mL/mmHg. The compliance chamber should be approximately 10 cm in height when the diameter of the chamber is 4 cm. It would be convenient for the compliance chamber to have a variable volume. The volume of the air tight chamber can be changed to achieve optimal outcome. The rubber band on the adjustable part makes sure that the chamber is air tight, see figure 15.

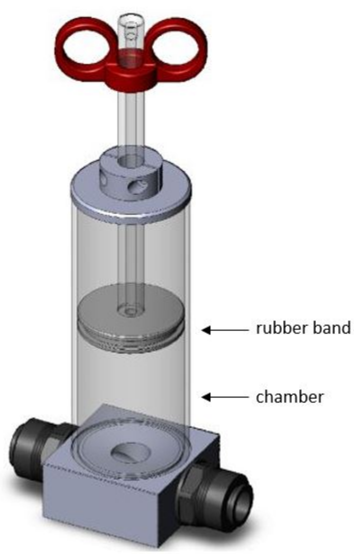


Figure 15: *compliance chamber with a variable chamber volume, an in- and outlet tube for fluid, a hollow pipe to connect the pressure meter at the top and the rubber band.*

Element J: Resistance

The peripheral resistance of the cardiovascular system is represented by a resistance in the flow circuit. The diameter of the vessel has the most influence on the resistance and can be changed by constricting or dilating the vessel wall. Therefore, the resistance in the flow circuit should be able to be altered manually by increasing or decreasing the diameter. When the diameter of the tube is decreased, pressure in the MCL is enhanced in front of the device. Two options are discussed to implement the resistance.

- A clamp could be used to pinch together the tube. The two jaws of the clamp hold the tube and the distance between the jaws can be adjusted. When the distance is reduced, the diameter of the tube is decreased. However, the tube may deform or burst under pressure as the tubes in the circuit are rigid and can not bend easily. This may result in a leak in the tube, which is not desirable. Furthermore, a clamp is not very accurate.
- A mechanism with a screw and nut could be implemented to adjust the diameter inside the tube. The screw is inserted in a device that is connected to the flow circuit in series. The inner diameter of the device is 3mm. The diameter can be adjusted easily and relatively accurate. On the other hand, the device has to be attached tightly in order to remain fixed.

By comparing the options, the device with the screw is chosen to be realized. It is more accurate and will not damage the tube. Furthermore, it is achievable to connect the device securely in the circuit to make sure the it does not detach under high pressure.

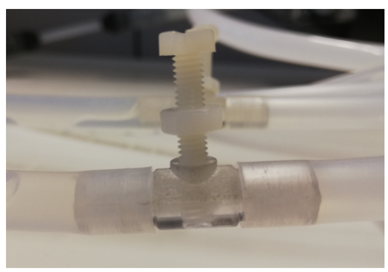


Figure 16: *resistance reducing the tube diameter with a screw*

Element K: BioTech flowmeter

After the resistance a flowmeter [BioTech, FCH-m-POM-LC] is positioned, which measures the average flow rate within a range of 0.015-0.8 L/min. The flowmeter has an inner diameter of 4 mm and therefore also contributes to the resistance in the MCL. A nozzle can be inserted at the entrance of the flowmeter. The inner diameter of the nozzle is 1.6 mm, so it reduces the cross sectional area. Therefore, the fluid experiences a pressure drop at the end of the nozzle and the flow velocity increases considerably. Consequently, the flowmeter measures more pulses per litre compared to a flowmeter without nozzle (8500 I/O 2500 pulses/litre). On the other hand, the resistance increases largely due to the inner diameter of the nozzle. This is not desirable, because it is not possible to adjust this resistance. Therefore, it is chosen to use the flowmeter without a nozzle.

Moreover, an electronic counter and rate indicator [Model CUB5, Red Lion] is connected to the flowmeter. On the indicator the value of the flow rate is displayed in [L/min]. The outlet tubes of the flowmeter exit in the fluid reservoir.

3.4 Implementation

All the elements discussed in section 3.3 are constructed to build the flow circuits. The simple MCL, displayed in figure 17, is made to configure the waveform in the carotid artery of older adults.

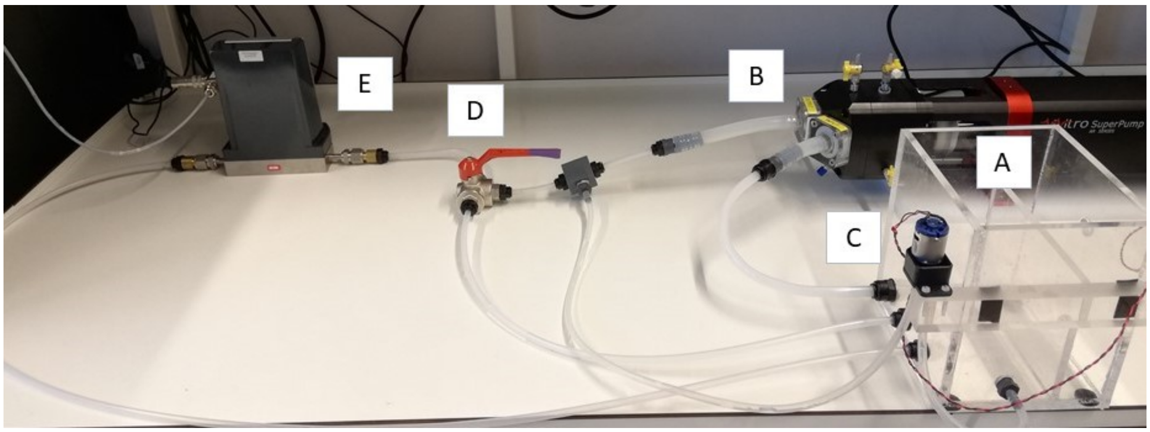


Figure 17: *overview of the simple mock circulatory loop with A: fluid reservoir, B: ViVitro pump, C: gear pump, D: bypass device, E: mass flowmeter*

After the desired waveform is modeled and analysed in chapter 4, the advanced MCL is constructed. Additional elements are assembled to set the hydrodynamic conditions in the phantom, see figure 18. The compliance, resistance, stroke volume and pulse ratio can be adjusted to mimic the physiologic conditions of the carotid artery.

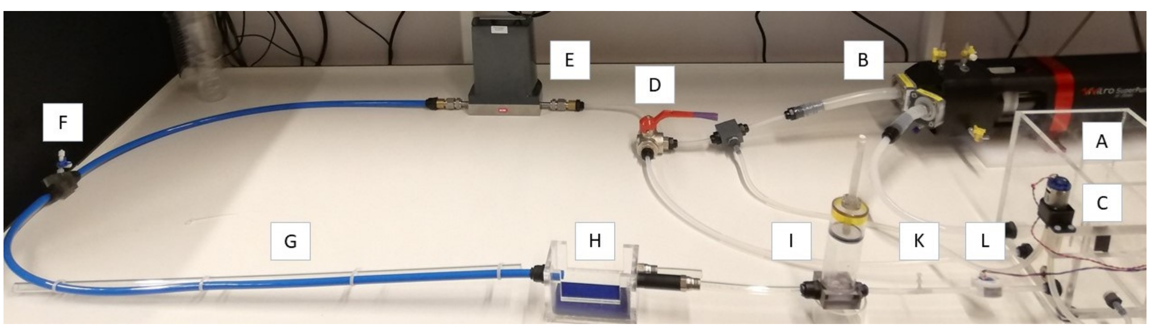


Figure 18: *overview of advanced mock circulatory loop with A: fluid reservoir, B: Vivitro pump, C: gear pump, D: bypass device, E: mass flowmeter, F: bubble injection device, G: straight tube, H: phantom container, I: compliance chamber, K: resistance, L: BioTech flowmeter*

3.5 Design evaluation

In order to evaluate the implemented flow circuit, the requirements of section 3.2 that are applicable on the design are reviewed. The remaining requirements are evaluated after the waveform characterisation and validation of the physiologic conditions.

First of all, *the MCL mimics the systemic circuit of the cardiovascular system.* The pulsatile conditions in the carotid artery can be generated by the ViVitro pump and the gear pump. The gear pump is unfortunately not able to operate for more than five minutes as discussed in appendix A, but it was the best option available. Therefore, *the flow in the setup is not consistent for minimally ten minutes.*

Also, *the physiologic conditions are implemented to regulate the pressure in the setup.* The peripheral resistance and compliance of the large arteries are simulated with a resistance and a compliance chamber. The compliance chamber is completely air tight, so the compliance in the setup can be controlled and adjusted. The resistance allows the diameter of the tube to be decreased, so the pressure can be elevated. However, some fluid leaks at the bolt due to pressure of the fluid. *Therefore, the flow circuit is not entirely watertight and this requirement has not been met.* A nut is positioned to reduce leakage, but it does not restrict the unwanted flow completely. The rest of the flow circuit is watertight.
Although the flow circuit resembles the cardiovascular system, the circuit is a simplification of the *in-vivo* situation. For example, in the circuit the resistance is induced at one point although the peripheral resistance in the body is distributed more along vessels of the cardiovascular circuit.

In addition, in the current design the compliance and the resistance components need to be adjusted manually. In the body, feedback mechanisms are present to maintain homeostasis. The implementation of automated feedback mechanisms in the MCL may be relevant to achieve better results. The feedback loop adapts or inhibits a certain component based on the output of the system.

Furthermore, *the phantom container allows the phantom to be insertable and removable from the setup* as the top of the container is not covered. Additionally, *the ultrasound transducer is able to measure from above and from the sides*, because they are partly uncovered.

Finally, the phantom container has two outlet tubes, *creating the possibly to insert different kind of phantoms.* However, the current design of the advanced flow circuit is not applicable for measurements with a phantom with a bifurcation. In order to achieve this, the MCL can be expanded. The improved circuit would require a resistance at each outlet tube to regulate the flow ratio between the ICA and ECA. Moreover, the tubes would combine in the compliance chamber where the pressure and compliance of the whole circuit are controlled. The flow terminate in the fluid reservoir after it has passed another resistance, located behind the compliance chamber.

4 Waveform characterisation

In this section, the volumetric flow profile of the carotid artery is modeled and analysed using the simple circuit. First, the desired waveform is displayed and the process of simulation and analysis is discussed. Then the results of the analysis are shown and discussed.

4.1 *In-vivo* waveform

The heart generates a specific waveform in the carotid artery. In order to replicate the waveform in the setup, a typical CCA waveform of older people is used, discussed in section 2.3. This volumetric flow profile is converted into figure 19 to compare the measured waveform with the *in-vivo* waveform. The cycle period of the desired waveform is fixed at 1000ms and the volumetric flow rate is changed from mL/min to mL/s using the feature points in [11]

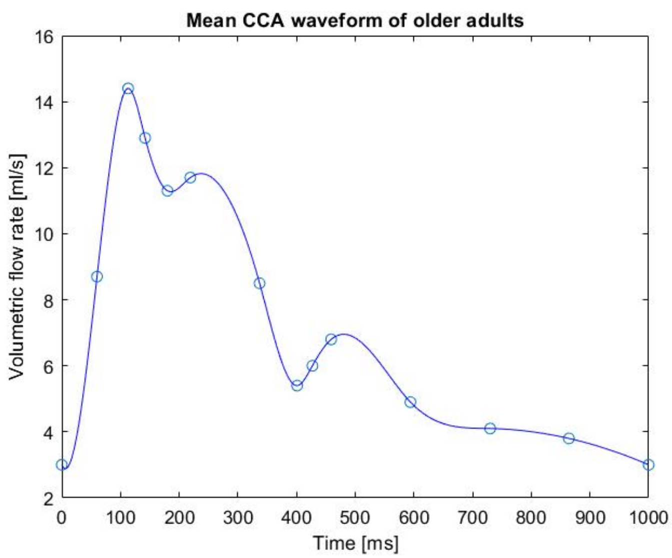


Figure 19: *mean common carotid artery (CCA) waveform of older adults fitted by splines with volumetric flow rate [mL/s] with respect to time [ms]* [11]

The desired waveform of the CCA is portrayed in figure 19. The early and late diastole are represented by spikes at 120 ms and 230 ms respectively. Another peak arises during early diastole at 480 ms and then the VFR gradually decreases during late diastole. The maximum flow rate is 14.4 mL/s and the minimum flow rate is 3 mL/s. The mean flow rate per cardiac cycle is 7.8 mL/s.

4.2 Method

The volumetric flow profile is modeled using the ViVitest software that is connected to the Vivitro pump. In this software the piston position of the pump can be controlled. The piston position directly controls the waveform as the piston pushes the fluid back and forward in the pump. The piston position profile is adjusted manually by trial-and-error and exported to the ViVitro pump as an external source.
Three different pulse rates are tested (60, 65 and 70 BPM) to analyse the performance of the Vivitro pump. The cycle time of the desired waveform is one second, so the pulse rate for the analysis of the modeled waveform is set at 60 BPM. The input voltage of the gear pump during measurements is approximately 4.5V. The flow profile is measured by the mass flowmeter and is displayed in FlowPlot. When the pumps generate a suitable waveform, the flow profile is recorded. Each measurement lasts between 40 and 60 seconds. The bypass device ensures that the recorded data can be analysed conveniently.

The analysis of the waveform is performed in Matlab (MATLAB, R2017b; MathWorks Inc, USA). With the information from the analysis, the piston profile is adapted in ViViTest. This process continues until the output meets the requirements relating the desired pulsatile waveform.
The data from FlowPlot is imported and the entire measurement is presented in a graph. In this graph the consistency of the cycles can be observed. In addition, each cycle is presented separately in row of a matrix with the data points of one second of the measurement. Then the mean of all the relevant cycles is calculated. Furthermore, the mean is also plotted together with the desired waveform. In this graph the average waveform and the desired waveform can be compared. The standard deviation (SD) of the mean waveform is taken to estimate the spread. The SD is used to form error bars, which graphically represent the variability of data at ten points along the curve of the average waveform.

4.3 Results

The plotted data of the measurements with a flow rate of 60, 65 and 70 BPM and displayed in figure 20- 22. They represents the volumetric flow profile recorded by the mass flowmeter. The beginning and the end of the measurement show the bypassing processes, where no fluid passed through the flow sensor. The middle region depicts the actual flow profile during the measurement. Figure 20 also visualizes four cycles of the measurement in more detail. The piston profile that is created to simulate the desired waveform is included in appendix B.

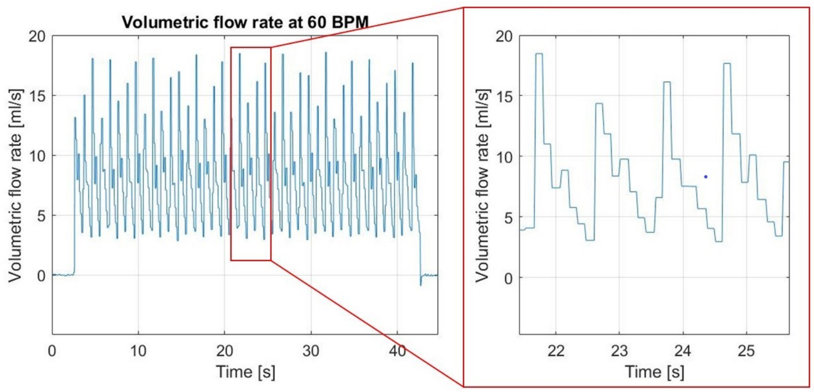


Figure 20: *measurement at 60 BPM of multiple cycles, with an enlargement of 4 cycles on the right.*

It can be observed that the waveform is not consistent at every cardiac cycle as the peaks during systole and diastole differ in height. The variation has a pattern that is occurring at specific intervals. This can be recognized best at a pulse rate of 65 BPM where the pattern is repeating itself approximately every 5 seconds.

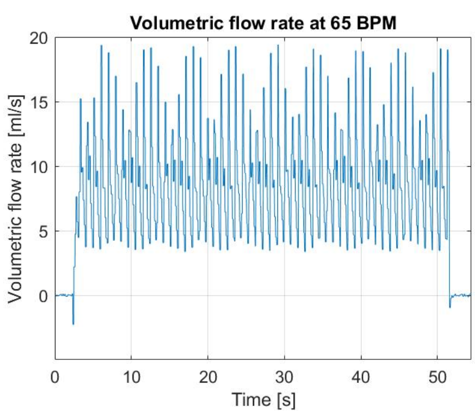


Figure 21: *measurement at 65 BPM*

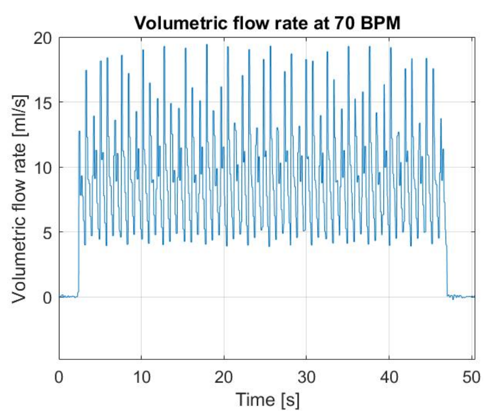


Figure 22: *measurement at 70 BPM*

The measured waveform is compared to the desired *in-vivo* waveform in figure 23. The documented waveform is the average VFP of every relevant cycle of the measurement in figure 20. The signal is composed of two distinct peaks, which resemble the desired waveform. However, the spikes of the early and late systole cannot be distinguished as they have merged together. The amplitude of the first peak is slightly larger than the value of the early systolic peak and the peak appears at 180 ms.
Furthermore, the top of the second peak is significantly higher (1.2 mL/s) than the diastolic peak of the desired waveform. The spike appears approximately 100ms after the desired peak.
In addition, the minimal flow rate of the *in-vivo* waveform is 3 mL/s. As can be seen in figure 23, the flow rate at the beginning and at the end of the signal is approximately 5.8 mL/s, which is much higher.

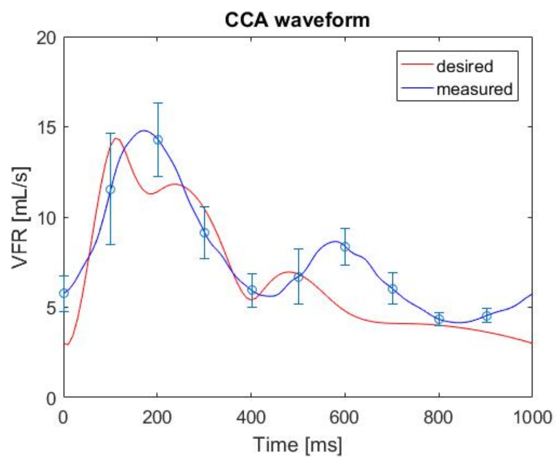


Figure 23: *mean CCA waveform and the mean measured waveform*

Moreover, the variation of the average signal is displayed by error bars at ten points along the curve. The variation at the upward slope and at the top of the systolic peak is relatively large with a standard deviation of 3.1 and 2.0 respectively. Also, the error at 500 ms is significant being 1.5. The variation along the remainder of the waveform is considerably small (SD<1.0).

4.4 Discussion

The minimal flow rate of the measured VFP is 2.8 mL/s higher than the desired value of 3 ± 0.5 mL/s and therefore this requirement has not been met. Consequently, the values of the rest of the signal are also higher, including the amplitudes of the two distinct peaks. This is a result of the performance of the gear pump. In order to achieve a lower minimum flow rate, the input voltage should be reduced. However, the gear pump is not able to operate with a lower input voltage, which is discussed in more detail in appendix A. Therefore, the gear pump should be replaced with another pump that is able to generate a minimal flow rate of 3 mL/s consistently.

The constructed piston profile results in a waveform which resembles the volumetric flow profile of the carotid artery. However, the spikes of the early and late diastole of the desired waveform have merged together in the measured waveform. This is probably caused by the performance of the pump, which appeared to be incapable of creating more details.
The systolic peak of the measured waveform appears at 180 ms, which is approximately in the middle of the early and late diastolic spikes. The requirement of the design is that the systole appears between 100 and 250 ms. Although the spikes of early and late diastole cannot be distinguished, the requirement has been met.

Furthermore, the diastolic peak emerges at 580 ms, which is 100 ms behind the desired profile. It is required that the diastole appears between 450 and 500 ms, so this has not been met. The piston profile was adjusted multiple times to try to shift the peak forward. However, even a small change caused the first and second distinct peak to coincide. The diastolic peak is not clearly visible anymore, which causes the outcome to be worse. This confirms that the ViVitro pump cannot create the desired waveform more accurately due to the inertia of the fluid that is pushed forward by the piston.

The variation of the error bars in the early systole and early diastole are relatively large. The spread can be explained by a sampling artefact due to the ViVitro pump. The sampling artefact has two consequences for the measured output. Firstly, a pattern of fluctuations is observed in the measurement in figures 20-22 and the amplitude of the first and second peak of the cycles varies a great deal. The fluctuations seem to increase at a higher pulse rate. Secondly, not every cycle seems to last exactly one second although the pump has a pulse rate of 60 BPM. Therefore, the peaks appear at slightly different time points.

In addition, the mass flowmeter has a sample rate of approximately 25 samples per second. This preprogrammed sample rate has been selected in FlowDDE software. However, in the enlargement of four cycles in figure 20 can be seen that the sample rate is less than 25 samples/second, so the flow rate is measured at less points. The resolution of the measurement will be better with a higher sample rate. In order to improve the resolution, the sample time needs to be minimized. Also, it may be able to select specific temporal points along the waveform when the mass flowmeter measures more samples per second.

Finally, during the experiment the piston position is adjusted manually by trial-and-error in ViViTest until the output waveform meets the requirements as much as possible. The process is done repeatedly and as accurate as possible, but the measured waveform slightly differs from the desired waveform as discussed above. Also, the process is time consuming. At this moment the relation between the piston position and the resulting waveform is not known. The measured waveform could be improved by analysing and establishing this relationship with Fourier analysis to be able to find the piston position directly for the corresponding waveform. This is not done during the thesis because establishing the relationship is presumably quite complicated and will not necessarily deliver better results due to the performance of the ViVitro pump.

5 Validation physiological conditions

In this section, the physiologic conditions of the carotid artery are mimicked using the advanced flow circuit. The influence of the additional elements on the flow in the MCL are analysed and each component is validated separately.

5.1 Method

The influence of each component of the advanced flow circuit is analysed by implementing them consecutively. The piston profile of a cosine wave is used as a reference signal to compare each output with. Since the relatively complex character of the carotid artery waveform, the cosine profile is applied to simplify the analysis of the components.

The reference signal is measured in FlowPlot using the simple circuit, so no additional elements are included. Then the resistance and the flowmeter are implemented to study their effect on the volumetric flow profile. The diameter of the resistance is set at approximately 1.5 mm. The flow is measured with the mass flowmeter and the BioTech flowmeter. The flow [L/min] of the BioTech flowmeter is displayed by the rate indicator and written down. After the waveform has been recorded, the compliance chamber with pressure meter is incorporated. The compliance is adjusted with the hand pump by releasing or increasing the amount of air above the water in the chamber. The resistance is also altered to achieve the diastolic and systolic pressure of 80 and 120 mmHg. It is not necessary to study the influence of the compliance without a resistance, because the resulting volumetric flow profile would be the same as the reference signal. Resistance creates pressure which is required for the compliance chamber to function.

Furthermore, the piston profile for the CCA waveform is also implemented in the advanced flow circuit. The resistance and compliance are adjusted to obtain the desired physiological conditions in the MCL. The flow profile is recorded in FlowPlot, the flow velocity is documented and the pressure is reported.

The influence of the physiological components on the reference waveform is analysed in Matlab [MATLABR 2017b; MathWorks Inc, USA]. The data of the measurements is imported in Matlab and the mean waveform of each measurement is plotted. In order to obtain the mean, each cycle of one second is taken separately and the average is calculated. The mean waveform of the reference signal and the mean waveforms of the additional elements are presented in one graph. These proceedings are done for the experiments with the cosine piston profile and with the CCA waveform. The waveforms are compared by looking at the time and amplitude of the peaks and valleys of the output signals. The average flow rate of the mass flowmeter is calculated by taking the mean of the mean waveform.

Furthermore, the Reynolds and Womersley number at the entrance of the phantom are calculated in appendix C. The Reynolds number must be smaller than 2000 to have a laminar profile and the Womersley number must be beneath 10.

5.2 Results

The effect of adding elements consecutively to the circuit on the waveform of the cosine piston profile can be seen in figure 24. The reference waveform is the outcome of the implemented cosine piston profile in the simple circuit, so no additional elements are included. The waveform has a characteristic peak of 16.2 mL/s and the average flow rate, measured by the mass flowmeter, is 9.4 mL/s. The BioTech flowmeter reported an average flow rate of 2.8 mL/s.
Adding resistance to the circuit, results in the red waveform that is more damped compared to the reference VFP. The slope of the characteristic peak is smaller and the maximum value has been reduced to 12.4 mL. The average flow rate documented with the mass flowmeter and the BioTech flowmeter are 8.6 mL/s and 2.7 mL/s, respectively.
The inclusion of the compliance chamber causes the waveform to transform again. The volumetric flow profile features the reference waveform. The value of the top is slightly larger and the minimum value has decreased a small amount. The average flow rate is equal to the flow rate of the reference waveform. The pressure meter measures a pulse pressure of 20 mmHg, varying from 40 to 60 mmHg.

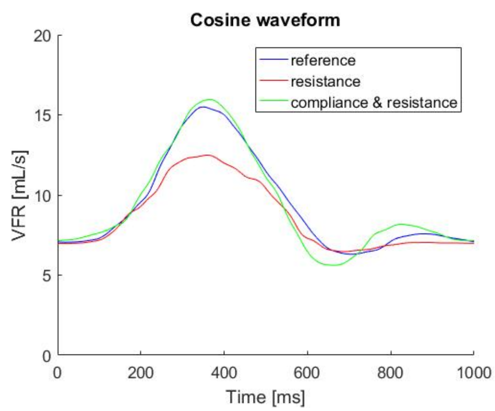


Figure 24: *the effect of the physiological components on the reference waveform fitted by splines*

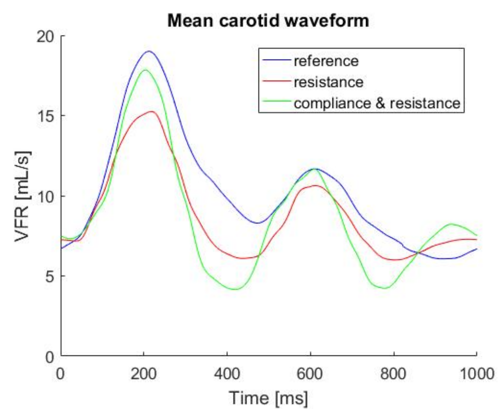


Figure 25: *the effect of the physiological components on the CCA waveform fitted by splines*

The influence of the additional components to the simulated CCA waveform are displayed in figure 25. The waveform from section 4.3 is used as a reference signal to compare the other profiles with. The waveform of the circuit with resistance has two distinct peaks that are both decreased with 3.8 mL/s, compared to the reference signal. The valleys between the peaks at 400 ms and 750 ms are also diminished to 6.1 mL/s. The mass flowmeter measured an average flow rate of 10.4 mL/s, while the BioTech flowmeter reported a value of 3.0 mL/s. When the compliance chamber is included in the flow circuit, the peaks rise to again. The values of the peaks are approximately the same as the reference signal. However, the valleys reduce more severely (4.6 mL/s) than the valleys of the circuit with resistance. The mass flowmeter reported an average flow rate of 10.4 mL/s, which is the same as the reference signal. The diastolic and systolic pressure in the circuit are 90 and 110 mmHg, respectively. This results in a pulse pressure of 20 mmHg.
The Reynolds and Womersley number are 500 and 5.5 respectively in in the phantom.

5.3 Discussion

The additional elements have an effect on the volumetric flow profile of the reference signal.
The resistance reduces the maximum flow rate of the waveform in figure 24 significantly. A smaller amount of fluid can pass the resistance due to the decrease of the tube's diameter. Therefore, the pressure in front of the device is elevated, which diminishes the flow rate. When the diameter of the tube is limited more severely, the flow rate drops more as well and the pressure is increased exceedingly. Therefore, also the values of the valleys in figure 25 are diminished. The flow rate of the valleys of the waveform of the circuit with the compliance and resistance are deeper, because during the measurement the resistance was larger.

Furthermore, the addition of the compliance chamber influences the volumetric flow profile. The chamber causes the flow rates of the peaks to increase again. The pressure that caused the flow rate to diminish, now results in fluctuations of the volume in the chamber. It stores and discharges energy for the circuit. Therefore, the pressure in the circuit can be measured in the chamber.
Moreover, the pressure meter measures a pulse pressure of approximately 20 mmHg, while the desired pressure difference is around 40 mmHg. Therefore, the compliance in the flow circuit is higher than in the body and this requirement has not been met completely. This is caused by the volume of air in the compliance chamber. The size of the chamber should have been adjusted to create a larger volume and therefore enlarging the pulse pressure.

The required pulse pressure for the circuit is approximately 40 mmHg, but the pulse pressure in older people is actually higher. This is caused by the stiffening of the artery wall. The compliance of the vessels declines which results in an elevated pulse pressure, because the difference between the systolic and diastolic pressure is increased. Therefore, pulse pressure in the circuit should be higher than 40 mmHg to mimic the compliance of the vessels of elderly.
The mass flowmeter and the BioTech flowmeter measure the average flow rate. However, the documented values of the flowmeters are very different. The desired mean flow rate of the CCA waveform is 7.8 mL/s. Therefore, the mass flowmeter shows more reliable results, considering that the minimal flow rate is higher in the measurements due to the gear pump. In addition, the flow rate measured by the BioTech flowmeter barely changes when a resistance is added to the circuit. This is caused because of the settings of the rate indicator, which were specified for a flowmeter with a nozzle instead of without nozzle. Therefore, the BioTech flowmeter could not function properly during the experiments and therefore its results are not taken into account.

Also, the values of the BioTech flowmeter and the pressure meter are displayed analogously. Therefore, it is quite likely that errors have been made during experiment when documenting the average flow rate and the pulse pressure. For example, the pulse pressure cannot be noted accurately as the pressure changes continuously. The circuit could be improved by measuring the pressure and mean flow rate digitally.
The Reynolds and Womersley number in the circuit are both higher than the *in-vivo* values of the CCA. This is a result of the larger inner diameter of the straight tube, which increases the numbers as expected. Also, the Reynolds number is larger due to the higher average flow rate of the measured volumetric flow profile.
The velocity profile in the circuit resembles the situation in the body although the values of the Reynolds and Womersley number are higher, so this requirement has been met. A Reynolds number at 500 produces a laminar flow, so this simulates the *in-vivo* flow. The Womersley number in

the MCL is smaller than 10, so the viscous forces are dominant over the transient inertial forces. Therefore, the velocity profile corresponds to the profile in the CCA.
The numbers are an estimation of the steady and pulsatile flow conditions in the circuit. The velocity profile could be visualised by dye injection instead of micro bubbles in the injection device. Ink can be released from a thin needle aligned to the flow in the tube to mark streamlines within the fluid in the straight tube. The density of the dye should match that of the BMF to ensure that the dye accurately follows the flow field.

In order to examine the influence of stents on flow characteristics with echoPIV, the conditions in the *in-vitro* flow circuit must be reliable and reproducible. The resulting waveform resembles the volumetric flow profile in the common carotid artery, but there are large fluctuations in amplitude between cycles throughout the entire measurement. Therefore, the flow circuit is less reliable for measurements with echoPIV.
Also, the flow circuit includes several elements that have to be reset each time the circuit is prepared for measurements. For example, all the air has to be removed from the ViVitro pump and the amount of air in the compliance chamber has to be adjusted. It is possible to perform reproducible experiments with the flow circuit, but the components have to be set very precisely.

6 Conclusion

In the study, an *in-vitro* carotid artery flow circuit with pulsatile flow conditions is designed and implemented. With the elements and their sequence in the current design, the *in-vivo* conditions can be mimicked. The ViVitro pump and a gear pump can generate a pulsatile waveform, the pressure can be regulated with a compliance chamber and resistance and the velocity profile is fully developed in the straight-tube phantom. The modeled waveform of the simple circuit resembles the waveform of the CCA waveform in older adults. However, some details of the desired waveform are disregarded, the flow rate is elevated and the spread is relatively large at some point along the curve due to the performance of the ViVitro pump and the gear pump. The additional components of the advanced circuit influence the modeled volumetric flow profile, but the resulting waveform features the reference signal. The pulse pressure in the circuit is smaller than in the body, but can simply be improved. Although the Reynolds and Womersley number are slightly larger, the profile mimics the velocity flow profile in the CCA. With several adjustments, the flow circuit can be used for reliable and reproducible experiments with echoPIV. Therefore, the aim of the study has been reached.

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7 Appendix

A Gear pump

The fuel gear pump [Modelgraft, F3007] has a feed rate of 0,6 L/min. The pump is equipped with a 12V DC Motor with a carbon brush. The pumping rate can be adjusted by varying the input voltage: it generates a flow of 3mL/s at approximately 5V. Unfortunately, this is relatively low so the pump is not able to run for more than five minutes. This is a result of the magnetic field of the motor that is too low to cross the layer of air between the magnet and the wires. Also, the housing of the pump heats up while operating and can not be cooled properly because the fluid is flowing slowly through the gears.
The problem with the magnetic field can be resolved by connecting a box that generates pulses of a higher voltage. The pulse duration and amount of voltage can be adjusted resulting in an average input voltage of approximately 3mL/s. Nevertheless, the pulses cause the flow in the circuit to become slightly pulsatile, unless the pulse duration is very short. The reduction of the pulse duration is limited because of the quality of the gear pump, so this is not optimal.
Another solution could be a bisection tube at the outlet of the gear pump. One tube at the bisection would go to the circuit and the other tube would terminate in the fluid reservoir. Hence, the pump can operate at a higher voltage while having the same constant flow in the circuit. However, considering that one tube goes to the reservoir and is linked directly to the circuit, this would result in an idle resistance. Part of the pulsatile waveform from the ViVitroPump would travel to the reservoir, so the waveform at the phantom would slightly be damped. This is an undesirable consequence, so a bisection tube is not an option.

The Peristaltic pump [Thomas, SR25] has a 24V DC Motor and rotates at 10-80 rpm, creating a flow between 2 – 287 ml/min. This pump can achieve a flow of 3 mL/s and it can operate for a longer period of time. However, the flow is not steady but pulsatile because of the pressure applied to the tube inside the housing. This results in unwanted fluctuations in the flow and disturbes the waveform, which is not acceptable.

The RS Micropump [RS Pro, D200] is a small pump with a DC power source of 4,5V. The pumping rate can be altered by varying the voltages between 1,0V and 4,5V. At first sight this seems like a suitable pump, but unfortunately it is not. The flow rate of the pump for fluids is much smaller than for gases. The maximum flow rate for fluids is 1,5 mL/s, which is does not meet the requirements for the MCL.

B Piston profile

The piston profile is created in ViVitest. The profile is adjusted manually to simulate the in-vivo waveform of the carotid artery. This resulting piston profile is displayed in figure 26.

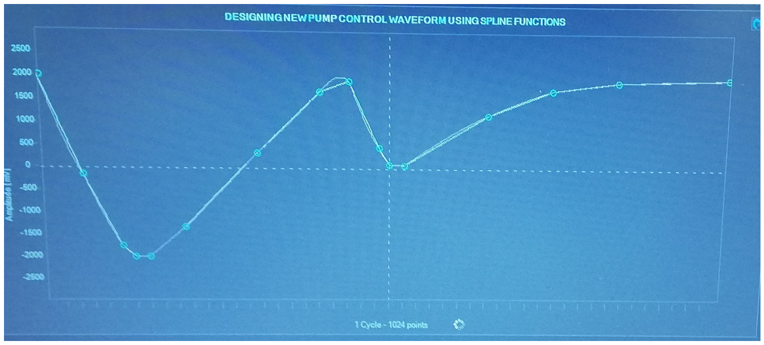

Figure 26: *piston profile for carotid artery waveform per cycle*

C Reynolds and Womersley number

C.1 Reynolds number

The Reynolds number (N_{RE})can be calculated using equation 3. u is the velocity based on the actual cross section area of the tube in [m/s]. v is the kinematic viscosity in $[\frac{m^2}{s}]$. ρ is the density of the fluid in $[\frac{kg}{m^3}]$. d_h is the diameter of the tube. μ is the dynamic viscosity of the fluid in $[Pa \cdot s$].

$$N_{RE} = \frac{\rho \cdot u \cdot d_h}{\mu} = \frac{u \cdot d_h}{v} \tag{3}$$

The kinematic viscosity of the BMF is $3.3 \cdot 10^{-6} \frac{m^2}{s}$, which corresponds to the viscosity of blood. The diameter of the straight tube is 0.008 m. The velocity depends on the measured flow rate (Q) of 10.4 mL/s and the cross sectional area (A) of $5.03 \cdot 10^{-5}$, see equation 4.

$$u = \frac{Q}{A} = \frac{10.4 \cdot 10^{-6}}{5.03 \cdot 10^{-5}} = 0.21 m/s \tag{4}$$

The values are substituted in equation 3, which results in a Reynolds number of ≈500.

C.2 Womersley number

The Womersley number (α) can be derived from equation 5, resulting in equation 6 . L is the radius of the tube in [m]. ρ is the density of the fluid in $[\frac{kg}{m^3}]$. w is the angular frequency in $[\frac{rad}{s}]$. μ is the dynamic viscosity in $[Pa \cdot s]$. v is the kinematic viscosity in $[\frac{m^2}{s}]$.

$$\alpha^2 = \frac{\rho \cdot w \cdot L^2}{\mu} = \frac{w \cdot L^2}{v} \tag{5}$$

$$\alpha = L \cdot (\frac{w}{v})^{1/2} \tag{6}$$

The radius of the tube is 0.004 m. The viscosity of the fluid is $3.3 \cdot 10^{-6} \frac{m^2}{s}$. The angular frequency can be calculated using equation 7, with f being the frequency in [Hz]. The pulse rate of the ViVitro pump is 60BPM.

$$w = 2\pi f = 2\pi \cdot 1 = 6.3 \tag{7}$$

The values are substituted in equation 6, which results in a Womersley number of $\approx$5.5.