DEVELOPMENT OF AN IN VITRO SYSTEM FOR CARDIOVASCULAR FLOW 
MEASUREMENTS AND COMPUTATIONAL STUDY OF CEREBRAL 
ANEURYSM HEMODYNAMICS

by

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Abstract

As the population ages, the prevalence of the cardiovascular disease, which is the leading cause of death in the world, is projected to increase. The aneurysm is a cardiovascular disease which can be defined as an excessive localized enlargement of an artery caused by a weakening of the artery wall. Abdominal aortic aneurysm (AAA) and intracranial aneurysm (IA) are the most propense aneurysm types to develop. When the aneurysm enlarges, there is a high risk of aneurysm rupture which can lead to serious bleeding, or even death. The causes of aneurysm initiation, progression, and rupture are complex and not fully comprehended. However, it is well accepted that hemodynamics has an essential role in the aneurysm development and progress. The main objective of this thesis is to implement a joint experimental-computational approach to study the aneurysms.

The first specific objective was to design and build an in vitro experimental setup which can mimic the hemodynamics for different circulatory regions with tunable physiological conditions. The benchtop system was specifically developed to increase experimental efficiency and maintain high experimental accuracy. The experimental setup was used to replicate the physiological flow and pressure conditions as found in an AAA. The second specific objective was to study intracranial sidewall aneurysms. A computational fluid dynamics (CFD) analysis was conducted to study sidewall aneurysm hemodynamics. An idealized aneurysm geometry was used to determine the effect that a stent treatment device had on aneurysm hemodynamics. Newtonian and non-Newtonian working fluids, matching the human blood density and viscosity, were considered. The study showed that using a Newtonian model, the hemodynamic parameters were overestimated in the intra-aneurysmal sac region in comparison to the non-Newtonian model. Furthermore, the presence of the stent device showed an alteration on the flow patterns inside the aneurysm sac by reducing the overall aneurysmal blood flow velocity.
Lay Summary

An aneurysm is an enlargement of an artery caused by a weakening of the artery wall. The aneurysm can gradually expand, and even rupture. The most common locations for aneurysms to develop are abdominal and cerebral. Today it is believed that one of the factors for progression and possible rupture is blood flow.

To experimentally investigate how blood flows inside an aneurysm, an experimental setup capable of mimicking the cardiac flow conditions was developed. The setup replicated the flow conditions accurately in an abdominal aortic aneurysm.

To investigate the blood flow inside different cerebral aneurysm geometries, computational models were built. The effect of an implanted stent on the blood flow inside the aneurysm has been investigated.

The simulations highlighted that the characteristics of the blood-analog considered affect the comparability of the results. Also, the results showed that flow alterations occur within the aneurysm following the stent implantation.
Preface

The present thesis was performed under the guidance and supervision of Dr. Dana Grecov.

Dr. Grecov identified the research project topic and provided the necessary tools and collaborations to conduct the research.

The work presented in this thesis was performed in the Industrial and Biological Multiphysics Laboratory as well as in the Pulp and Paper Centre at the University of British Columbia, Vancouver. All the research described in the thesis, experimental setups construction, phantoms manufacturing, numerical simulations, and data analysis was performed by me.

Rob Fraser (ViVitro Labs, Inc; General Manager), provided guidance for the experimental setup developed in Chapter 3.

A section of Chapter 4 was presented at The Joint Canadian Society for Mechanical Engineering and CFD Society of Canada International Congress 2019. An abstract was submitted for the conference in addition to the presentation.

The preliminary results of Chapter 4 were presented in a poster presentation at the UBC School of Biomedical Engineering 2nd Annual Symposium.

Based on the study described in Chapter 4, an abstract has been submitted and accepted to be presented as a poster at the American Physical Society (APS) in the 72nd Annual Meeting of the APS Division of Fluid Dynamics.
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List of Symbols

\( \alpha \) System Poles
\( \theta_A \) Inflow angle
\( \Delta t \) Change in time
\( \Delta x \) Change in x position
\( g \) Gravity
\( I \) Principal stress invariance
\( K_d \) Derivative gain
\( K_i \) Velocity in y direction
\( K_p \) Proportional gain
\( \lambda \) Relaxation time constant
\( \zeta \) Damping factor
\( u \) Velocity in x direction
\( \mu \) Viscosity
\( \mu_\infty \) Viscosity at infinite shear-rate
\( \mu_0 \) Viscosity at zero shear-rate
\( n \) Power law index
\( \eta \) Viscosity
\( p \) Pressure
\( Q \) Flow Rate
\( \rho \) Density
\( s \) Laplace transform
\( t \) Time
<table>
<thead>
<tr>
<th>Symbol</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\dot{\gamma}$</td>
<td>Shear rate</td>
</tr>
<tr>
<td>$\tau$</td>
<td>Stress</td>
</tr>
<tr>
<td>$V$</td>
<td>Voltage</td>
</tr>
<tr>
<td>$V$</td>
<td>Blood velocity</td>
</tr>
<tr>
<td>$v$</td>
<td>Velocity in y direction</td>
</tr>
<tr>
<td>$v_m$</td>
<td>Measured flowrate</td>
</tr>
<tr>
<td>$v_p$</td>
<td>Prescribed flowrate</td>
</tr>
<tr>
<td>$\omega_0$</td>
<td>Undamped natural frequency</td>
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List of Abbreviations

AAA  Abdominal Aortic Aneurysm
ABS  Acrylonitrile Butadiene Styrene
ACA  Anterior Cerebral Artery
ACh  Anterior Choroidal Artery
AR   Aspect Ratio
CAD  Computer-Aided Design
CFD  Computational Fluid Dynamics
DAQ  Data Acquisition
DPSS Diode Pumped Solid State
EVAR Endovascular Repair
FD   Flow Diverter
FSI  Fluid Structure Interaction
IA   Intracranial Aneurysm
ICA  Internal Carotid Artery
LDV  Laser-Doppler Velocimetry
MRI  Magnetic Resonance Imaging
OphA Ophthalmic Artery
PCA  Posterior Cerebral Artery
PCoA Posterior Communicating Artery
PDMS Polydimethylsiloxane
PED  Pipeline Embolization Device
PI   Proportional-Integral
PID  Proportional Integrative Derivative
PIV  Particle Image Velocimetry
PLA  Polylactic Acid Filament
PTV  Particle Tracking Velocimetry
RMS  Root-Mean-Squared
SAH  Subarachnoid Hemorrhage
SR   Size Ratio
VA   Vertebral Artery
WSS  Wall Shear Stress
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First and foremost, I would like to thank my supervisor, Dr. Dana Grecov for her continued support and guidance. During the project, there were instances when things were not going as planned. However, she remained patient and made me realize that research requires a lot of patience, along with dedication.

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Finally, I would like to express my deepest gratitude to my wife, Aurora. She has been my partner in life, no matter the obstacles we have faced, she has always remained supportive and humble. Thank you for your support during these arduous days. I love you.
Dedication

To my wife, my only reason to be.
Chapter 1

Introduction

In the human body, the blood is periodically pumped by the heart and transported by a network of vessels with various configurations according to their roles, geometry, and position in the body. The arteries are the vessels that originate in the heart and resist higher pressures than the return vessels, the veins. Arteries and vessels walls have different elastic properties depending on their location. During each periodic discharge of blood, a pressure pulse that propagates through the elastic network of arteries is produced, thus inducing a pulsatile flow with a mean forward motion [1]. The elasticity of the arterial wall permits the circulatory system to quickly adapt to the vital changes in the cardiac blood flow output dictated by the increasing requirement for nutrients and oxygen to the tissues and organs when needed [2].

In addition to their elastic properties, arteries must withstand stresses due to the hemodynamic forces exerted by the pulsatile blood flow. To do so, the arterial walls have cyclic resilience and strength properties [3].

Since arteries can adjust to long-term physiological conditions while maintaining their integrity and function throughout an individual’s life, arterial cells, as well as most cells in the human body, must regenerate and repair [4]. However, there may be failures in this regeneration, making the arterial walls thinner and fragile, and increasing their arterial diameter. This process is multifactorial and degenerative, influenced by biological and hemodynamic factors. When the increase in arterial diameter is permanent and equal to or greater than 50% of the original vessel diameter, it can be characterized as an aneurysm [5]. An aneurysm can be defined as a localized protrusion filled with blood that forms on the walls of blood vessels. Aneurysms are more propense to develop within the aorta, near the thoracic and
abdominal region [6], as well as in the cerebral arteries [2]. There exists a high risk of aneurysm rupture when the aneurysm enlarges, leading to bleeding and physiological trauma or even death [7].

1.1 Motivation

The cardiovascular disease is currently the leading cause of death in the world and is projected to increase in the following years [8], [9]. In Canada, the direct and indirect economic cost of cardio and cerebrovascular diseases is estimated to be $22.2 billion per year [8]. Among the cardiovascular diseases, aneurysms require special attention due to their mortality rates and impact on health.

Throughout the past decade, aortic aneurysm associated death has been the 12–15th leading reason for mortality among people over 55 years old in the USA, UK, and numerous European countries [3]. Due to population growth and aging, aortic aneurysm deaths have increased by 52% between 1990 and 2013 [3]. Abdominal aortic aneurysms (AAA) accounts for an overall mortality rate of 80% when ruptured [10]. The progressive growth of AAA occurs over several years and will eventually lead to aneurysm rupture, usually having fatal consequences. 90% of patients suffering from AAA rupture die before arriving at the hospital, and of those who manage to reach, only 25% - 65% survive [11].

On the other hand, intracranial aneurysms (IA’s) rupture and hemorrhage are the principal cause of hemorrhagic stroke, which has an overall prevalence between 2% and 5% in the global population [12], [13]. Ruptured intracranial aneurysms can result in subarachnoid hemorrhage (SAH) [14]. SAH occurs at a rate of 10/100,000 people, and 85% are caused by ruptured aneurysms [15]. This corresponds to approximately 11,000 deaths per year attributable to SAH due to IA rupture in the United States only. About 10% to 15% of subjects with
ruptured cerebral aneurysms perish before visiting a hospital. Of the survivors, 42% are independent, 46% suffer from a disability, and 12% are severely impaired [9].

From the different factors leading to aneurysms formation, the hemodynamics has been considered to be related to aneurysm genesis, progression, and rupture [2], [16]–[21]. The behavior of the blood flow in the aneurysmal sac is a complex phenomenon due to the simultaneity of the processes that occur within it. These phenomena cause changes in the mechanical properties of the arterial wall, inducing variations in the shape of the aneurysm over time. The aneurysm shape variations lead to changes in blood flow patterns inside the aneurysm and, consequently, alterations in the distribution of hemodynamic stresses [2], [22], [23].

Due to the importance of hemodynamics, different approaches have been undertaken to study aneurysm hemodynamics, which includes *In vivo*, *in vitro*, and computational studies [21], [52]–[57], [60]–[65].

*In vivo* studies on aneurysms are often invasive, hence imposing a risk on the patient. Computational and *in vitro* studies such as numerical simulations and the construction of three-dimensional bio-models in conjunction with *in vitro* benchtop systems, are presented as less invasive alternatives and are shown as key options to facilitate the study of the aneurysm hemodynamics. These techniques allow the construction, simulation, and validation of hemodynamic parameters such as flow, pressure, and stress in simplified anatomical models as well as patient-specific models [31]–[33], [124]–[133]. Furthermore, numerical and *in vitro* approaches allow investigating aneurysm hemodynamics without compromising the integrity of the patient.

Due to aneurysms risk, it is necessary to understand their hemodynamic behavior. Even more, since hemodynamics may have a significant impact on both the aneurysms rupture and treatment efficacy, precise experimental-computational investigations of flow related to clinical outcomes are required. A broader knowledge of aneurysm hemodynamics will be beneficial for
clinical research and disease management future studies. Thus, the present thesis implements a joint experimental-computational approach to study aneurysms.

The in vitro study of the aneurysm hemodynamics was initiated and sponsored through an Engage project by Vivitro Labs Inc., which is cardiovascular equipment and a laboratory testing company. The company provides the assessment of the hydrodynamic performance of cardiac devices, which is used for submission with regulatory bodies such as the FDA. Vivitro's heart simulator is used for conducting both research and engineering testing of mechanical, prosthetic heart valves and transcatheter aortic valve implantation.

Furthermore, the study focused on cerebral aneurysm hemodynamics originated from our collaboration with a Vancouver based medical device company. The main objective of this collaboration was to compare the effectiveness of an existing endovascular stent and a novel stent design, under various anatomical configurations of common sidewall cerebral aneurysms using computational fluid dynamic studies. Given that one of the primary purposes of an endovascular cerebral aneurysm stent is to divert and prevent blood flowing into the aneurysm sac, the simulations were conducted with the focus on the difference in hemodynamic evaluations of the stents inside in vitro cerebral aneurysm phantoms. The results from the stent comparison are not disclosed in this thesis, as requested by the company. However, the results for different cerebral aneurysm configurations and an aneurysm case treated with an existent endovascular stent are presented in this thesis.

1.2 Thesis Objectives

The main objective of this thesis is to implement an experimental and computational approach to study the aneurysms.

- The first specific objective is to design and build an in vitro experimental setup, which can mimic the hemodynamics for different circulatory regions with tunable physiological
conditions. The system is developed to increase experimental efficiency and maintain high experimental accuracy and precision compared to commercial systems and previously published setups.

- The second specific objective is to evaluate the sidewall intracranial aneurysm hemodynamics by performing CFD simulations.

1.3 Thesis Organization

The thesis content is organized in four chapters, Chapters 2, 3, 4, and 5.

Chapter 2 presents an overview of the relevant information regarding abdominal and cerebral aneurysms, such as the common location where they develop, prevalence, aneurysm configurations, and treatment options.

Chapter 3 discusses the design and construction of an in vitro experimental setup, capable of mimicking the hemodynamics for different circulatory regions with tunable physiological conditions. A literature review on the existing commercial and in-house-built setups to replicate physiological flow conditions is presented. A detailed description of the experimental setup working principles, working fluid used, and anatomical phantom manufacturing process is addressed. Additionally, the implementation of PID feedback in conjunction with a feed-forward controller to improve experimental accuracy is discussed.

Chapter 4 discusses the study of hemodynamics in sidewall cerebral aneurysms. In this chapter, a literature review on experimental and numerical techniques used to study intracranial aneurysms is presented. Also, a detailed description of the CFD simulation conditions is presented. Furthermore, a description of a stent device considered in the numerical simulation and the process for virtually implanting the device in an aneurysm model is discussed. Finally, numerical results are presented.
Chapter 5 presents a summary of the conclusions and limitations presented in Chapters 3 and 4. In this chapter, the possible future path of work to continue the research is discussed.
Chapter 2

Background Information

The objective of this chapter is to provide an overview of the knowledge required for the design and implementation of experimental and computational models capable of reproducing human systemic circulation to study aneurysms. Hence a literature review was carried out on the physiological functioning of aneurysms, their hemodynamics, common locations and geometries, and finally, their treatment options.

2.1 Aneurysm Definition and Classification

An arterial aneurysm is defined as an uncharacteristic localized dilation in the wall of an artery [2]. The dilation represents at least a 50% increase in its standard diameter. Depending on its origin, it can be congenital or acquired [34].

Aneurysms can be classified based on their etiology, as cylindrical dilations (true aneurysms) and traumatic dilatations due to wall rupture (false aneurysms). True aneurysms occur in healthy arterial or myocardial walls, in which the thickness of the wall is thinned. False aneurysms (pseudoaneurysms) develop from an arterial rupture in which hemorrhage from adjacent tissues is contained, forming a perfused cavity at the outer layer of an artery. In this case, the adventitial tissue of the blood vessel limits the clot on the outer surface, preventing its spread. Classic examples of false aneurysms include ventricular rupture, pericardial adhesion after myocardial infarction and blood leakage from the junction of graft sutures or traumatic lesions of the arteries [5].
Figure 2-1: True aneurysm: (a) Fusiform subtype, symmetrical dilation of the entire circumference. (b) Saccular, localized dilation. (c) Pseudoaneurysm partial section of the artery wall affected.

True aneurysms are also categorized according to their form and dimension. By their shape, they can be saccular or fusiform [2]. Saccular aneurysms are a spherical dilation that only affects a portion of the vascular wall. Fusiform aneurysms, on the other hand, have a circumferential dilation of an extended longitudinal part of a blood vessel. Fusiform aneurysms are regularly found in the abdominal region of the aorta, whereas saccular usually develop at the principal arteries of the cerebral circulation.

Figure 2-2: General types of aneurysms; (a) Fusiform and (b) saccular aneurysm. Illustration created with BioRender (https://biorender.io).

Finally, aneurysms are also classified by their anatomical location, the most common locations being the thoracic and abdominal aorta regions, and the cerebral vasculature [2].
2.2 Pathology

The blood vessel wall is made up of three layers: an inner layer called tunica intima, an intermediate layer named tunica media, and an external layer called tunica externa. In the arteries, the tunica media has smooth muscle fibers and elastic fibers necessary for vasomotor processes related to blood pressure regulation. These arterial wall layers are constantly undergoing remodeling based on blood pressure, nutritional status, and genetic conditions of the individual that leads to alterations of the extracellular matrix and other external effects such as trauma or infections [2]. It is considered that aneurysms appear as an alteration in the structure and function of the connective tissue of the tunica media wall layer, mainly related to the extracellular matrix. Aneurysms frequently emerge when the hemodynamic forces exerted to the arterial wall exceed the stress that the arterial wall can resist [35]. Consequently, the vessel wall loses significant tensile strength; therefore, it experiences continuous aneurysmal dilatation and finally ruptures [36].

![Muscular artery cross-section](https://biorender.io)

**Figure 2-3**: Muscular artery cross-section. Layers of the artery wall are labeled as tunica externa, tunica media, and tunica intima. Figure created with BioRender (https://biorender.io).
Concerning aneurysm pathogenesis, some of the promoters and trigger factors that alter the shape and function of the vascular wall include [5], [37]–[39]:

1) Weakening of the vascular wall due to the disappearance of myocytes from the tunica media and insufficient synthesis of extracellular matrix components.

2) Atherosclerotic and hypertensive processes. They represent the most critical processes in the formation of aortic aneurysms. Atherosclerosis is the most crucial factor in the formation of abdominal aneurysms, while arterial hypertension is an essential factor in the development of aneurysms of the ascending aorta. The primary complications of atherosclerosis that occur during normal physiological activities, potentiated by hypertension, are all attributable to acquired wall fragility or pathological loss of vessel resistance [5].

3) Remodeling of connective tissue and extracellular matrix of the vascular wall. It includes multiple nutritional, inflammatory, and genetic syndromes.

Other processes related to the weakening of the vascular wall are traumas, vascular inflammations, and congenital disabilities.

After addressing the general principles of aneurysm formation, the following sections will focus on abdominal aortic and cerebral aneurysms. These two types of aneurysms display different geometrical dimensions and arterial wall structure properties due to the anatomical location where they develop [40].

2.3 Abdominal Aneurysms

The aortic artery (aorta) is the conduit through which oxygenated blood ejected from the left ventricle is distributed to the arterial tree in each cardiac cycle. During blood circulation, the aorta is divided into different branches, first in large vessels, then into medium-sized arteries, small arteries, and, finally, into capillaries.
The aorta is mainly divided into two large sections: thoracic and abdominal. The thoracic aorta is subdivided into the ascending aorta, aortic arch, and descending aorta, as shown in Figure 2-4.

The aorta of young and healthy people has better elasticity compared to that of individuals over the age of 50, in whom the arteries lose elasticity and become hard and rigid, a fact that might favor arterial wall expansion [5].

The abdominal aortic aneurysm (AAA) is a local dilatation of the abdominal aorta, being the most prevalent form of aortic aneurysm [3], [41].

![Figure 2-4: Main two sections of the aorta, thoracic (upper section), and abdominal (lower section).](https://biorender.io)

In AAAs, the behavior of blood flow within the aneurysm sac is a complex phenomenon due to the simultaneity of the processes that happen inside it. These phenomena cause alterations in the arterial wall mechanical properties, inducing variations on aneurysm shape over time. Shape alterations lead to changes in blood flow patterns inside the aneurysm sac. Consequently, they cause alterations in the distribution of hemodynamic stresses on the
innermost layer of the aneurysm arterial wall [42]. This cascade of events can, under certain pathological conditions, ultimately cause aneurysm rupture.

Today it is recognized that the clinical guidelines used for managing AAA risk of rupture require improvement [42]. As a result, researchers and clinicians have tried to identify new criteria that will allow predicting, with a higher degree of reliability in a patient-based manner, the likelihood of aneurysm breakage. Many studies agree that the prediction of AAA rupture could be based on a biomechanical approach [2]. This approach establishes that, as the AAA grows, there is an increase in enzymes that are degrading the vascular wall and a rise in the inflammatory cells infiltration causing destruction of the collagen and elastin layer in the vessel’s wall [5]. The biomechanical approach also allows the models of different geometric, structural, and biological characteristics of AAA to be integrated over time, which qualitatively describes possible areas of AAA collapse. Through this approach, blood flow and wall shear stress have been identified as one of the critical factors that can predispose and induce aneurysmal wall rupture.

2.3.1 Abdominal Aneurysm Treatment

Treatment options are dependent on the dimension and position of the aneurysm and the overall health status of the patient. Treatments can be divided into the following:

2.3.1.1 Medical Observation

Depending on aneurysm size, doctors may decide to keep the patient under observation and assess the nature of further interventions. Doctors may also prescribe medications, such as beta-blockers, to lower blood pressure and reduce pressure on the aortic walls. Drugs are particularly useful in cases where the risk of surgery outweighs the risk associated with the aneurysm.
2.3.1.2 Open Surgery Repair

During open surgery, the surgeon performs a long incision in the abdomen where the aneurysm is detected. Consequently, the region degraded by the aneurysm is surgically segregated from the principal portion of the aorta and substituted by a synthetic tube (known as aortic graft), which is stitched to the arterial wall.

2.3.1.3 Endovascular Repair

A minimally invasive surgical technique allows surgeons to insert a stent graft into the iliac artery and displaced it up to the site of rupture. The stent is then attached to the healthy artery above and below the aneurysm to build a distinct channel for blood to circulate. Blood flows through the stent, therefore reducing pressure on the wall of the weakened artery. Pressure reduction can prevent the aneurysm from rupturing. This technique is useful for treating patients for whom surgical intervention would be too dangerous due to their general state of health.

Figure 2-5: Illustrations displaying AAA treatments. (a) Open surgical repair of AAA involves clamping the aorta and applying a graft (Stent for AAA, Image under Creative Commons License) [43]. (b) Endovascular
aneurysm repair (EVAR) of the abdominal aneurysm (Aneurysm Endovascular, Image under Creative Commons License) [44].

In conclusion, as previously stated, the goal of treating an abdominal aortic aneurysm is to prevent it from exploding or breaking. According to the size and condition of the aneurysm, it can be carried out by careful observation or repair of the aneurysm.

2.4 Intracranial Aneurysms

The aneurysms formed in the cerebral vasculature are referred to as intracranial aneurysms (IA), cerebral aneurysm, or brain aneurysms. These are mainly formed at curvatures or bifurcations of arteries, especially in the vicinity of the Willis Polygon, which is the area of union of several arteries in the lower part of the brain supplying oxygenated blood to more than 80% of the brain. The IA geometry resembles to an unusual dome that grows from the wall of the artery.

Studies show that the frequency of IA’s in the general population is between 2% to 5%, suggesting that between 10-15 million individuals just in the United States have or would have intracranial aneurysms [7].

Intracranial aneurysms can be classified as saccular or fusiform and identified by their size. By size, they can be identified as micro(<3 mm), small (4-6 mm), medium (7-10 mm), large (11-24 mm) and giants (> 25 mm) aneurysms [12], [45].

Approximately 85% of saccular intracranial aneurysms develop within the Willis polygon. The most common locations are the anterior communicating artery with 35%, the internal carotid artery with 30%, the middle cerebral artery with 22%, and the rest appearing in the posterior circulation such as in the basilar artery tip and cerebellar arteries [46]. Figure 2-6 shows the typical locations of intracranial aneurysms to develop.
Figure 2-6: Common places of cerebral aneurysms and frequency of appearance within the Willis Polygon.

1) Anterior communicating artery (35%). 2) Middle cerebral artery (22%). 3) Internal carotid artery/posterior communicating artery (30%). 4) Vertex basilar artery (5%). 5) Superior cerebellar artery (3%). 6) Vertebrbasilar union (2%). 7) Posterior inferior cerebellar artery (3%). Figure created with BioRender (https://biorender.io).

Saccular aneurysms can further be classified according to their location with respect to the vessel from which they are originated, as sidewall and bifurcation, as shown in Figure 2-7.

Figure 2-7: Types of saccular aneurysms; (a) Sidewall and (b) Bifurcation. Illustration created with BioRender (https://biorender.io).
Sidewall aneurysms are a type of saccular aneurysm and are characterized by a round outpouching with a distinct aneurysmal dome and neck attached to the parent vessel [12]. Sidewall aneurysms extend off one parent artery, unlike bifurcated saccular aneurysms, which extend off the connecting Y-junction of two-parent arteries [12]. Baharoglu et al. [47] have presented the most common locations where sidewall aneurysms develop. These locations are summarized in Table 2-1.

**Table 2-1: Common Locations for sidewall aneurysm to develop.**

Internal carotid artery (ICA), posterior communicating artery (PCoA), ophthalmic artery (OphA), anterior choroidal artery (AChA), anterior cerebral artery (ACA), vertebral artery (VA), and posterior cerebral artery (PCA).

<table>
<thead>
<tr>
<th>Location</th>
<th>Prevalence</th>
<th>Vessel Diameter</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICA</td>
<td>38.2%</td>
<td>4.2</td>
</tr>
<tr>
<td>PCoA</td>
<td>28.7%</td>
<td>1.45</td>
</tr>
<tr>
<td>OphA</td>
<td>17.6%</td>
<td>1.8</td>
</tr>
<tr>
<td>AChA</td>
<td>7.4%</td>
<td>0.94</td>
</tr>
<tr>
<td>ACA</td>
<td>3.7%</td>
<td>2.3</td>
</tr>
<tr>
<td>VA</td>
<td>2.9%</td>
<td>3.6</td>
</tr>
<tr>
<td>PCA</td>
<td>1.5%</td>
<td>2.15</td>
</tr>
</tbody>
</table>

The causes of brain aneurysm initiation, progression, and rupture are complex and not fully comprehended. However, it is well accepted that hemodynamics has an essential role in aneurysm development and progression [19]. In particular, recent developments of techniques for endovascular treatments have indicated that it is necessary to understand better the hemodynamic effects.

Pathological evidence has related the size of aneurysms and rupture, suggesting that the damage of the endothelium is related to the characteristics of the flow. A correlation between high wall shear stress and endothelial degradation has been demonstrated [48]. Furthermore, some authors postulate that this is the key to the initiation of an aneurysm. If the layer of cells protecting the arterial wall innermost layers are damaged, blood may be able to harm the fibers
that support the structure of the arterial wall, thus progressively decreasing its mechanical characteristics. [49].

![Figure 2-8: (a) Unruptured sidewall aneurysm and (b) Ruptured sidewall aneurysm (Image reprinted with permission for noncommercial use) [50].](image)

Additionally, it is known that the flow inside an aneurysm relies on its geometric arrangement and connection to its parent artery, neck diameter, and aneurysm size [2]. Therefore, bifurcated and sidewall intracranial aneurysms exhibit different hemodynamic responses [2], requiring distinct flow analyses. Consequently, the probability of developing an aneurysm would mainly depend on blood vessel geometry, arterial wall properties, and blood flow characteristics. Other authors believe that the beginning of aneurysm growth is primarily related to congenital defects in the wall of the artery [45].

### 2.4.1 Intracranial Aneurysm Treatment

There are two families of treatments: surgical and endovascular [51]. Figure 2-9 displays an illustration of the different intracranial aneurysm treatments.

#### 2.4.1.1 Surgical Treatment

Among the surgical treatments, surgical clipping is the most common treatment option. Clipping involves craniotomy, aneurysm exposure, and clip affixation around the aneurysm neck. The positive side of this approach is the low possibility of aneurysm regrowth. On the
other hand, because of the open-skull operation, the preoperative process can be associated with high injury and death due to potential infection, stroke, and seizure. As a consequence, surgical clipping is not always applicable. Thus, a newer approach was developed — endovascular treatment.

2.4.1.2 Endovascular Treatment

The endovascular treatment is the second method for intracranial aneurysm treatment and can be divided into coil embolization and flow diversion [12], [37].

2.4.1.2.1 Coil Embolization

Coil embolization is a minimally invasive technique that involves filling the aneurysm sac with tiny coils to impede blood entering [12]. Various coils need to be applied to guarantee occlusion of the aneurysm dome.

Sometimes, for aneurysms with a wide neck or unique appearance, a stent-like device will also be implanted outside the aneurysm in the parent blood vessel to secure the coils. Although this approach is used to treat unruptured aneurysms for those who cannot survive the craniotomy, on the other hand, recurring symptoms may occur, which means the aneurysm may regrow. Also, it has the same foreign body reaction issue and the likelihood of incomplete occlusion as the clipping method. Moreover, in some cases, because intracranial blood vessels are all fragile and the walls are already weak, the aneurysm may rupture if catheters or the coils pierce the wall. Thus, for this treatment, factors like the aneurysm geometry, mechanical and material properties of the stent and coils, as well as biocompatibility, are all significant for successful long-term results [52].
2.4.1.2.2 Flow Diversion

The device used in this technique is known as flow diverter, which is a stent with finer mesh compared to the one applied to hold the endovascular coils in place. The basic working principle is that with the use of stent, blood flow entering the aneurysm cavity can be significantly reduced and decelerated as it will be forced to pass through the small holes from the stent wall. Researchers have found that the mechanical properties of the stent will affect its flow reduction effects [53]. For flow diverters, their meshing patterns are different. Therefore, the two geometric characteristics directly associated with the flow reduction effects: pore density and porosity, are essential for stent assessment. The pore density of a diverter gives the number of pores per unit area, and the porosity represents the percentage of the open and metal-free stent area [53]. Prior studies have shown that high pore density and low porosity will result in higher efficiency of the flow diverter, as they can adequately divert the amount of blood and reduce the blood flow velocity into the aneurysm dome. These will help alter the hemodynamics at the aneurysm neck, and in time, thrombosis will automatically emerge in the sac, which acts like bio-coil occlusion [23].

![Figure 2-9](image-url): Intracranial aneurysm treatments: (a) Surgical clipping, (b) Endovascular coiling, (c) Flow Diverter Stenting (Image reprinted with permission for noncommercial use) [50].

In general, although flow diversion might be an ideal treatment for patients suffering from giant wide-necked brain aneurysms that cannot accept other types of procedures, unlike
the surgical approach, it is limited to unruptured aneurysms. The restriction occurs due to the postoperative medicine – antiplatelet agents, which on the one hand, help to decrease the risk of thrombosis in the parent artery and stroke. On the other hand, their side effects lead to a higher possibility of hemorrhagic complications and aneurysm rupture even after the implantation of the flow diverter. As a result, even flow diversion seems the most promising treatment; clinicians will need to account for both theoretical optimizations of the geometric characteristics of the diverter and practical situations of the patients [21].
Chapter 3

Development of an *in vitro* benchtop system for cardiovascular flow measurements

3.1 Introduction

The cardiocirculatory system can be thought, in a simplified way, as a hydraulic circuit made up of ducts with different diameters (the blood vessels), and a positive displacement pump: the heart. The heart allows the circulation of the blood in the various areas employing four passive regulating valves.

Building a closed hydraulic circuit that simulates the cardiac circulation is essential to perform *in vitro* experimentation to study the behavior of heart valves, or ventricular assist devices and for studies on cardiovascular pathologies such as aneurysms.

Therefore an *in vitro* experimental setup which can mimic the hemodynamics for different circulatory regions with tunable physiological conditions has been developed. The system is designed to increase the experimental efficiency and maintain high experimental accuracy and precision compared to commercial systems and previously published setups. Given that abdominal aneurysm is a common type of aortic aneurysm, the system was verified by replicating the physiological flow conditions found in the abdominal aorta.

Hence, in this chapter, a literature review regarding existent experimental setups used for mimicking cardiac physiological flows is presented. The development of the modular *in vitro* benchtop system for cardiovascular flow measurements under variable physiological conditions is described. The results from testing the *in vitro* experimental setup under different flow
conditions are presented. The developed *in vitro* setup sets the basis for further experimentation geared towards aortic aneurysm hemodynamics.

### 3.1.1 Replicating Physiological Flow Conditions

To emulate cardiac circulation is required to recreate first the heart, which comprises the pumping mechanism and the heart valves, which help the blood to flow in one direction only. Secondly, a circulatory system that includes compliance and vascular resistance chambers, which represent the arterial tree vasculature resistance to flow; and finally, an instrumentation and control system which can control the blood velocity and cardiac output, for example.

In order to simulate the pulsatile cardiac flow, pumps capable of replicating physiological flow conditions, are used either in a mock loop that represents the entire cardiovascular system [54]–[57], or loops that recreate the physiological conditions from a specific region of interest by recreating flow and pressure waveforms [58]–[62]. For both cases, custom made experimental setups and commercial pumps are available. Many of these setups are used to study heart valve prosthesis [63], cerebral aneurysm [64], [65], atherosclerosis [66], [67], and abdominal aneurysms among others [22], [68]–[70].

There are different ways in which the physiological flow has been recreated, for example, through the use of gear pumps combined with a servomotor that serves as a pulsatile flow actuator or a combination of a gear pump with stepper motors [71]–[74]. Another example is the use of piston-controlled pumps and combinations of piston pumps driven with servo motors [61], [70], [75], [76].

Finally, peristaltic pumps have all been adapted to replicate specific low flow rate waveforms; however, these are not regularly used due to their capacity limitations [77]. Regardless of the pump selected, all *in vitro* setups generally require a microcontroller or a computer to operate them in order to replicate clinically acquired physiological waveforms.
3.1.2 Commercially Available Pump Systems

One of the commercially available systems for replicating cardiac flow profiles is the Vivitro Pulse Duplicator system® (Vivitro Labs, Victoria, BC, Canada) shown in Figure 3-1. The pulse duplicating equipment is made up of a model of the left heart, a piston pump to provide the flow, peripheral resistance and compliance chambers, and the necessary hardware and software for the monitoring and the analysis of data.

This system replicates flow characteristics from the heart down the specific anatomical location of interest, which implies that reproducing a particular flow waveform requires extensively tuning for the resistance and compliance parameters.

![Vivitro pulse duplicator system](Image obtained from Vivitro Labs website) [78]

Other commercial options include the Harvard pump (Harvard Apparatus, Holliston, MA, USA), the Shelly CardioFlow (Shelley Medical Imaging Technologies, London, Ontario, Canada), the BDC pulsatile pump from BDC Laboratories (Biomedical Device Consultants and Laboratories, Colorado, US) and the MP3 Pulse Duplicator from Dynatek (Dynatek Labs Inc; Missouri, US). Each of these pumps has different limitations, such as the programmability and limited versatility of the equipment, as well as the cost [79].
Commercially available pump systems can accurately replicate only specific physiological waveforms making it hard to use them to recreate different waveforms to the ones they were designed to replicate. Usually, expanding the original waveform settings requires developing a custom setup for the compliance and resistance requirements [80]. Another limitation is the maximum operation flow rate, which is usually different from pump to pump and has a limited range. Furthermore, these devices require a custom workstation or software to operate, which makes it challenging to adapt the system to specific requirements such as recreating the flow in a particular anatomical location. Finally, the cost of these devices varies depending on the particular peak flow rate to be replicated and ranges from $15,000 to $40,000 plus extra expenses related to the setup [81].

Due to these reasons, researchers have opted to create custom made experimental setups either by partially using commercial devices, such as the ones presented or by constructing in-house-built setups. An in-house-built setup provides the advantage of being able to reproduce different physiological waveforms modifying primarily software instead of hardware, therefore making it more programmable and versatile.

3.1.3 Existent Experimental Setups

The first attempt to replicate pulsatile human arterial flow dates to 1972 by Hoppmann and Liu [82]. They developed a pump that used an elastic reservoir, which was periodically squeezed by a cam with pressure-actuated check-valves to provide the flow direction. Since then, different approaches have been designed to replicate physiological flow conditions.

Segers et al. [57] built a physical model of the arterial tree using elastic rubber tubing. This model incorporated the aorta, arteries from the upper and lower circulation, carotid arteries, and branching arteries for the different abdominal sections. All the arteries modeled required resistance and compliance to be tuned to replicate physiological and pathological
conditions. The cardiac flow replication was performed by a synthetic heart chamber filled with blood mimicking fluid, which was contracted and expanded using compressed air.

Law et al. [83] used a custom peristaltic pump to replicate physiological waveforms found in the carotid artery. The main advantage of Law’s methods is that, contrary to previous models where the fluid was grinded and compressed, the use of peristaltic pumps avoided this issue. Fluid compressing is a significant disadvantage in models where small particles, such as Doppler ultrasound scattering particles, are used to perform flow visualization. When the working fluids are compressed, the small molecules they contain are broken down, leading to flow alterations, which could be compared to the hemolysis processes in a physiological system.

Hoskins et al. [60] proposed the use of a gear pump operated by a stepper motor to recreate a variety of physiological waveforms, only building an arterial tree and avoiding making a heart model. Hoskins used a working fluid that mimicked blood characteristics, composed of 42% glycerin and 58% water by weight, flowing through rigid and elastic tubing. Their study showed that their pump controller had a limited flowrate range and a significant change in flow waveforms when using elastic tubing.

Frayne and Holdsworth et al. [76], [84] proposed a similar design consisting of two pistons driven by a micro-stepper motor. These setups allowed for custom waveform signals to be programmed into the setup software. Both Frayne’s and Holdsworth’s designs showed good accuracy overall; however, the accuracy was dependent on the impedance present in the flow loop. Some of the typical limitations for these setups were that the replicated waveforms showed fluctuation when the pistons changed fluid motion direction and the lack of feedback control to improve system accuracy.

Eriksson et al. [85] proposed the use of a progressive cavity pump for replicating cardiac flow conditions. This pump was driven by a servo motor to mimic arterial physiological
waveforms. Their system was able to pump the working fluid in a gentle manner and without fluid sedimentation, making it suitable for biological working fluids. Also, the pump was able to produce negative and positive flow directions without the use of valves. However, the significant limitation of this setup was that the pump required a high operating torque, a custom stand-alone controller, and the cost for the progressive cavity pump.

Petersen et al. [62] used two variable speed gear pumps to recreate physiological flow behavior. The flow motion was controlled through computer-controlled valves. However, the system was affected by valve control errors due to the lack of controller feedback.

Tsai and Savas [58] used a combination of a piston pump in series with a gear pump to produce a pulsatile and a steady flow. This system was capable of negative flow reproduction and allowed for commercial packages implementation such as MATLAB and LabVIEW for waveform signal generation. The limitations of the setup were that the system lacked for flow feedback correction, and the voltage supplied to the pump for control required careful and precise fine-tuning. Also, the pump combination generated flow disturbances, making it difficult to be used on different flow loops where fluid impedance could be different.

Chaudhury et al. [61] presented a computer-controlled piston pump capable of generating high flow rates with little turbulence. The pump used an electric cylinder as an actuator for the piston and a smoothly contracted asymmetric pump head for fluid motion. The major limitation of the design was that it did not allow for continuous non-zero flow output as the piston must be pulled back at the end of each stroke. Therefore, waveforms with an important backflow component were challenging to be reproduced due to negative pressure accumulation. Furthermore, the system lacked a feedback control loop for a better waveform matching generation.

Similarly, Chodzyński et al. [86] designed an in vitro test bench capable of replicating pulsatile flows using a gear pump in conjunction with a piston pump. The system relied on
proportional-integral-derivative (PID) controllers to accurately replicate transient flow conditions. Furthermore, the system used a PID controller for temperature control of the working fluid to model physiological temperature levels. The main limitations of Chodzyński's system were the restricted flow rate range of 40 to 700 ml/min and the hardware requirements for feedback control (CompactRIO NI9024), which made the setup expensive.

Recently, Mechoor et al. [81] presented a fully programmable pump capable of reproducing custom physiological waveforms. The pumping system consisted of a servo motor-gear pump combination that allowed the implementation of commercial software to add pump programmability and automation in a compatible manner. The system included a closed feedback algorithm from the generated flow to the servo motor, which improved pulsatile waveform accuracy even for flow waveforms containing backflow and high oscillations. The major limitation for this setup, as stated by the author, was that the feedback algorithm “induced distortion of the control waveform due to an addition of sensor noise” [81], which limited the flow waveform generation accuracy for flowrates higher than 170 ml/s.

Overall both in-house-built and commercial setups have different limitations and therefore different accuracies, however the standard in regards of accuracy for the in-house-built setups ranges from ±1% to ±15% [60]–[62], [74]–[76], [85], [86] and from ±2% to ±4% for commercial setups [74], [87].

Table 3-1 displays a summary of previous studies for the development of pulsatile pumps and experimental setups for physiological waveform replication.
Table 3-1: Technologies and limitations for different in-house developed experimental setups.

<table>
<thead>
<tr>
<th>Authors</th>
<th>Technology</th>
<th>Maximum Flowrate</th>
<th>Limitation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Segers et al. [57].</td>
<td>Piston Pump</td>
<td>30 mL/s</td>
<td>Required a replica of the arterial tree</td>
</tr>
<tr>
<td>Law et al. [83].</td>
<td>Roller pump – stepper motor</td>
<td>Determined by tubing diameter</td>
<td>Replicates flow waveforms under non-physiological pressure conditions</td>
</tr>
<tr>
<td>Frayne et al. and Holdsworth et al. [76], [84].</td>
<td>Double piston pump piston - stepper motor</td>
<td>30 mL/s</td>
<td>No feedback control implementation</td>
</tr>
<tr>
<td>Eriksson et al. [85].</td>
<td>Cavity pump</td>
<td>250mL/s</td>
<td>Impossibility of system integration.</td>
</tr>
<tr>
<td>Petersen et al. [62].</td>
<td>A dual gear pump system</td>
<td>250mL/s</td>
<td>Valve control inaccuracy</td>
</tr>
<tr>
<td>Hoskins et al. [60].</td>
<td>Signal controlled gear pump-servomotor</td>
<td>&lt;20 mL/s</td>
<td>No feedback control stability Limited flowrate &lt;20ml/s</td>
</tr>
<tr>
<td>Tsai and Savas. [58].</td>
<td>Gear–piston pumping system</td>
<td>300mL/s</td>
<td>Pump combination generated flow disturbances</td>
</tr>
<tr>
<td>Chaudhury et al. [61].</td>
<td>Piston pump</td>
<td>850mL/s</td>
<td>Waveforms with a high backflow component cannot be replicated</td>
</tr>
<tr>
<td>Chodzyński et al. [86].</td>
<td>Gear–piston pumping system</td>
<td>12mL/s</td>
<td>Limited flowrate operation range Costly control hardware</td>
</tr>
<tr>
<td>Mechoor et al. [81].</td>
<td>Servo motor – Gear pump</td>
<td>170 mL/s</td>
<td>Sensor noise accumulation</td>
</tr>
</tbody>
</table>
3.1.4 The rationale for *In vitro* Experimentation

The study of pathogenesis and progression of abdominal aortic aneurysm (AAA) has been a multidisciplinary effort since the processes involved in AAA are complex, involving multiple factors related to the structural remodeling of the arterial wall. Since AAAs are usually asymptomatic, which prevents the rupture from occurring with "prior warning," any effort that is made to study aneurysms is valuable.

Recently, many studies have used computational models to study abdominal aneurysm hemodynamics and wall rupture [27], [79], [88]–[91]. These models permit to recreate the biomechanical properties found in the arterial wall as well as to accurately recreate the flow conditions found within the aneurysm. On the other hand, *In vivo* experiments are conducted because the biological cardiovascular characteristics are entirely represented; however, these studies represent a high economic cost as well as ethical considerations due to animal usage [92].

Hence, *in vitro* experimentation is particularly useful in cardiovascular research because such experiments emulate in-vivo conditions. *In vitro* studies usually require a circulatory mock loop model where physiological flow and pressure conditions are replicated, an anatomical phantom which can be manufactured from rigid or compliant materials, a blood mimicking fluid, and a flow measurement system [22], [24]–[30]. *In vitro* experimental studies also provide a validation source for computational studies where more variables that are difficult to measure experimentally and clinically can be calculated, such as blood flow velocities and arterial wall stresses.

Therefore, to build an in vitro setup capable of mimicking aortic flow conditions such as the ones found in abdominal aneurysms, we decided to base our development on improving the experimental setup presented by Mechoor *et al.* [81]. This setup was chosen since it represents the most updated state-of-art published work, it is a low-cost system, it has the capacity of
implementing commercial software such as LabVIEW and MATLAB, and it has been validated for replicating physiological flow conditions found in the abdominal aorta.

In this work, we focused on the improvement of Mechoor’s system by refining the feedback control and expanding the flow loop test section.

3.2 Methods

In the design of the experimental setup capable of replicating aortic aneurysm hemodynamics, an extensive list of hardware was required. The essential elements for the construction of such setups were pressure transducers, flowmeters, valves, blood-mimicking fluid, piping, and compliance calculations. In the following section, a detailed description of the components used for this work will be presented.

3.2.1 Experimental Setup

3.2.1.1 Flow Loop

The experimental setup consisted of a pumping section, a test section, which had the function of placing different anatomical phantoms to be studied, and a reservoir tank where the fluid is heated and supplied to the flow circuit. The setup was designed in a modular fashion to make easier its future modification and implementation of new features.

A schematic of the experimental setup and its major components are shown in Figure 3-2. The flow circuit started with a 7 liter reservoir filled with a blood mimicking fluid which was heated by a precision heater (Anova A2.2, Anova Inc, California, USA), placed within the reservoir, to maintain a physiological temperature condition of 37°C. Throughout the flow loop, the working fluid circulated through clear High-Flex Tygon tubing (McMaster-Carr, Georgia, USA) with an inner diameter of d=25.4 mm, a shore hardness of 55A and wall thickness of 1.587 mm.
Pulsatile flow motion was produced by a gear pump (Dayton 4KHH8, Grainger, Inc., Illinois USA) with a maximum flowrate output of 300 ml/s. The gear pump was driven by a servo motor (AKM42E-ANCNC-00, Kollmorgen Corporation, Virginia, USA) that required a voltage signal ranging from 0-10V to generate different flowrates. Downstream the pump, a mechanical aortic heart valve (LivaNova, British Columbia, Canada) was placed to prevent backflow to the pump during fluid displacement. The total distance from the pump output to the testing section is 100 tubing diameters to allow the flow to fully develop [18].

![Diagram of experimental setup with components labeled](image)

**Figure 3-2:** Experimental setup schematic with components labeled

The vascular resistance to blood flow (exerted by arteries geometrical characteristics) and compliance (generated due to the vascular tone of large arteries) was defined based on a three-element-Windkessel model [93]. The Windkessel model is used to describe the relationship between blood pressure to blood flow, and it allows characterizing the arterial system in terms of parameters such as compliance and peripheral resistance.

The resistance to blood flow was achieved by using a proximal restrictor valve, a compliance chamber, and a distal restrictor valve. The compliance chamber was constructed
from Acrylic (Pexiglass®) and confined a specified volume of air to serve as compliance and damper to the flow motion in order to replicate realistic physiological pressure waveforms [30]. Manual tuning of compliance and resistance was performed after system calibration.

In the test section, a custom-made silicone phantom resembling the geometrical characteristics of the artery to be studied was placed. In our setup, after performing the testing and calibration to the system, a flexible silicone phantom was built similar in size to the abdominal aorta in the infrarenal location, presenting a saccular aneurysm.

Finally, flow rate and pressure signals were measured throughout the flow loop by an electromagnetic square wave flowmeter (FM501, Carolina Medical Electronics, North Carolina, USA) and by two pressure transducers (Argon DTX Plus, Argon Medical Devices Inc; Texas, USA) and a dual-channel pressure control unit which served as signal filtering and amplification (Millar PCU-2000, Millar Inc; Texas, USA).

Figure 3-3: Top view photograph of the experimental setup
3.2.1.2 Working Fluid

The circulating fluid was a water-glycerol mix (40.9% and 59.1% by weight) based on the work presented by Bouillot et al. [94], heated at 37°C to maintain physiological temperature conditions, resulting in a fluid density of 1142 kg/m$^3$ and kinematic viscosity of 4.60 cP. The working fluid viscosity was measured using a commercial rheometer (Kinexus rheometer, Malvern Instruments Ltd., Worcestershire, UK). The manufactured blood mimicking fluid displayed a Newtonian behavior, which is a valid assumption in bigger diameter vessels such as the abdominal aorta [95]. The working fluid was similar to the Newtonian fluids used by previous studies [22], [68]–[70].

3.2.1.3 Test Phantom Manufacturing

The geometry selection of the modeled abdominal artery phantoms was based on the work presented by Vorp et al. [88]. The phantom was modeled after an abdominal artery with an asymmetric aneurysm bulge that included a bifurcation representing the division into the iliac arteries. The phantom geometry is presented in Figure 3-4.

![Figure 3-4: Phantom geometrical dimensions. (a) Anterior and (b) Lateral plane projections](image-url)
The first step of the phantom-manufacture process was designing CAD (Computer-aided design) phantom molds using SolidWorks (SolidWorks®, Dassault Systemes, MA, USA). The molds were then 3D printed using a commercially available 3D printer (Monoprice, CA, USA) and polylactic acid filament (PLA). The 3D printed molds were connected and filled with water-based clay to form a smooth phantom core similar to the one in Figure 3-5

![Image of 3D CAD designed phantom core](image)

**Figure 3-5:** 3D CAD designed phantom core

Subsequently, the phantom core was suspended in plaster to form negative molds that were later filled with soft silicone, Dragon Skin™ FX-Pro™ (Smooth-On Inc., Easton, USA). The Dragonskin silicone has been recently used in the literature to produce artificial organ models, vascular geometries, and simulators due to its elastic properties [96]–[98], making it suitable for compliant models. A constant phantom wall thickness (2mm) was attempted. Figure 3-6 displays a picture of the plaster molds and the manufactured phantom.

![Image of plaster molds and manufactured AAA silicone phantom](image)

**Figure 3-6:** a) Plaster molds and; b) Manufactured AAA silicone phantom
The final manufactured phantom preserved the geometrical dimensions presented in Figure 3-4 and displayed a smooth surface at the inner and a rough surface at the outer layer of the phantom. The thickness of the phantom varied (2-3 mm) across the phantom being the bulge region, the one with the largest thickness of 5.8 mm. The thickness variation is explained since the silicone was not entirely distributed uniformly across the mold and the phantom core.

The test phantom created in this study served for evaluating the setup at incorporating anatomical phantoms, in studies where the primary focus is to study a specific region of interest, more careful considerations need to be taken regarding the thickness and quality of the phantom.

![Image of phantom dimensions](image)

**Figure 3-7:** Phantom thickness dimension. (a) Anterior and (b) Lateral plane projections

### 3.2.1.4 System Design

This section deals with the equipment used in the setup, the data acquisition, the control system, and the setup calibration. A more detailed explanation regarding the system calibration is presented in Appendix A.
3.2.1.4.1 System Instrumentation

The instrumentation used in the experimental setup is as follows:

- Argon DTX Plus Disposable pressure transducers (operating pressure range from -50 to 300 mmHg; sensitivity of 5.0 µV/V/mmHg ± 1%; hysteresis and nonlinearity of ±2% and sensor frequency response of 1200 Hz) and a Millar PCU-2000 pressure control unit which served as a signal conditioner and power source for each transducer.

- An electromagnetic flowmeter (FM501, Carolina Medical Electronics, North Carolina, USA), which can measure a range of 5mL/min to 19.99 L/min with ±1% non-linearity and accuracy of ±5%.

- A servo drive (AKD-P00306-NBAN-0000, Kollmorgen Corporation, Virginia, USA), which provided power and control to a servo motor. The driver was able to receive analog voltage signals, which can serve as inputs to the servo driver. The servo driver communicated with the motor using the Kollmorgen’s motion control software.

- A multifunctional NI USB-6215 DAQ module (National Instruments, Texas, USA) with 16-Bit resolution and data transmission speed of 400 kS/s were used for signal generation. The analog voltage output of this DAQ was connected to the servo driver to produce the pump motion.

- The data acquisition was performed by the NI USB-9205 DAQ module (National Instruments, Texas, USA). This DAQ module has 16-Bit resolution and can receive analog input voltage signals of ±10 V at a speed of 250 kS/s. All the sensors were connected to analog voltage input pins, where pressure and flow data were transmitted to the computer and processed with LabVIEW. All the signal control and data acquisition were done using LabVIEW software (2018 version).
3.2.1.4.2 Data Acquisition and System Control

This section deals with the materials, procedures, and results obtained in the implementation of the experimental setup, data acquisition, and the control system. As previously mentioned, the setup had some elements that were manually controlled and, therefore, they are not considered in this section, namely, resistance, compliance, and the precision heater.

The control system was intended to drive the servo-gear pump via its servo drive operating parameters, and the data acquisition system considered the peripheral instrumentation elements of the setup. Both control and data acquisition systems were implemented primarily through a computational program in LabVIEW (2018).

The program implemented in LabVIEW 2018 was designed to perform: three analog signal inputs, an analog voltage waveform generation, a PID feedback control loop and to load custom flowrate waveforms which are interpreted by the software.

Data acquisition

Two analog input channels were assigned for pressure measurement and control. An analog input was used to record signals from the flowmeter, and a control system was used to allow for the correct voltage waveform to be sent to the servo driver.

Two program-specific modules were used to calibrate the pressure transducers (2 analog input signals) and the flowmeter (1 analog input signal), as discussed in the calibration sections of these instruments found in Appendix A. The computed calibration parameters were incorporated into the main LabVIEW code. The acquired analog voltage signals were sampled at 1KHz for all the acquisitions. Signals were filtered by a low-pass filter controlled in LabVIEW. Additionally, signals were also filtered by the pressure control unit and the flowmeter equipment, which consisted of a first-order Butterworth filter of 20Hz.
Using LabVIEW, the waveform signals were associated with a 100-element median filter to reduce signal noise. The program allowed the visualization in real-time of the measured pressure and flow waveforms as well as an option to save the acquisition data to a text file.

**Control Strategy**

Since the motor driver controlled the servo motor through the received analog voltage input, the easiest way to control the pump motion was to modulate the voltage signal sent to the servo motor driver. This signal was controlled by a DAQ module (as a signal generator), then the generated signal was feedback-controlled using the PID (proportional–integral–derivative) technique, in conjunction with a feed-forward controller. In this way, our controller was more robust, allowing forward control of disturbances that might appear in the system.

The controller regulated the pulse and flow according to parameters and data captured with the DAQ module. The control scheme is presented in Figure 3-7 where $H(s)$ represents the system transfer function, $Y(s)$ the output function, $R(s)$ the prescribed setpoint waveform, and $u_{ff}$ the feed-forward signal.

![Figure 3-8: Control Structure](image)

In our experimental setup, the flowrate voltage signal acquired by the flowmeter was used as feedback for pump-motion control. To establish a control criterion, the difference between the prescribed flow waveform to be replicated, and the measured waveform at the
pump’s outlet was computed. Equation (3-1) represents the difference between the prescribed flowrate waveform (\(v_p\)) and the measured flowrate (\(v_m\)) waveform in terms of voltage. This equation allowed calculating the difference at each time step of the flow waveform to be replicated against the actual value measured by the flowmeter.

\[
e(t) = v_p(t) - v_m(t) \tag{3-1}
\]

After the difference between the measured and prescribed signals was calculated, the result was then computed using the PID equation (3-2), named as \(V_{pump}\). This equation allowed to calculate the voltage to be sent to the pump, taking into consideration the proportional (\(K_p\)), integral (\(K_i\)) and derivative (\(K_d\)) PID gains.

\[
V_{pump}(t) = K_p e(t) + K_i \int_0^t e(\tau) d\tau + K_d \frac{de(t)}{dt} \tag{3-2}
\]

For the PID controller to work correctly, the custom flow waveform to be replicated was loaded into LabVIEW either by inputting a time-step array, an equation (reconstructed Fourier series), or .txt file containing the time and flowrate values. Once the data was entered into LabVIEW, it was converted to voltage units, a new reference flowrate waveform was generated and was sent directly to the servo-pump to produce the prescribed flow waveform.

PID gains were firstly tuned using LabVIEW autotuning functions. This feature generated PID coefficients for the system, given an input and output signal based on the Ziegler-Nichols method. From this operation, arbitrary gain values were derived. Secondly, after self-tuning, a representative abdominal aorta flowrate waveform was used as a reference signal to perform a simple manual tuning. Manual tuning was carried carefully by keeping a constant integral and proportional gains, and gradually varying the integral gain until the measured flowrate matched the prescribed waveform with negligible overshoot. Then the derivative gain was varied until the higher frequency oscillations damped. Finally, the proportional gain was adjusted to maintain system stability.
To make our controller more precise, system identification was performed by using LabVIEW prebuilt system identification toolkit. The system identification allowed to estimate a transfer function (mathematical model) of the system by prescribing a different stimulus and numerically analyzing its response. Step functions with variable amplitudes were prescribed to the system, and according to the response a linear dynamic response is generated. The obtained transfer function showed a higher-order system represented by the transfer function structure shown in equation (3-3).

\[
H(s) = \frac{\alpha \cdot \omega_0^2}{(s + \alpha)(s^2 + 2\zeta\omega_0 s + \omega_0^2)}
\]

(3-3)

Where \( \zeta \) is a damping factor, \( \omega_0 \) is the undamped natural frequency and \( \alpha \) the poles of the system.

The mathematical model obtained allowed the feed-forward signal (\( u_{ff} \)) to be computed by performing the inverse transform of the system’s transfer function [80], [99], [100]. The feed-forward controller allows rejecting the disturbances inherent in the system. Usually, the feedforward controller is measuring disturbances constantly and correcting the disturbances in the system; to do so, commonly a sensor is assigned for the measuring of the disturbances. In this way, the system becomes open loop. Another way to reject the disturbances is to invert the mathematical model of the system [99], [100]. In this manner the feed-forward is predicting the setpoint changes before they occur.

When used in conjunction with a feedback controller, the feedback controller maintains systems stability and improves error rejection, while the feed-forward controller improves tracking performance. In the control strategy selected, the feed-forward signal (\( u_{ff} \)) which is a suitable proportion of the prescribed setpoint waveform (\( v_p \)) is computed. The final controlled voltage signal provided to the servo motor is, therefore, the sum of \( V_{pump} \) and \( u_{ff} \).
3.2.2 System Performance Assessment

After performing the system calibration, the experimental setup performance was evaluated in two different scenarios. Two clinically obtained abdominal aortic flow rate waveforms were used, one represented a resting condition (heart rate 73 bpm) and the other an exercise condition (heart rate 110 bpm)[101]. The flowrate waveforms are illustrated in Figure 3-8.

![Flow Rate Waveform](image)

**Figure 3-9:** Representative Flowrate waveforms obtained from [101]. (a) Resting condition and (b) Exercise Conditions

The flowrate waveform representing an exercise condition served to assess the system performance when a high flowrate waveform was prescribed. The flowrate waveform involving a resting condition served to test the system for waveforms with a backflow component as well as rapidly decelerating.

Flowrate waveforms were acquired after the 5th cycle to have cycle to cycle uniformity and feedback control stability. A total of 30 waveforms were acquired and averaged to compare the flow rate error between the prescribed waveform and measured waveform. Experiments were conducted using the custom-made working fluid presented in section 3.2.1.2 in
conjunction with 500 mg of salt to ensure the proper functioning of the electromagnetic flowmeter. Furthermore, the experiments were performed using two kinds of tubing material for the testing section, Tygon (High-Flex) tubing, and flexible silicone tubing. This design was used to determine if there was a significant effect on the pressure and flowrate waveform magnitude and phase due to the tubing material.

To assess how the system behaved when a silicone compliant phantom representing an abdominal aortic aneurysm was placed in the flow loop, flowrate and pressure measurements were performed. The incorporation of the silicone abdominal aneurysm phantom served as a verification approach to our system capability of incorporating anatomical phantoms in the testing section as well as to verify that our system was capable of replicating the flow conditions found in an AAA.

### 3.3 Results and Discussion

The results obtained by testing the setup at replicating physiological flow and pressure conditions in the abdominal aorta are presented in this section.

Figure 3-9 (a) presents the error plot of 30 acquired physiological flowrate waveforms against the reference prescribed waveform to be reproduced. The cycle to cycle measured waveforms were almost identical to the prescribed waveforms, implying that system accuracy was high. Quantitively, the measured waveforms differed from the prescribed waveform within a 2% range and with an overall coefficient of determination \((R^2)\) greater than 0.998 for the averaged 30 waveforms. The measured pressure waveform and an error plot representing the acquired 30 pressure samples are presented in Figure 3-9(b). The pressure waveforms were within the physiological range of 80 mmHg – 120 mmHg and displayed a normalized RMS (root-mean-squared) error of 4.23%. The variability in pressure was expected since the PID controller was set to only track and control the flowrate waveform.
Figure 3-10 (a-b) displays the acquired flowrate (peak flowrate 115 ml/s) and pressure waveforms (80-120 mmHg) for a resting condition, a flowrate waveform with a backflow component. These figures present one cycle acquired waveform after the 5th cardiac cycle where the PID controller is expected to have achieved stability.

**Figure 3-10:** (a) Error bars showing the difference between the prescribed flowrate (shown in blue line) and the measured flowrate waveform. (b) Error bars showing the difference between the reference pressure waveform (shown in red line) and the measured pressure waveforms.
Figure 3-11: Measured flowrate (a) and pressure waveforms (b) corresponding to a resting condition using two tubing materials, High-Flex Tygon and Flexible Silicone. Prescribed flowrate waveform (shown with dark blue line) and measured the pressure waveform (dark blue line).

Two different tubing materials with different elastic properties were used in the setup to determine if there was a significant effect on the waveform magnitude and phase, especially in the pressure waveform since the PID controller would only adjust each cycle to the pump’s output flow rate waveform.

Results showed that the flowrate waveform reproduction was accurate when flexible silicone tubing is implemented in the setup, showing almost negligible time-shifting between the desired waveform and the prescribed one (blue line). The RMS error integrated across the period is 2.07%, with an $R^2$ value of 0.989. In contrast, the Tygon tubing showed a time-shifted waveform (27 ms), an RMS error of 2.13% and $R^2$ value of 0.981.

Figure 3-10 (b) shows that there is a more significant difference between the pressure waveforms when using the compliant tubing instead of the rigid tubing. The waveform shape acquired from the Tygon tubing presented some degree of distortion in contrast to the reference pressure waveform with an RMS error of 6.13%. The waveform obtained from the
flexible silicone, on the other hand, showed that the pressure waveform presented a similar shape to the reference waveform but with higher amplitude overall and an RMS error of 5.57%. A higher magnitude waveform could be explained by the expansion of the silicone tubing when the pressure wave propagates through the tubing, implying that the tubing material affected the system’s compliance as previously presumed by Holdsworth et al. [76], [84].

Figure 3-11 (a-b) presents the flowrate and the pressure waveforms corresponding to an exercise condition [101]. A higher flow rate (peak flowrate 220 ml/s) was implemented, as shown in Figure 3-11 (a). In return, the controller reacted quickly and accurately to the sudden acceleration and deacceleration in each cycle.

The results showed good agreement between the prescribed flowrate waveform and the waveforms acquired using both Tygon tubing and flexible silicone tubing. Both waveforms showed a minimal time shift between them. The flowrate waveform was replicated accurately for both tubing cases during early systole (0s-0.1s). However, after peak systole and at the beginning of diastole the measured waveforms were different compared with the desired flowrate waveform. The flexible silicone waveform showed an RMS error of 2.24% with an R² value of 0.971, and the Tygon tubing presented an RMS error of 2.39% and R² value of 0.976.

The measured pressure waveforms presented in Figure 3-11 (b) showed good agreement with the reference pressure waveform. Tygon tubing showed a lower amplitude waveform in contrast to the flexible silicone tubing that presented a higher amplitude waveform. The waveform shape showed almost an identical shape compared to the reference one. A possible explanation for this could be the reduced oscillation presented in the waveform in contrast to the multiple oscillations presented for the resting condition waveform. The flexible silicone pressure waveform had an RMS error of 2.97% with an R² value of 0.969. And the Tygon tubing presented an RMS error of 2.75% and R² value of 0.974.
The prescribed peak flowrates, occurring during peak systole at around 0.29 s, were always higher for both exercise and resting conditions in comparison to the measured waveforms. That would imply that the system was able to avoid system overshooting, making it suitable to replicate a high range of physiological waveforms.

*Figure 3-12:* Measured flowrate (a) and pressure waveforms (b) corresponding to an exercise condition using two tubing materials, High-Flex Tygon and Flexible Silicone. Prescribed flowrate (shown with dark blue line) and reference pressure waveform (dark blue line).

Results incorporating the AAA silicone phantom in the flow loop are shown in Figure 3-12 (a-b). The flow and the pressure waveforms were acquired at three different locations, at the phantom inlet (Inlet), which represented the abdominal aorta conduit, at the two phantom outlets, which represented the infrarenal arteries (I1 and I2). The results presented are the average of 30 measured waveforms.

The acquired flow rate waveforms were almost overlapping with the reference waveforms for both the inlet and outlet sections, with an RMS error of 1.64% for the inlet section, 1.86% for I1, and 1.81% for I2. The pressure waveforms showed an RMS error of 6.12% for the inlet section, 4.37%, and 4.13% for I1 and I2, respectively.
These results showed that the current setup could incorporate anatomical phantoms with minimal accuracy deviation on the physiological waveform to be replicated while maintaining physiological conditions such as pressure range, blood mimicking fluid, variable flow rate (based on cardiac output) and arterial compliance.

The current system had a better performance than the previous experimental setups due to the incorporation of feedback and feed-forward controller. For example, Frayne et al.[76] measured an RMS deviation of 7% in their setup when reproducing a carotid waveform with a limited flow rate of 15 ml/s.

Tsai and Savas found that their system was susceptible to the impedance present in the system with an RMS error varying between 3%-10% depending on the waveform to replicate, with a maximum flow rate of 300 ml/s. This variation could be minimized by implementing a PID feedback system as we presented in our methods section.

Mechoor et al. [81] implemented a semi-real time iterative feedback algorithm, which reduced error in each iteration. After the 7th feedback iteration, it measured a normalized RMS deviation of 3.4%. However, it was found that even though the feedback algorithm improved accuracy after several iterations, it also distorted the waveform replication due to the sensor noise accumulation and disturbances. This limitation was minimized in our setup by implementing a feed-forward control, which accounted for sensor disturbances as well as by applying optimal signal noise filtering techniques.

The feedforward controller in conjunction with the PID feedback controller represented an improvement compared to the current commercially available setups such as the Vivitro Pulse Duplicator system® and the Harvard Pump, as well as the existent setups found in the literature where usually an iterative controller was used or only a PID controller was implemented. Furthermore, system accuracy can be increased by implementing a PID gain scheduling technique, as recently proposed by Reza et al.[73]. Gain scheduling allows dividing
the physiological waveform to replicate into different segments to optimize PID gains for each section. For example, since rapid acceleration is needed in the onset of systole; specific gains can be selected to achieve accurate acceleration, instead of applying the same gains to all the waveform segments.

Therefore, the presented setup increased experimental efficiency while maintaining high experimental accuracy thanks to a high-frequency data acquisition system and fast response controller.

Figure 3-13: Measured flowrate (a) and pressure waveforms (b) corresponding to a resting condition and incorporating an abdominal aneurysm silicone phantom in the flow loop testing section. Reference (solid line) and measured (dots) waveforms are presented.
3.4 Limitations

Although in our *in vitro* experimental setup, it was found a good correlation between the prescribed waveform to the measured waveform, further improvements need to be made in order to reduce the error found in the measured waveforms.

Flowrate waveform generation was limited by the pump range of 50 ml/s – 300 ml/s as well as by sensor resolution. Therefore, waveforms with lower flow rates could not be replicated in the current setup, such as the ones found in the cerebral vasculature and carotid waveforms. The transfer function derived for the system was based on a system identification procedure on where step functions were applied to identify the system’s response. Therefore, the controller was not measuring disturbances in real-time and instead relying on the initial setup calibration conditions. Thus, the controller can be improved by continually measuring disturbances. Flow disturbances could be caused by tubing fittings, bends, and material roughness, to name a few.

Furthermore, the developed *in vitro* setup relied on the manual tuning of the compliance present in the system, even though its tuning was minimal it would be necessary to fully automate such process to maintain the same parameters when experiments are being conducted at different time intervals. The compliance chamber automation is a feature that most of the commercial setups lack.

Finally, the presented results should be validated against experimental data that allows visualizing the flow patterns inside the test phantom. A suitable option for this task is to implement PIV measurements in the experimental setup in conjunction with transparent silicone phantoms.
3.5 Conclusion

A fully automated cardiovascular benchtop measuring system was developed to mimic the hemodynamics in different circulatory regions with tunable physiological conditions. The major challenge for current pulse duplicating systems is the adaptability to the change in various anatomical and physiological conditions on demand. Therefore, our automated benchtop system was specifically developed to increase the experimental efficiency while maintaining high experimental accuracy and precision.

The experimental setup was able to replicate cardiac flow and pressure conditions through the use of commercially available components, allowing this system to be implemented and modified for different applications. The current system consisted of a software-controlled servo-gear pump coupled with either a flow or a pressure sensor through a high-frequency data acquisition system and a LabView interface. The main difference between the in vitro setup developed and the other setups, lies in the control system which was based on a PID controller in conjunction with a feed-forward controller, thus allowing the system to reproduce flow and pressure waveforms that represented different physiological conditions.

Compared to commercial setups, our setup can produce waveforms that differ from the prescribed waveform by 2.07\% and has a lower cost. The accomplished accuracy falls under the acceptable accuracy for commercial setups of ±2\% to ±4\% [74], [87].

Compared to the previous in-house-built setups, our setup showed improved performance at replicating physiological conditions with high flow rates and elevated pressures through the use of the controller that accounted for the system’s response time and disturbances.

Our system was tested using different tube materials to analyze the tubing effect on the waveform to be replicated. The results showed that the impact of tube compliance is minimal
for the flowrate waveform. However, it has a more significant impact on the pressure waveform variations.

The present study sets the basis for further experimental studies in aortic aneurysms. Using an \textit{in vitro} system, different cardiac characteristics can be programmed to be replicated in a reliable and low-cost manner, as shown for the abdominal aneurysm verification case.
Chapter 4

Hemodynamics of Cerebral Aneurysm: Computational Study

4.1 Introduction

Intracranial aneurysms (IA’s), also denoted as brain or cerebral aneurysms are cerebrovascular lesions characterized by the weakening and dilation of a localized area of the wall of an intracranial artery [102]; once ruptured an IA may lead to severe disability or death [103]. Bifurcated and sidewall aneurysms are the most usual configurations for IA’s. Bifurcated aneurysms are characterized as aneurysms that occur at a branching point in an artery, while sidewall aneurysms extrude from the sidewall of arteries [47]. Sidewall aneurysms extend off one parent artery, unlike bifurcated saccular aneurysms, which extend off the connecting Y-junction of two-parent arteries [12]. These are types of saccular aneurysms, which are often described as “berry-shaped” and correspond to roughly 90% of aneurysms [37].

Hemodynamics strongly depends on the anatomical configuration, and in turn, hemodynamics affects aneurysm characteristics [45]. Therefore, in this chapter, we investigate the hemodynamics of intracranial sidewalls aneurysms using experimental and computational techniques on different aneurysm geometries. In the next section, a literature review of these techniques is presented. The study presented in this chapter originated from our collaboration with a cardiovascular medical device company that specializes in cerebral aneurysm treatment devices. Through this collaboration, the effectiveness of an existing endovascular stent compared to a novel stent design was investigated.
4.1.1 Computational Studies

Computational Fluid Dynamics (CFD) has been employed in recent years to study hemodynamics; since it allows to study blood flow dynamics and its effect on a variety of cardiac diseases [104]. This versatile and non-invasive technique allows increasing the current knowledge of dynamic and structural conditions of brain flow. CFD simulates the conditions produced when a change in the anatomy of the blood vessels takes place. Likewise, it can be used for studying intracranial aneurysms and its mechanism of rupture [105]. CFD simulations in 2D and 3D, based on finite elements for non-Newtonian and Newtonian pulsating blood flow on sidewall aneurysms, were firstly developed by Perktold, Low, and others [106].

In previous computational hemodynamic simulations of intracranial aneurysms, blood was usually considered as a Newtonian fluid [31]–[33]. In these simulations, several assumptions were made. First, it was assumed that the wall of the blood vessel was rigid; second, it was assumed that the inlet-velocity boundary conditions applied were known; Finally, it was assumed that the pressure at the outlet was constant [33]. In other studies, blood was considered as a non-Newtonian fluid, displaying the characteristic shear thin behavior of blood [107], [108]. Some authors have compared both models and concluded that non-Newtonian models could deliver similar results to Newtonian models on giant (25mm) aneurysms [109]. Likewise, the effect of the properties of blood modeled by a non-Newtonian fluid on wall shear stress (WSS) is significant only in arterial regions with high-velocity gradient [31], or in regions with relatively low velocities such as saccular sidewall aneurysms [33].

Cebral et al. and Castro et al. [109], [110] performed sidewall aneurysm studies where they analyzed blood flow as both Newtonian fluid and non-Newtonian fluid, in order to find the differences. Rays et al. [110] confirmed the effects of slow recirculation flow regions on the initiation and progression of thrombosis. Slow recirculation flows can lead to long residence times and result in the transfer of endangered mass, causing blood to clot. Pulsatility also has
an essential effect on flow patterns; it can induce changes in the recirculation regions during the cardiac cycle.

Xiang et al. [111] showed that assuming the blood as Newtonian can minimize the viscosity effect and overestimate the shear rate and wall shear stress in slow recirculation zones with secondary vortices, usually in the dome of elongated saccular aneurysms or those of complex shape.

Baharoglu et al. [112] sought to evaluate distinguishing morphometric features between ruptured and unruptured intracranial sidewall aneurysms by adjusting the inflow angle in idealized CFD cases. In Baharoglu’s study, it was found that the inlet angle of a ruptured sidewall aneurysm was larger than the unruptured one. Using CFD techniques, by adjusting the inflow angle from 60° to 140° in 10° increments (and maintaining all the other parameters constant), the authors also found that there was a deeper progression of the flow velocity jet into the aneurysm with increasing angle.

Wang et al. [108] conducted a purely computational analysis of sidewall and bifurcated intracranial aneurysms before and after stent placement. They created idealized CAD models, used the Carreau Yasuda blood model, and a flow rate profile that varied based on cardiac output. The vessel wall was considered rigid with no deformation, the inflow rate was based on a cardiac output model, and there was no pressure at the outlet. In the unstented sidewall case, they found that the flow impinging on the distal aneurysm region created an anticlockwise vortex. In the stented sidewall case, less blood flow entered into the aneurysm sac and resulted in a more significant stagnation section.

Furthermore, due to the complexity of the flow patterns within the aneurysm sac and the simplifying assumptions in CFD simulations, an *in vitro* experimental validation is required to assess the constraints and precision of CFD modeling. Therefore, *in vitro* experimental studies including flow visualization techniques such as ink injection, plastic particles with laser light
sheets, laser-Doppler velocimetry (LDV), particle tracking, and particle image velocimetry (PTV/PIV) [113], [114], have been performed.

Numerical and experimental studies are usually run in parallel by implementing simplified aneurysm models. These models are used in the numerical virtual environment as 3D CAD models and physically as phantoms manufactured from glass, acrylic, or silicone.

In conclusion, the literature review highlights that, since hemodynamics may have a significant impact on both the cerebral aneurysms rupture and treatment efficacy, precise experimental investigations of the flow correlated with the clinical outcomes are required. In most of the previous studies of cerebral aneurysms, the flow dynamics have been analyzed using both experimental and computational modeling.

Therefore, the current study focuses on developing CFD simulations capable of modeling cerebral circulation flow conditions, which will allow us to conduct study different hemodynamic parameters on intracranial aneurysm models.

To investigate the influence of different anatomical configurations, artificial aneurysm models are built based on the common aneurysm conditions, as reported in the literature. Different morphological aneurysm configurations were tested, allowing the assessment of geometrical configuration on intra-aneurysmal hemodynamics. The selected cerebral aneurysm cases are compiled using CAD software.

To investigate the effects of Newtonian vs. non-Newtonian blood analog fluids in intracranial aneurysm hemodynamics, simulations are conducted using Newtonian and non-Newtonian blood mimicking fluids. The study assesses the hemodynamic changes when using both working fluids in different aneurysm cases, including an aneurysm case treated with stent device.

Finally, the results from the CFD simulations are presented, focusing on analyzing the intra aneurysmal blood flow velocity.
4.2 Methods

The literature review offered a broad overview of the diverse methods implemented by different authors for the study of sidewall aneurysms. This section describes the current methods used to construct and verify the numerical simulations. Additionally, a section addressing the boundary conditions and parameters used in the CFD simulation is also presented.

4.2.1 Intracranial Aneurysm Morphological Characteristics

The different characteristics of aneurysm geometry and their influence on aneurysm rupture have been widely studied in the literature. To date, it is well known that aneurysm size, [115], shape [116], aspect ratio (AR) [7], [117], size ratio (SR) [118], parent vessel size, and inflow angle [7] have an essential role in aneurysm rupture. A large body of literature has focused on describing aneurysm size influence in rupture incidents; however, the correlation between IA size and rupture potential has yet to be explained [119], [120]. On the other hand, several research groups have shown the relevance of aneurysm shape, and it has been found that specific shape parameters have a more significant association with the rupture than aneurysm size [119]–[121]. The aspect ratio (AR), which is defined as the aneurysm height divided by the neck diameter, and the aneurysm inflow angle has been considered to have a significant effect on hemodynamics. Different parameters are added in each new study to characterize their impact on aneurysm hemodynamics[117]. The most common morphological parameters specified for sidewall aneurysms are displayed in Figure 4-1.
Figure 4-1: Schematic representation of the morphological parameters of the aneurysm with their definitions.

4.2.2 Computational Models

The ideal intracranial aneurysm (IA) anatomical parameters that were selected in this study are based on the published data by Dhar et al. [117]. Dhar et al. obtained angiography images of 45 patients suffering from saccular sidewall and terminal aneurysms located at the internal carotid artery and monitored the aneurysmal progression for two years. Geometry measurements on the aneurysm configurations and parent vessels were performed during three-month intervals. The geometries of the intracranial aneurysms were then 3D reconstructed to study different morphological parameters and to perform statistical analysis. From a total of 29 sidewall aneurysms, 14 remain unruptured during the study and 15 ruptured. A summary of the results of the statistical analysis performed by Dhar et al. is presented in Table 4-1.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Ruptured mean</th>
<th>Unruptured mean</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aneurysm size</td>
<td>5.5 ± 1.9</td>
<td>5.1 ± 2.3</td>
<td>0.46</td>
</tr>
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<td>Aspect ratio</td>
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<td>1.2 ± 0.55</td>
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</tr>
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<td>$\theta_A$</td>
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<td>88° ± 24°</td>
<td>0.036</td>
</tr>
<tr>
<td>Size ratio</td>
<td>2.8 ± 1.6</td>
<td>1.8 ± 0.84</td>
<td>0.0002</td>
</tr>
</tbody>
</table>
Based on the data obtained from Dhar et al. [117] the geometric models of idealized sidewall-type saccular aneurysm were created. The geometric model was based on the internal carotid artery morphology since this is one of the most frequent sites for sidewall aneurysm [47], and it is a common location that is treated with stent-like devices such as the flow diverters [122].

A total of four cases were considered. Case 1 was based on the mean values of ruptured aneurysms; Case 2 was based on the mean values of unruptured aneurysms, and; Case 3 was based on the upper values from the ruptured aneurysm cases as reported in Table 4-1.

The rationale for selecting different cases relies on the idea that due to the different geometrical configurations, the hemodynamics of each case should be altered. The parameters used for the three cases are presented in Table 4-2.

Table 4-2: Morphological parameters used for the different sidewall aneurysm cases.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Case 1</th>
<th>Case 2</th>
<th>Case 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aneurysm size</td>
<td>5.5</td>
<td>5.1</td>
<td>6.4</td>
</tr>
<tr>
<td>Aspect ratio</td>
<td>1.5</td>
<td>1.2</td>
<td>1.95</td>
</tr>
<tr>
<td>$\theta_A$</td>
<td>118°</td>
<td>88°</td>
<td>139°</td>
</tr>
<tr>
<td>Parent artery diameter</td>
<td>4.5 mm</td>
<td>4.5 mm</td>
<td>4.5 mm</td>
</tr>
</tbody>
</table>

Furthermore, Case 4 was added. In this particular geometry, blood flow was studied under two different conditions: with and without stent implantation. This case consisted of a parent artery with a width of 4.5 mm in diameter, a sphere-shaped dome with 6 mm in diameter neck size of 4.5 mm with inflow angle of 90 degrees, and an aspect ratio of 1.10. This case represented a simplified idealized geometry that allowed for a uniform stent deployment and symmetry plane. This is the most simplistic plausible model to be incorporated in the study. A rounded IA with a straight parent artery is commonly used for simulations and experimental validation [17], [52], [94], [123]–[127].
4.2.3 Implanted Device

A stent-like structure, called flow diverter, was virtually implanted in the IA aneurysm model. This type of device is intended to isolate the aneurysmal sac from the parent artery, creating a significant flow alteration at the neck of the aneurysm, decreasing stress in the vascular wall, with subsequent stagnation of blood flow inside the sac aneurysm and its subsequent thrombosis, producing vascular reconstruction [21], [122]

4.2.3.1 Pipeline™ Embolization Device

The Pipeline embolization device (PED) by Chestnut Medical Technologies (Menlo Park, CA) was used in this study. This device is a self-expanding stent, composed of 25% platinum tungsten and 75% cobalt-chromium in 48 interwoven strands.

The PED device has a dense mesh geometry with a very high metallic coverage (30-35% in the inner part of the vessel), and pore sizes ranging from 0.02 to 0.05 mm² [128], [129]. The single-strand filaments measure between 28 and 33um in diameter [130], [131]. Figure 4-2 shows a picture of a characteristic pipeline device.

![Figure 4-2](image)

**Figure 4-2:** The picture of the Pipeline Embolic Device considered in the study. The picture shows the device implanted in a silicone aneurysm phantom filled with the matched refraction index blood mimicking fluid.
4.2.4 Computational Fluid Dynamics Analysis

The simulations of the sidewall cerebral aneurysms were done with COMSOL Multiphysics® (COMSOL Inc., Burlington, MA) software version 5.4. Simulations were performed based on the flow conditions from the Internal Carotid Artery. COMSOL is a finite element based commercial software.

4.2.4.1 Boundary Conditions

To model the blood flow, the built-in CFD module was used for solving the flow governing Navier–Stokes equations. The following conditions were imposed, blood flow was considered as incompressible, pulsatile, and in the laminar region, the aneurysm-model wall was considered rigid, and the no-slip boundary condition was applied at the wall surface. Blood was modeled as Newtonian and Non-Newtonian per case. A steady-state study was performed firstly to obtain better start values for the time-dependent studies, allowing for the computation time to be reduced [132]. After the initial conditions were obtained, the time-dependent studies were performed.

Time-dependent pulsatile flowrate waveform and pressure waveform were applied at the inlet and outlet of the model, respectively. These profiles were obtained from experimental data. Flow at the model inlet was considered as fully developed. Density and viscosity values were similar to those of the experimental working fluids.

Simulations were run for five flow cardiac cycles for solution convergence and transient-independent results [133], [134]. Results from the final cardiac cycles were selected for analysis. A line graph of the corresponding flow inlet velocity and outlet pressure versus time can be found below in Figure 4-3.
Time-dependent studies were conducted for all the different cases using two different blood models, a Newtonian model with a constant dynamic viscosity and a Carreau model with a varying viscosity with the shear rate [135]. This relation is modeled by equation (4-1).

\[
\mu(y') = \mu_\infty + (\mu_0 - \mu_\infty)(1 + (\lambda y')^2)^{(n-1)/2}
\]  

(4-1)

Where \( y' \) is the shear rate, \( \mu_\infty \) is the viscosity at infinite shear-rate, \( \mu_0 \) is the viscosity at zero shear-rate, \( \lambda \) is the relaxation time constant, and \( n \) is the power-law index [135].

CFD simulations frequently implement simplifying assumptions of blood characteristics. One of the assumptions is that blood is a fluid which displays a Newtonian behavior when in large blood-vessels where high shear rates are present [136], [137]. However, within the intraneurysmal sac region, the blood is nearly stagnated, therefore it is dominated by lower magnitude shear rates in contrast to the parent artery. Therefore the non-Newtonian behavior of blood has a more significant impact in this region [111].

For this reason, the current study explored the effects of a non-Newtonian fluid in a sidewall aneurysm. To do so, the experimental data from a Non-Newtonian experimental fluid
was fitted to the Carreau model using the Carreau-model curve fitting function from the commercial software Origin Pro (Version 2019b, OriginLab Corporation, Northampton, MA, USA).

Table 4-3: Values for the parameters of the fluid models

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Newtonian model</th>
<th>Non-Newtonian model</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>λ</td>
<td>0.39</td>
<td>0.39</td>
</tr>
<tr>
<td>μ₀</td>
<td>3.50</td>
<td>13.94</td>
</tr>
<tr>
<td>μ∞</td>
<td>1.23</td>
<td>1.23</td>
</tr>
<tr>
<td>n</td>
<td>0.63</td>
<td>0.63</td>
</tr>
</tbody>
</table>

Figure 4-4: Carreau model fitting to the non-Newtonian working fluid viscosity. Blue dots indicate the experimental viscosity data obtained.

Figure 4-5 renders an example-mesh generated for case 4, an idealized aneurysm geometry. Further details regarding the meshing are discussed in section 4.2.4.3.
4.2.4.2 Flow Diverting Stent

A flow diverter device was modeled to be virtually implanted within the aneurysm. This model was based on the Pipeline device dimensions discussed in section 4.2.3.

A braided stent was created in two steps. Firstly, a total of 48 helices were used to weave the pattern of a flow diverting stent built around the geometrical characteristics of the pipeline embolization device. Two sets of helices: 24 clockwise and 24 anti-clockwise with 1.5 turns and a braiding angle of 75° were created. The wire diameter was 0.030 mm, which is similar to the pipeline embolization. The nominal dimension of the stent was set to 4.5 mm in diameter and 12 mm in length. Secondly, stent implantation was accomplished through the built-in COMSOL Boolean operations [138]. The 3D designed stent was oriented to match the parent artery and wrap it around. Then a Boolean subtraction of the stent and the aneurysm model was executed to eliminate the stent from the aneurysm model domain and produce a single flow domain.
Figure 4-6: (a) 3D model of the braided wire stent. (b) Idealized sidewall aneurysm with flow diverter stent implanted
Figure 4-7: Method for aneurysm-stent model construction.

a) A 3-D solid model is created by performing the union of a solid sphere and solid cylindric model.

b) A solid model of the stent mesh is wrapped around the aneurysm model.

c) The stent is then subtracted from the aneurysm model to produce a single flow domain.

d) A fine mesh is created for the aneurysm-stent model with finer elements on the stent structure.
4.2.4.3 Mesh Convergence Study

To verify the domain discretization independence in the simulations, a mesh convergence study was performed for all the cases.

For all the fluid domains and all the cases, tetrahedral elements were used, since most studies conducted on stent simulations [132], [139], [140] this type of element was used. For the stent model, the software automatically refined the mesh in the stent area.

Blood flow velocity magnitudes at the inlet and outlet middle section during systole onset, peak systole, and diastole after the 5th cardiac cycle were analyzed. Simulations were run using four different predefined mesh sizes: normal, fine, finer, and extra fine. It was found that the finer and extra fine mesh solution converges with a difference within 3%.

Due to the computation time required to run simulations using an extra-fine mesh, especially for the stent case, the finer mesh was selected. Computations for the stent case required a total of 7 days to be completed. The defined element size remained invariant in all cases so that the results obtained only depend on the geometry of the cases, and not on the size of the elements, allowing a consistent comparison between all cases. The number of elements varied in each case ranging from 600,000 for the aneurysm models to 1.5 million elements for the aneurysm-stent case.

4.3 Results and Discussion

The results shown in this section represent selected cases to be analyzed in more detail. Specifically, cases 1 and 3, as well as pre and post stented case 4.

Velocity contour plots are presented to qualitatively analyze the results from the CFD simulations. The plots display the flow velocity at the middle cross-sectional plane of the aneurysm geometry.
CFD simulations enabled to visualize the flow patterns qualitatively for each case. It also allowed to quantitatively measure the hemodynamical changes, namely the impact of the placement of the stent on flow properties.

Different lines of cut-across at the aneurysm are presented to quantify flow velocity across the aneurysm sac. A midline line cutting the aneurysm sac horizontally through the center plane was used. Also, a vertical line from the aneurysm neck to the aneurysm tip through the center was used to assess the velocity distribution at the aneurysm neck surface to the top of the aneurysm. Figure 4-8 shows the lines of cut-across at the aneurysm.

![Figure 4-8](image)

**Figure 4-8**: Lines of cut-across the aneurysm. A midline line cutting the aneurysm sac horizontally (shown as the red line) and a vertical line from the aneurysm neck to the aneurysm tip (shown as the blue line).

Velocity contours and velocity profiles for the selected cases at different time steps of the cardiac cycle are displayed from Figure 4-10 to Figure 4-25. The figures and graphs show the velocity magnitude based on equation (4-2).

\[ |V_i| = \sqrt{u^2 + v^2} \]  \hspace{1cm} (4-2)

Where \( u \) represents the velocity in the \( x \) direction and \( v \) the velocity in the \( y \) direction.

The numerical intra-aneurysmal velocity vectors presented show the blood flow direction, as can be seen on all the figures for the different cases. Also, it can be observed that CFD simulations captured the vortex center moving towards the aneurysmal dome, for all the cases, with a non-stented configuration.

In general, the results of the intra-aneurysmal flow considering a Newtonian fluid are relatively similar in all the cases. For all cases, the flow enters the aneurysm and impacts on
the right wall (distal end), observing a fluid recirculation inside the aneurysm sac, where the magnitude of the velocity decreases as the fluid recirculates through the aneurysm back to the parent artery through the left wall (proximal end), displaying the lowest velocity magnitudes.

During systole, it is observed that the fluid enters with a greater velocity magnitude compared to diastole, so that the fluid reaches the top of the aneurysm dome, producing greater recirculation. This flow behavior is in accordance to previous published CFD simulation results in the literature [20], [32], [109], [110], [140], [141].

In both diastole and systole, there is a decrease in flow velocity when blood is flowing upwards the dome. There are areas of higher velocity in the left and right ends of the aneurysm geometry, obtaining a greater magnitude in the right end due to the fluid entry pattern to the aneurysm. Also, a lower flow velocity zone is generated at the center of aneurysm where recirculation occurs. The flow behavior is similar in diastole and systole; however, the magnitude of the flow velocity in diastole is approximately 50% smaller.

In Case 3, the inflow jet was more dispersive at its tip compared to Case 1 and Case 4. On the other hand, the flow jet at the proximal end of the aneurysm neck plane was the largest in Case 3, although the magnitude gradually decreased from Case 1 to Case 4. Also, by observing the entire flow pattern inside the aneurysm, Case 3 displayed the strongest swirl, even its aneurysm size was the highest among all cases. It also had the lowest neck plane velocity of 0.0954 m/s.

Results considering a non-Newtonian fluid display similar flow patterns to those using a Newtonian fluid in terms of the flow direction. The presence of a main vortex inside the aneurysm, and also the relative size of the inflow and outflow jets for all the cases.

By comparing the Newtonian and non-Newtonian cases, similar to what has been reported in the literature [111], [142], maximum flow velocity, the size of the vortex, and the height of the inflow and outflow jets were all smaller when simulating with the non-Newtonian
fluid model. Therefore, in general, regardless of the fluid models used to simulate the blood flow, the flow patterns would show similar profiles, entering the aneurysm from the distal end of the neck plane, forming a vortex, and then exiting from the proximal end. Despite the different magnitudes of the maximum flow velocities, the underlying trend was the same: an unruptured aneurysm case would display the highest neck plane flow velocity compared to the ruptured cases. Then, differentiating between the two-fluid models, non-Newtonian fluid would provide smaller flow eddies, lower inflow, and outflow jets and smaller maximum flow velocities. The percentage difference between the Newtonian and non-Newtonian at the maximum velocity point during peak systole is 46% for case 1, 55% for case 3, 24% for pre-stented case 4 and 14% for the pos-stented case 4.

Table 4-4: Mean velocity in the aneurysmal sac with Newtonian (N) and non-Newtonian (nN) fluids, CFD comparison.

<table>
<thead>
<tr>
<th>Configuration</th>
<th>Mean velocity in the aneurysmal sac [m/s] x 10^3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case 1</td>
<td>N: 4.73, nN: 2.56</td>
</tr>
<tr>
<td>Case 3</td>
<td>N: 22.13, nN: 9.87</td>
</tr>
<tr>
<td>Pre-stented Case 4</td>
<td>N: 38.04, nN: 28.76</td>
</tr>
<tr>
<td>Post-stented Case 4 (FD)</td>
<td>N: 1.52, nN: 1.30</td>
</tr>
</tbody>
</table>
Figure 4-9: 3D velocity distribution in m/s for different cases (a-d) during peak systole.
Case 1 - Newtonian

Figure 4-10: Case 1 - Newtonian - CFD velocity contours at different cardiac cycle times through the center plane.
Case 1 – Newtonian

Velocity profiles

Figure 4-11: Case 1 - Newtonian - Numerical velocity profiles cutting the aneurysm sac diametrically a) horizontally and b) vertically, passing through the vortex center.
Case 1 - Non-Newtonian

![CFD velocity contours at different cardiac cycle times through the center plane.]

**Figure 4-12:** Case 1 – non-Newtonian - CFD velocity contours at different cardiac cycle times through the center plane.
Case 1 – non-Newtonian

Velocity profiles

Figure 4-13: Case 1 - non-Newtonian - Numerical velocity profiles cutting the aneurysm sac diametrically a) horizontally and b) vertically, passing through the vortex center.
Figure 4-14: Case 3 - Newtonian - CFD velocity contours at different cardiac cycle times through the center plane.
Case 3 – Newtonian

Velocity profiles

Figure 4-15: Case 3 - Newtonian - Numerical velocity profiles cutting the aneurysm sac diametrically a) horizontally and b) vertically, passing through the vortex center.
Case 3 – non-Newtonian

Figure 4-16: Case 3 – non-Newtonian - CFD velocity contours at different cardiac cycle times through the center plane.
Case 3 – non-Newtonian

Velocity profiles

Figure 4-17: Case 3 – non-Newtonian - Numerical velocity profiles cutting the aneurysm sac diametrically

a) horizontally and b) vertically, passing through the vortex center.
Pre-stented Case 4 – Newtonian

Figure 4-18: Pre-stented Case 4 – Newtonian - CFD velocity contours at different cardiac cycle times through the center plane.
Figure 4-19: Pre-Stented Case 4 – Newtonian - Numerical velocity profiles cutting the aneurysm sac diametrically a) horizontally and b) vertically, passing through the vortex center.
Figure 4-20: Pre-stented Case 4 – non-Newtonian - CFD velocity contours at different cardiac cycle times through the center plane.
Pre-stented Case 4 – non-Newtonian

Velocity profiles

Figure 4-21: Pre-Stented Case 4 – non-Newtonian - Numerical velocity profiles cutting the aneurysm sac diametrically a) horizontally and b) vertically, passing through the vortex center.
Figure 4-22: Post-stented Case 4 – Newtonian - CFD velocity contours at different cardiac cycle times through the center plane.
Post-stented Case 4 – Newtonian

Velocity profiles

Figure 4-23: Post-stented Case 4 – Newtonian - Experimental and numerical velocity profiles cutting the aneurysm sac diametrically a) horizontally and b) vertically, passing through the vortex center.
Post-stented Case 4 – non-Newtonian

Figure 4-24: Post-stented Case 4 – non-Newtonian - CFD velocity contours at different cardiac cycle times through the center plane.
Figure 4-25: Post-stented Case 4 – non-Newtonian - Numerical velocity profiles cutting the aneurysm sac diametrically a) horizontally and b) vertically, passing through the vortex center.
The presence of the stent device in post-stented Case 4 modified the flow patterns inside the aneurysm sac by reducing the overall intra-aneurysmal blood flow velocity and the size of the recirculation (Figure 4-22) in comparison with the baseline pre-stented case (Figure 4-18). Also, once the device was implanted, the inflow region to the aneurysm sac was displaced from the distal to the proximal aneurysm region. Previous studies conducted on sidewall-aneurysm models have found comparable results in regards to the flow reduction and the interchange on the aneurysm sac inflow region. [21], [143], [144].

The reduction in flow velocity generated by the stent is almost an order of magnitude, meaning that the device is efficient in reducing flow motion inside the aneurysm sac. Furthermore, in the pre-stented baseline case, most of the blood is recirculated throughout the aneurysm. In the post-stented case, the recirculation of the blood is not completely suppressed due to the stent porosity. However, part of the blood has been diverted to the parent artery. CFD predicted flow patterns for both Newtonian and non-Newtonian fluids, showed that the majority of the blood flowing into the aneurysm sac occurs through the proximal end.

The overall CFD results are in good agreement with other similar numerical results found in the literature [145]–[147].
Figure 4-26: Pre-stented vs Post-stented Case 4 – non-Newtonian - Numerical velocity profiles cutting the aneurysm sac diametrically horizontally, passing through the vortex center at peak systole ($t = 221\text{ms}$)

4.4 Limitations

Although, for the most part, the final results are in agreement with published results, there were some limitations in this study.
Firstly, the sidewall aneurysm geometries and models were created using CAD instead of using a patient-specific model. Furthermore, the geometries used in the CFD computations were mainly straight from the parent artery and almost entirely rounded in the aneurysm dome.

Secondly, in the CFD study, the vessel wall was considered rigid, which is not entirely accurate since the arteries are not rigid. Although this simplification may cause differences between the results of CFD simulation and experimental/clinical data, the critical hemodynamic qualities are considered to be maintained, although, in future work, this consideration could be implemented. Furthermore, since the hemodynamic change produced by the stent depends on its geometry, diameter, parent vessel curvature, and stent deployment location, such characteristics need to be considered in the numerical simulations for more accurate results.

4.5 Conclusion

Cerebral aneurysm hemodynamics influence clinical management and treatment. Therefore, experimental and computational studies are necessary to study cerebral aneurysms also referred to as brain aneurysms or intracranial aneurysms.

A literature review of the studies on cerebral aneurysms was presented. From the different techniques used, computational fluid dynamics (CFD) is particularly useful since it allows for the identification of velocity within the aneurysm domain. Computational models capable to mimic the hemodynamics of cerebral circulation were constructed to study hemodynamics on different aneurysm geometries.

Working fluids, which mimicked blood density and viscosity characteristics were considered in the simulations. The CFD analysis allowed the evaluation of blood flow velocity distributions within the aneurysm sac and it allowed to assess the intra-aneurysm flow changes for a stent device in a control case and three aneurysm cases with different configurations using Newtonian and Non-Newtonian working fluids. It was observed that the stent reduced intra-
aneurysmal flow velocity and motion by almost an order of magnitude. The dominant flow pattern changes occurring after stent implantation were characterized and compared with different untreated aneurysm configurations.

Further improvements need to be implemented to address the limitations of the current study. However, this study served as a good foundation for future studies on cerebral aneurysms.
Chapter 5

Conclusion and Contributions

5.1 Summary

The main objective of the thesis was to study the aneurysm hemodynamics experimentally and numerically. In order to perform in vitro experiments, a new in vitro experimental setup was designed and developed to mimic the hemodynamics for different circulatory regions with tunable physiological conditions. The current automated benchtop system was specifically developed to increase experimental efficiency, and maintain high experimental accuracy and precision compared to commercial systems and existent in-house built setups. To our best knowledge, this setup is the first one to implement a different control design to reproduce pulsatile flow waveforms through the use of a PID-feedforward controller.

The setup performance was assessed by replicating an abdominal aneurysm flow conditions based on clinically obtained blood flow waveforms. Results showed that the current experimental setup is capable of replicating blood flow waveforms under physiological pressure with an error of 2.07% between the prescribed and measured flow waveform.

Since hemodynamics plays an essential role in intracranial aneurysm progression, a numerical simulation analysis was conducted to mimic the cerebral circulation hemodynamics. The simulations were conducted using computational fluid dynamics (CFD) to measure the flow in different sidewall aneurysm models found at the internal carotid artery. Also, the effect that a stent device has on aneurysm hemodynamics was studied in an idealized aneurysm geometry. To mimic the shear-thinning behavior of blood, a non-Newtonian working fluid that exhibited elastic and viscous properties was considered in conjunction with a Newtonian fluid matching
density and viscosity of blood. Computational model verifications were conducted. Similar intra-
aneurysmal flow patterns were found in all the cases studied.

The study also showed that using a Newtonian fluid resulted in overestimated hemodynamic parameters. For example, intra aneurysmal blood velocity in the aneurysmal sac was overestimated compared to the non-Newtonian model, showing that the shear-thinning effects are more prominent in the aneurysm sac. Furthermore, the presence of the stent device modified the flow patterns inside the aneurysm sac by reducing the overall aneurysmal blood flow velocity and circulation.

5.2 Contributions

The main contributions of the present work are presented as follows:

• A fully automated cardiovascular benchtop measuring system was developed to mimic the hemodynamics of different circulatory regions with tunable physiological conditions.
  o The current in vitro setup relies on a PID controller in conjunction with a feed-
    forward controller to replicate physiological flow and pressure conditions, making it unique across the literature.
  o The setup can easily be modified and implemented for different applications.

• CFD simulation analysis on different sidewall intracranial aneurysm cases.
  o The study incorporated Newtonian and non-Newtonian working fluids. This allowed studying the non-Newtonian shear-thinning effect within the aneurysm sac numerically.

5.3 Future Work

Future work can be aimed towards resolving the limitations presented in sections 3.4 and 4.4. Specifically, the in vitro experimental setup can still be improved by adding a way to
control the impedance present in the flow loop. This would allow to more accurately replicate
the flow and pressure profiles. This could be achieved by incorporating a variable-controlled
compliance chamber to the experimental setup. A feasible option could be to implement and
improve the work of Gregory and Taylor [148], [149] where a real-time proportional integral
(PI) controller was developed to adapt compliance parameters and more accurately replicate
physiological pressure conditions.

Since the in vitro setup can incorporate anatomical phantoms (as described in section
3.2.1.3) and it was mainly tested for aortic flow replication, different anatomical phantom
geometries resembling a variety of aortic aneurysm configurations can be implemented.
Furthermore, the setup can be used to expand the study to a different circulatory region, such
as the ascending thoracic aorta. Additionally, incorporating a flow visualization (such as particle
image velocimetry) will allow verifying that the flow patterns generated matched with the blood
flow patterns published in the literature.

The computational study from Chapter 4 can be expanded to study different
hemodynamic parameters across multiple aneurysm configurations within the cerebral
vasculature. Furthermore, it would be worth to investigate the effectiveness of endovascular
stents on cerebral aneurysms. The numerical data presented in this thesis for different cerebral
aneurysm cases only showed velocity contours and velocity magnitude. However, a vast amount
of parameters can be obtained. This would allow to study different hemodynamic parameters
related to aneurysm rupture such as vorticity, shear rate, and shear stress.
Bibliography


1995.


Appendix

Abdominal Aneurysm - Experimental Setup Verifications and Validations

A.1 Pressure Transducer

**Pressure transducer calibration:** The pressure transducers calibration was performed using the built-in calibration signals of the Millar pressure control unit and a custom LabVIEW program. Three different pressure signals of 25mmHg, 100mmHg, and 125mmHg were applied. The voltage output of the pressure control unit was then recorded via LabVIEW for 10 seconds with a resolution is 1000 points per second. The signal value was averaged for the last five seconds to generate a calibration curve that correlated voltage and pressure.

**Pressure transducer validation:** To validate the transducer's calibration, a column of water with a known height and fluid density was used. The validation experiment consisted of checking the induced voltage for each established water column height, to obtain a curve that correlated such parameters. The recorded values were in good agreement with the calibration curve obtained. For each calibration curve, 142 measurements were made. Each point is the result of an average (RMS) from 1,000 samples via a specific computer program through the multifunctional DAQ module.
A.2 Electromagnetic Flowmeter

**Electromagnetic flowmeter calibration:** The electromagnetic flowmeter used has two analog outputs: one for constant flow and one for pulsatile flow. The latter was selected in the setup. Flowmeter calibration involved a software implemented in LabVIEW 2018, capable of acquiring data from an analog input signal through the DAQ NI USB-9205 module. To perform the calibration, a hydrodynamic bench for permanent flow was constructed and used. To complete the flow transducer calibration, it was necessary to pass a known amount of fluid through the flowmeter probe over a time also known. Calibration consisted of obtaining the curve that relates flow ranges and the voltages induced by the flowmeter.
Although calibration curves were obtained by acquiring voltage signals for constant flow ranges, the equipment is intended for pulsed flow measurement (depending on the sensor). The phase change of the cardiac cycle (systole, diastole) usually induces a portion of the flow in the opposite direction (regurgitation). To record this phenomenon, it was necessary to validate the flowmeter calibration curve, including a negative flow range. In the equipment calibration procedure, this was possible by changing the mounting side of the sensor, changing the input through the output in the hydraulic circuit.

The experimental setup for the flowmeter calibration procedure can be seen below in Figure A-5-2. Due to the flowmeter's working principle, about 500 g of NaCl was added to the water.

![Figure A-2: a) Calibration benchtop used and; b) Carolina Flowmeter](image)

**Electromagnetic flowmeter validation:** Due to laboratory limitations, the flow meter calibration presented a restriction with respect to the verification of the linearity of the calibration curve (expected to vary by ± 1%) and another one with respect to the reading range of the equipment (from -19.99 L/min to 19.99 L/min). This is because the experimental setup provided a maximum flow rate of 18 L/min. This fact implies that the calibration curve obtained for the flowmeter refers to three flow values, namely: 18, 0 and -18 L/min. The flow
rate of 18 L/min imposed on the bench corresponds to the maximum permissible reading for the flowmeter (19.99 L / min.). The no-flow condition was quickly imposed on the bench by stopping servo motor motion. The measurement of the negative induced voltage expected for mounting the equipment sensor in the inverted position (-18 L/min condition) was performed. Thus, the flow rate of -18 L/min was correlated to a negative voltage. Multiple steady flowrates were prescribed, and data acquired by the flowmeter showed good accuracy.

A.3 Gear Pump

Pump calibration: After performing sensors calibration, a pump calibration was performed in order to correlate the flowrate to the motor speed (revolutions per minute). This was achieved by operating the gear pump at a range of different speeds for a duration of 5s, respectively. The relationship between motor speed and gear-pump output flowrate is crucial for generating a reliable control system. Equation (A-1) represents the calibration function.

Figure A-3: Pump-motor calibration curve. The calibration function is also displayed.
\[ \text{MotorSpeed (RPM)} = \text{Flow rate} \left( \frac{ml}{s} \right) \times 7.391 \] (A-1)

**Pump validation:** Having generated a calibration curve, different motor speeds were tested to validate their correlation to the flowrate. The values measured showed good agreement with the calibration obtained, with flowrates measured within 2\% of the predicted value, showing that the motor speed-flowrate function modeled well the linear behavior of the pump when a steady flow is applied.