# Biomechanical Modeling and Hemorheological Assessment of Ascending Thoracic Aortic Aneurysm, Aortic Heart Valve, and Blood Clot

by

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### Abstract

Cardiovascular diseases account for the most cause of death over the globe annually, summarized by the World Health Organization. An aortic aneurysm is one of the cardiovascular diseases with localized abnormal growth of a blood vessel with the primary risk of aneurysm rupture or aortic dissection. The precise pathological pathway for disease progression in aneurysm formation is not completely understood; however, biomechanically, disrupted blood flow from a diseased heart valve and thrombus formation potential in the dissection could contribute to the increased risk. The current ascending thoracic aortic aneurysm (ATAA) management rely heavily on ATAA diameter and blood pressure rather than biomechanical and hemodynamical parameters including arterial wall deformation or wall shear stress (WSS). Therefore, this thesis firstly evaluated the biomechanical contributions to ATAA progression under the influence of anatomy, hypertension, and hematocrit using fully coupled fluid-structure interaction (FSI) with arterial wall anisotropy to provide additional information in patient evaluations. The investigation was then extended to study the effect of blood rheology on the hemodynamics of a bileaflet mechanical heart valve with particle image velocimetry (PIV) validation. Finally, the rheological experimentations were conducted to analyze the coagulation process and the interactions between heparinized blood and the anticoagulation reversal agents. The ATAA analysis showed significant variations in the maximum WSS despite minimal differences in flow velocity between normotension and hypertension. The three different ATAA models identified different aortic expansions that were not uniform under pulsatile pressure and a geometry depended on elevated wall stress under hypertension. The investigation on the heart valve revealed the hematocrit influenced the shear stress distributions over a cardiac cycle. The structural stresses in the iii

mechanical valve were affected by the shear stress distributions in the blood flow. Parameter dependencies study indicated that the hematocrit is influential when conducting patient-specific modeling of prosthetic heart valves. Finally, the use of small amplitude oscillatory shear (SAOS) rheometry for studying blood coagulation provided a comprehensive assessment with the combination of multiple rheological parameters for untreated and heparin neutralized blood. The coagulation characterization could be used towards the existing FSI models to account for potential blood clot formations in future studies.

### Lay Summary

When an artery abnormally enlarges locally, the disease is typically identified as an aneurysm. An ascending thoracic aortic aneurysm (ATAA) is an aneurysm at the ascending part of the thoracic aorta, which is the largest artery bridging the heart and the rest of the body. The current clinical ATAA managements rely mostly on aneurysm diameter, blood pressure, and lifestyle; however, other mechanical and biological factors can also contribute to aneurysm progression. To investigate the biomechanical influence on ATAAs, computer models were built to simulate blood flow through ATAA and a mechanical heart valve. It was found that the aneurysm's geometrical characteristic, hypertension, and hematocrit can all affect the mechanical load and fluid-induced stress on ATAA and heart valve. Furthermore, experiments and characterizations on the blood coagulation process were conducted for future integration to the existing computer models for simulating blood flow through ATAA and heart valve with potential blood coagulation.

### Preface

This thesis presents the research work conducted originally by the author. Different parts of the work in the current research were developed with collaboration with the different research centers. This includes Dr. Rabkin from the Department of Medicine (Cardiology) at Vancouver General Hospital; Dr. Oshki and Dr. Barannyk from the Department of Mechanical Engineering at the University of Victoria; as well as Dr. Kizhakkedathu and Dr. Yu from Centre for Blood Research at the University of British Columbia.

Chapter 2 of this thesis is combining the work of

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Dr. Grecov and I originated the investigation for the study while Dr. Rabkin and I further designed and refined the study. I conducted all the work associated with the construction of the numerical models of ascending thoracic aortic aneurysm and analyzed all the numerical results. I

wrote the manuscripts with Dr. Rabkin and Dr. Grecov. All authors contributed to the editing and revisions of the manuscripts.

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- Yeh, H. H., Barannyk, O., Grecov, D., & Oshkai, P. (2019). The influence of hematocrit on the hemodynamics of artificial heart valve using fluid-structure interaction analysis. *Computers in Biology and Medicine*, *110*, 79-92.
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Dr. Grecov and I originated and designed the study on an artificial heart valve. I conducted all the work associated with the construction of the numerical models and analyzed all the numerical results. Dr. Barannyk conducted the *in vitro* experiment that was used in the numerical validation section of the manuscript. I wrote most of the manuscript with Dr. Barannyk wrote the sections related to the experiments. All authors contributed to the editing and revisions of the manuscript. The experimental description on the testing of an artificial heart valve in the current document was abstracted from the published work.

Chapter 4 of this thesis is a version of

 Yeh, H. H., Yu, K., Vappala, S., Kalathottukaren, M., Abbina, S., Luo, H., Grecov, D., Kizhakkedathu, J. N., (2019). Rheological and Clot Microstructure Evaluation of Heparin Neutralization by UHRA and Protamine. Submitted Dr. Grecov, Dr. Yu, and I originated the investigation of blood rheology and coagulation. Dr. Yu assisted in the preparation of chemical reagents. Dr. Kalathottukaren and Dr. Abbina synthesized the reversal agent, UHRA-7. I designed the experimental conditions and test protocols. Dr. Grecov and Dr. Kizhakkedathu assisted in the further refinement of the experimental planning. I conducted the rheological experiments as well as analyzed all the rheological data and SEM fibre analysis. Sreeparna helped with the interpretation of the data analysis. Haiming helped with SEM sample preparations. All authors contributed to the editing and revisions of the manuscript.

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## Nomenclature

$a_1, a_2$	Holzapfel model direction vectors
a <sub>i</sub> , b <sub>i</sub> , c	Fung type material constants
c, k1, k2	Holzapfel model material parameters
$C_{10}, C_{01}$	Mooney-Rivlin material parameter
Cd	Diastolic circumference
Cs	Systolic circumference
$\mathbf{D}_{\mathrm{d}}$	Diastolic diameter
Ds	Systolic diameter
E	Young's modulus
$E_{ij}$	Green's strains
F	Deformation gradient
g	Gravity
G'	Storage modulus
G'eq	Equilibrium storage modulus
G"	Loss modulus
Htc	Hematocrit
J	Volume ratio
$k_0, k_\infty$	Maximum volume fraction at zero and infinite shear rates
n	Normal vector
<b>n</b> Carreau	Power-law index for Carreau model
Р	Fluid pressure

S	Second Piola-Kirchhoff stress tensor
t <sub>0</sub>	Delay time for coagulation initiation
t <sub>c</sub>	Coagulation dynamics characteristic time
t <sub>mid</sub>	Sigmodal function midpoint
V	Fluid velocity
α <sub>i</sub>	Ogden phenomenological physical constants
3	Strain tensor
η	Viscosity
η*	Complex viscosity
$\eta^*_{eq}$	Equilibrium complex viscosity
ηο	Viscosity at zero shear rate
$\eta_{\infty}$	Viscosity at infinite shear rate
$\eta_{plasma}$	Blood plasma viscosity
κ	Bulk modulus
μ	Shear modulus
V	Poisson's ratio
ξ	Relaxation time
σ	Stress tensor
σνм	von Mises stress
τ	Viscous stress tensor
Ψ	Strain energy density function
$\bar{I}_i$	Invariants

$\lambda_i$	Principal stretches
Ē	Cauchy-Green deformation tensor
Ϋ́	Shear rate
Ϋ́ <sub>c</sub>	Critical shear rate for erythrocytes agglomeration
$\mathcal{E}_{ heta  heta}$	Circumferential cyclic strain
$k_{coagulation}$	Coagulation formation kinetics

### List of Abbreviations

AAA	:	Abdominal Aortic Aneurysm
ATAA	:	Ascending Thoracic Aortic Aneurysm
CFD	:	Computational Fluid Dynamics
СТ	:	Computed Tomography
FSI	:	Fluid-Structure Interaction
MRI	:	Magnetic Resonance Imaging
SAOS	:	Small Amplitude Oscillatory Shear
SEM	:	Scanning Electron Microscopy
TAA	:	Thoracic Aortic Aneurysm
UFH	:	Unfractionated Heparin
UHRA	:	Universal Heparin Reversal Agent
WSS	:	Wall Shear Stress

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## Dedication

To my parents

To my sister

&

To my friends

for all your unlimited support

#### **Chapter 1: Introduction**

Cardiovascular mortality accounts for a major proportion of total deaths in industrialized societies. According to the data released by the Centers for Disease Control and Prevention (Figure 1.1), there is an overall decrease in the total number of people who lost their battle to the diseases of arteries, arterioles, and capillaries. However, the mortality for aneurysm and dissection remained relatively constant over the past decade. In fact, in 2017, there was approximately 39% of the death associated with aortic aneurysm and dissection from the category of arteries diseases [1]. An aortic aneurysm occurs when an aorta enlarges abnormally at a localized region. When the enlargement occurs around the thoracic aorta, it is classified as thoracic aortic aneurysm (TAA). By the same token, when the enlargement occurs around the abdominal aorta, it is classified as abdominal aortic aneurysm (AAA). The illustration of aortic aneurysm can be seen in Figure 1.2.



Figure 1.1 Total number of deaths in the US by disease of arteries, arterioles, and capillaries



Figure 1.2: Illustration of aortic aneurysm with (a) healthy thoracic and abdominal aorta, (b) thoracic aortic aneurysm, and (c) abdominal aortic aneurysm [2]

The complications of aortic aneurysm are significant and are of considerable concern as the prevalence of the condition is increasing [3–6]. Blood pressure is a critical parameter that predicts aortic enlargements in conjunction with other factors such as the imbalance between protein synthesis and degradation of matrix proteins [7–9]. While several other well known risk factors, such as age, gender, smoking and genetics, may lead to the development of TAA formation, the precise causes, physical or biochemical, of aneurysm formations is unknown in most cases [10,11].

The current standard practices for patients, who have aortic aneurysms and dissections, are primarily managed by evaluating the size of the dilated blood vessels as well as patients' blood pressures. More specifically, the assessments and managements of TAA, ascending thoracic aortic aneurysm (ATAA), and AAA relies heavily on the diameter of an aneurysm and blood pressure rather than biomechanical and hemodynamic parameters such as arterial wall deformation or wall shear stress. However, in some circumstances, the patients with smaller vessel diameter may develop an aortic dissection before blood vessel diameter reaches the recommended threshold for surgery [5]. Once a surgical option is deemed to be suitable, an open procedure remains the gold standard for a treatment. Given an approximately 30% of the patient population are not suitable for open procedures due to potential complications, the risk of surgery is preferred over the risk of further developments of aneurysms and dissections [12-16]. One of the potential alternative treatment option of aortic aneurysm would be endovascular aortic repair (EVAR), which avoid the need of introducing open surgical procedures with the increased risk [12,13]. However, EVAR is not risk-free as the stent graft relies on the outward expansion force generated from the stent frame, the imperfections from the repair would introduce further series complications including endovascular leakages and retrograde dissections [17,18].

Ascending aortic curvature [19,20], aortic stiffness [21–23], peak wall stress (PWS) [24– 26], as well as wall shear stress (WSS) [27–29] are biomechanical factors that may provide information for the disease progression. Unfortunately, besides the aortic geometries, most of these factors cannot easily be directly measured *in vivo*. A method for calculation of arterial wall stress, blood flow velocity, and WSS would be of considerable value for disease assessments.

Although the size of the aorta has been studied in TAA [20]; the impact of increasing aortic arch curvature has received less attention. The curvature might dramatically increase the force

experience by ascending aorta even if under the conditions of lower systole pressure and smaller vessel diameter [19]. Data suggest that the aorta and aortic aneurysm might be influenced considerably by its geometrical configuration [11,12] but this has not been studied in detail. It is reasonable to begin an investigation on aortic aneurysm from a biomechanical perspective and to consider blood vessel displacement under pulsatile blood pressure. Since arterial wall stiffness increase with aging especially in patient with hypertension [21–23], investigation of aortic wall stress should provide important insights on how the stress is distributed. In addition, evaluation of PWS, or overall arterial wall stress, should assist in identifying regions of the aorta that are subject to high stress rendering them at high risk for aneurysm rupture and/or dissection. Additional attention should also be focused on the localized strain and aortic wall thinning for aneurysm rupture assessment [30].

#### **1.1 ATAA Pathogenesis**

There were just approximately over one hundred and ten thousand patients diagnosed with thoracic aneurysm or dissection in 2016 based on Agency for Healthcare Research and Quality data from Healthcare Cost and Utilization Project [31]. While the exact disease pathway for the progression of an aneurysm is still unclear, there are several key factors identified that prompt the aneurysm developments. As proposed by Shimizu *et al.* for the progression of aneurysms, there should be a two-step process where the normal healthy blood vessel undergoes initial aortic wall damage after the first trigger due to environmental or genetic events [32]. A second trigger, which is caused by environmental factors, would be followed such that the progression of an aneurysm is continued [32]. Although their work is limited to the investigation of AAA, the same process for TAA and ATAA may apply [33]. The primary cause of ATAA progression is the degradation

of the media layer, which has decreased elastin concentration and reduced smooth muscle cells. Since the environmental factors are the second trigger, it can be argued that biochemical or biomechanical factors are the main factors in ATAA progression. As ascending thoracic aorta receives the highest amount of the blood flow from the heart, the investigation of ATAA progression from the biomechanics point of view could provide further clinical insights for the patients.

Additionally, it was found that one or more characteristic clinical factors can be linked to each of the three pathological pathways, degeneration, arteriosclerosis, and inflammation, contributing to the progression of an ATAA [34]. More specifically, each pathway could be associated to different risk factors affecting aneurysm development. A degenerative ATAA can be associated with BAV [34] with medial layer degeneration over time, which lead to aneurysm formation with advancing disease progression by high blood pressure [35]. For younger patients, genetics, such as Marfan's syndrome, play a more important role [35]. An arteriosclerotic ATAA can be associated with older patient with history of hypertension, hypercholesterolemia, diabetes, smoking, and coronary arteries disease [34]; however, atherosclerotic hypertensive smoking patients are more likely to have a descending thoracic aortic aneurysm than ATAA [36]. While an inflammatory ATAA can be associated with older female with larger ascending aorta diameter [34], vascular inflammation could be triggered by adverse fluid-induced stress and WSS [37,38].

It is known that fluid shear stress would initiate the remodeling of blood vessels as well as create damage to blood cell; however, to directly calculate fluid shear stress without influencing fluid flow in real-time can be very challenging [39,40]. Due to the shear stress generated under pulsatile blood flow, it was shown that the endothelial cells and the adhesion of the neutrophils to endothelial cells responded to the gradients of WSS and potentially influenced the stability of the

atherosclerotic plaque [41,42]. Given the main components of blood are red blood cells (erythrocytes), white blood cells (leukocytes), platelets (thrombocytes), and plasma, the biomechanical factors should have majority effects on these four components. Combining the evidence of blood damage under high shear stress and the thrombus generation under shear flow [43–46], one can argue that platelets initiate thrombus formation due to abnormal hemodynamics under pathological conditions.

A further investigation reveals that there is a close biophysical connection between the interaction of platelets and fluid shear stress [47–51]. Briefly, the increase in blood shear stress would cause platelets to release and upregulate tissue growth factors [47,48,50]. Specifically, human aortic smooth muscle cell (SMC) apoptosis [52] has been observed with the overexpression of connective tissue growth factor (CTGF), which is released by platelets [53]. Additionally, CTGF has been shown to increase the risk of a cardiovascular event and proposed as an independent risk predictor for the atherosclerotic disease [54]. 4D magnetic resonance imaging (MRI) study has revealed a potential linkage by concluding that the bicuspid aortic valve (BAV) patients with aortic dilation are experiencing higher shear stress than the patients with tricuspid aortic valve (TAV) [55].

#### **1.2** The Disease of the Aortic Valve

BAV is the most common congenital defect affecting up to 2% of the population [56,57] with complications associated to aortic stenosis, regurgitation, and the dilation of the ascending thoracic aorta, which is the most relevant to the current study. With severe aortic stenosis, the aortic valve would typically have to be replaced with an artificial heart valve, either with a mechanical heart valve or a bioprosthetic tissue valve. Approximately 49% (458 out of 932) of the

patient receiving an aortic valve replacement had a BAV [58]. When BAV is associated with the dilation of the ascending thoracic aorta, the growth rate of the aorta for BAV patients is higher than aneurysm patients with a TAV [59,60]. As the arterial wall stresses and the fluid shear stresses contribute to the pathogenesis of BAV, hemodynamical influence in both BAV and ATAA is identified as one of the key factors for the disease progression [59,61]. The use of 4D MRI has concluded that BAV patients had a significant difference in the shear stress at the arterial wall and the generation of helical flow across the aortic arch from the ascending thoracic aorta [55,62–65]. The earlier study concludes the curvature of the aortic arch would play an important role in the generation of secondary flow patterns such as helical flows [66]. Therefore, the formation and progression of an ATAA could not only be caused by altered hemodynamics with a defective BAV but also due to the geometrical curvatures of the aorta generating helical flows. A higher degree of thoracic aorta curvature could result in higher amount of normal force the aortic wall received, which may increase the risk of a patient developing aortic dissection [19].

#### **1.3** Biomechanical Characterizations of Aortic Wall

As the heart mechanically pumps the blood through the aorta and distributes the blood to all parts of the body, a deeper understanding in the biomechanical interactions between the aortic wall and the blood would further bridge the gap between the progression of an aneurysm and the management of a patient. With a better understanding of an aneurysm development, it is possible to better predict the outcome of the patients by translating the knowledge to clinical settings.

Mechanical loadings including forces, stresses, and deformations are some of the biomechanical factors that would have a more direct influence on aneurysm's progression. To account for the force transfer, the internal wall stress, as well as the structural deformation for biological soft tissue, it is essential to consider how the material composition of tissue would affect the overall tissue properties under various loading conditions. For the case of the aorta, it is understood that each layer consists of various portion of elastin and collagen that provide overall structural support as shown in Figure 1.3 [67]. The arterial wall consists of three main layers: intima, media, and adventitia. Each layer, separated by elastic lamina, has its own characteristic that provides the overall structural function of the arterial wall. For example, intima primarily provides internal protection of the blood vessel with a smooth endothelial cell layer, elastin, and fibre-reinforced layer. Media, which is considered as transversely isotropic, provides the flexibility to expand and contract under pulsatile blood flow with smooth muscle. Adventitia provides external structural support for the blood vessel with an anisotropic collagen fibre layer. The distribution of microstructures, such as elastin fibres and collagen fibres has been shown to be one of the main contributors that affect the macroscopic biomechanics of arterial wall [67–71].



Figure 1.3: Cross sectional presentation for an idealized arterial wall (reprint with copyright permission)[67]

It is well summarized in Tsamis *et al.* and Back *et al.* that elastin and collagen content would be affected by age, diseases, genetic or developmental defects including, hypertension, aneurysm, dissection, atherosclerosis, bicuspid aortic valve, Marfan syndrome, and other factors [68,72]. Specifically for the aortic aneurysm cases, the overall elastin content would decrease with fragmented, disrupted, and irregular elastin while the overall collagen content would remain the same with thin scattered collagen fibres [68]. The change in elastin and collagen content would result in a less anisotropic aorta [68,72]. Similarly, for the aortic dissection cases, elastin and collagen concentration also decrease and thus affecting the aorta's global response to pulsatile
pressure. It was also shown that structure integrity would be adversely affected by elastin removal [71] and aneurysm remodeling [73] in the media layer. The tissue toughness of the media layer of the ATAA was shown to be independent of different regions of the aneurysm but depended on both the collagen and elastin fibres [73].

To further understand the progression of arterial diseases and construct physical models from a biomechanics perspective, it would be necessary to determine the macroscopic material properties of the arterial wall. Recently, many research groups have used uniaxial or biaxial tensile measurements to model the properties of the aortic wall using constitutive equations that account for hyper-elasticity [74,75] or anisotropy [70,76,77]. The characterization of the arterial wall can, therefore, be categorized into isotropic linear elastic material, isotropic hyper-elastic material, and anisotropic hyper-elastic material as discussed in the following sections.

### **1.3.1** Isotropic linear elastic material

The constitutive equation of an isotropic elastic material is a simple linear relationship between stress and strain as shown in Eq 1.1 [78]. This relationship is known as Hooke's Law where the given material is characterized by only Young's modulus and Poisson's ratio, defined in Eq 1.2, assuming isothermal condition. Since the strain, or more specifically the engineering strain, used in linear elastic relationship is only valid when deformation is small and within linear range, Eq 1.1 will not be sufficient to account for material with large non-linear deformation such as biological soft tissue, which could have a strain ranging between 30-70% [79]. Therefore, depending on various stress-strain definitions, it is recommended to apply the true (instantaneous changes) stress and true strain relationship for soft tissue experiments [80].

$$\boldsymbol{\sigma} = E\boldsymbol{\varepsilon} \qquad \qquad \text{Eq 1.1}$$

where  $\sigma$  is the stress tensor in [Pa], E is the Young's modulus in [Pa], and  $\varepsilon$  is the strain tensor

$$v = -\frac{\text{lateral strain}}{\text{axial strain}} = -\frac{\varepsilon_y}{\varepsilon_x} = -\frac{\varepsilon_z}{\varepsilon_x}$$
, where  $\varepsilon \equiv \frac{\text{change in length}}{\text{original length}}$  Eq 1.2

where v is the Poisson's ratio

Fluid-structure interaction (FSI) methods has been used for investigating the arterial wall stress under pulsatile blood flow with an assumption of a linear elastic arterial wall. The assumption of applying isotropic linear elastic material to the arterial wall was made to compensate more relevant global evaluation on aneurysm rupture, asymmetry and wall thickness, stent graft implantation, and multiple arterial layers [81-84]. Additionally, a uniform aortic wall thickness of a single arterial wall layer could be assumed [81,83]. Torii et al. compared the single layer linear elastic and hyper-elastic cerebral aneurysm model and concluded that the hyper-elastic model resulted in a 36% smaller maximum displacement, but with similar displacement patterns, compare with the linear elastic model [81]. To address the rupture risk due to the arterial wall thickness and asymmetry, Scotti et al. found that the non-uniform wall thickness model would result in up to four times greater wall stress, thus increasing AAA rupture risk based on the von Mises failure stress criteria [82]. It is therefore recommended to accurately reproduce the aortic geometry when predicting the biomechanics of aortic aneurysm. Similarly, Li and Kleistreuer numerically investigated the biomechanics of AAA before and after endovascular stent graft implantation and analyzed the wall stress and aneurysm sac pressure [83]. The use of fully coupled FSI for both AAA and endovascular stent graft resulted in a significant decrease in maximum wall stress for

stented AAA when compare with non-stented AAA. The authors also discussed that from their preliminary studies, aneurysm sac pressure and wall stress might increase by 60% with an increase of only 3% endoleak volume as well as a greater endograft drag force from aortic geometrical factors [83].

Nevertheless, since the arterial wall structure consists of three layers and most biomechanics investigation on aortic aneurysm is modeled as an equivalent single wall layer, Gao *et al.* considered the multilayer mechanics of arterial wall and analyze stress distribution across each arterial layer [84]. The authors presented an idealized aorta, from the ascending aorta to the descending aorta, (without the aortic branches) with a three-layered aortic wall with a corresponding thickness ratio of 1/6/3 (media thickness of 1.2mm) and isotropic linear elastic properties ( $E_{intima}$ = 2.98 MPa,  $E_{media}$  = 8.95 MPa,  $E_{adventitia}$ = 2.98 MPa) [84]. The circumferential stress was concluded to be directly related to blood pressure resulting in high composite stress around ascending aorta and highest stress at the media layer, suggesting the formation of an aortic dissection [84].

Applying isotropic linear elastic properties to the aortic wall reduced the modeling complexity while provided an overall macroscopic evaluation on the progression of an aneurysm. However, given the linear elasticity would only be valid within the linear proportional limit, the estimation of the rupture stress for aortic aneurysm would not be accurate as the failure strength is beyond the linear region.

### **1.3.2** Isotropic hyper-elastic material

There are several well-established constitutive equations for isotropic hyper-elastic relationship. The main difference between different relationships, besides the material constants, is the method of material properties fittings: exponential or polynomial, listed below from Eq 1.3

to Eq 1.7. Note that all constitutive equations are for solving strain energy density function,  $\overline{\Psi}$  in [J m<sup>-3</sup>], which will be used to relate to the Cauchy stress tensor for further stress calculation.

• Neo-Hookean [85]

$$\overline{\Psi} = \frac{1}{2}\mu(\overline{I}_1 - 3) + \frac{1}{2}\kappa(J - 1)^2$$
 Eq 1.3

where  $\mu$  is the shear modulus in [Pa],  $\overline{I_i}$  are the invariants,  $\kappa$  is the bulk modulus in [Pa], *J* is the volume ratio

• Fung [74,86]

$$\overline{\Psi} = P + \frac{c}{2}(e^Q) \qquad \qquad \text{Eq 1.4}$$

where

$$P = \frac{1}{2} \left[ b_1 E_{\theta\theta}^2 + b_2 E_{zz}^2 + b_3 \left( E_{\theta z}^2 + E_{z\theta}^2 \right) + 2b_4 E_{\theta\theta} E_{zz} \right]$$
$$Q = a_1 E_{\theta\theta}^2 + a_2 E_{zz}^2 + a_3 \left( E_{\theta z}^2 + E_{z\theta}^2 \right) + 2a_4 E_{\theta\theta} E_{zz}$$

 $E_{ij}$  are Green's strains and  $a_i$ ,  $b_i$ , and c are the dimensionless material parameters

• Mooney-Rivlin [87,88] Two-parameter model:

$$\overline{\Psi} = C_{10}(\overline{I_1} - 3) + C_{01}(\overline{I_2} - 3) + \frac{1}{2}\kappa(J - 1)^2$$
 Eq 1.5

Where  $C_{10}$  in [Pa] and  $C_{01}$  in [Pa] are material parameters

Five-parameter model:

$$\overline{\Psi} = C_{10}(\overline{I}_1 - 3) + C_{01}(\overline{I}_2 - 3) + C_{11}(\overline{I}_1 - 3)(\overline{I}_2 - 3)$$
 Eq 1.6  
+  $C_{20}(\overline{I}_1 - 3)^2 + C_{02}(\overline{I}_2 - 3)^2 + \frac{1}{2}\kappa(J - 1)^2$ 

where  $C_{ij}$  in [Pa] are material parameters and  $\bar{I}_i$  are the invariants

• Ogden [89]

$$\overline{\Psi} = \left[\sum_{i=1}^{N} \frac{\mu_i}{\alpha_i} (\lambda_1^{\alpha_i} + \lambda_2^{\alpha_i} + \lambda_3^{\alpha_i} - 3)\right] + \frac{1}{2} \kappa (J-1)^2$$
 Eq 1.7

where  $\mu_i$  in [Pa] and  $\alpha_i$  are phenomenological physical constants from experiments, and  $\lambda_i$  are principal stretches

The material constants used in each constitutive equation are determined experimentally with uniaxial and biaxial tension test using cadaveric, resected, or animal tissue specimens. The collected data from tensional experiments are usually fitted using multivariable least square analysis. Although the anisotropic material relationship would provide better experimental fit, the use of the neo-Hookean model would be sufficient for describing the material behavior of the media layer [71]. The characterization of the aortic wall model can be extended to the solid mechanics modeling for multilayer stenotic artery modeling with stent deployment [88,90] or modeling the device-wall interaction in coronary sinus [91]. More specifically, Schiavone *et al.* conducted a finite element simulation on the stent deployment in the stenotic artery using a combination of constitutive equations to model the transcatheter balloon (Mooney-Rivlin 2-parameter), three arterial wall layers, and plaque (Ogden, based on [90,92]) [88]. Their artery-plaque-stent simulations would result in significantly different stress distribution with different

stent designs. Furthermore, Zahedmanesh and Lally numerically investigated that blood vessel is more likely to get restenosis if the wall stress is greater [90]. Studies have modeled the arterial wall as a composite of isotropic hyperelastic materials with the material properties derived from experimental studies [93–96]. However, given that the elastin, collagen fibres and other components in the media and adventitia layer of the aorta affect the deformation and stress distribution of the arterial wall [67,68], considering material anisotropy due to collagen fibres when modeling the arterial wall could result in better predictions.

### **1.3.3** Anisotropic hyper-elastic material

To further improve the biomechanics model for arterial wall, anisotropy can be added to the isotropic hyper-elastic model. Such an addition will account for the different fibre groups embedded within each arterial wall layer in order to capture the effect of fibre-reinforced deformation in biological soft tissue. Several key studies on the constitutive equations for modeling the anisotropic hyper-elastic arterial wall has been conducted intensively [67,70,76,77,97,98]. The strain energy density function  $\overline{\Psi}$  in [J m<sup>-3</sup>] is proposed as the superposition of the isotropic portion and the anisotropic portion shown below in Eq 1.8.

$$\overline{\Psi}(\overline{C}, a_1, a_2) = \overline{\Psi}_{iso}(\overline{C}) + \overline{\Psi}_{aniso}(\overline{C}, a_1, a_2)$$
 Eq 1.8

where  $\bar{C}$  is Cauchy-Green deformation tensor and  $a_i$  are direction vectors

Eq 1.8 can be further simplified to

$$\overline{\Psi}(\overline{C}, a_1, a_2) = \overline{\Psi}_{iso}(\overline{I}_1) + \overline{\Psi}_{aniso}(\overline{I}_4 + \overline{I}_6)$$
 Eq 1.9

where  $\bar{I}_i$  are the invariants

The isotropic portion can be written using neo-Hookean model similar to Eq 1.3

$$\overline{\Psi}_{iso}(\overline{I}_1) = \frac{c}{2}(\overline{I}_1 - 3)$$
 Eq 1.10

And finally, the anisotropic portion is modeled using exponential function for representing arterial wall behavior [76,99]

$$\overline{\Psi}_{aniso}(\overline{I}_4 + \overline{I}_6) = \frac{k_1}{2k_2} \sum_{i=4,6} \{ e^{[k_2(\overline{I}_i - 1)^2]} - 1 \}$$
 Eq 1.11

where  $k_i$  are the material parameters, with  $k_1$  in [Pa] and  $k_2$  unitless

Substituting Eq 1.10 and Eq 1.11 into Eq 1.9 gives the full expression of anisotropic hyper-elastic constitutive equation shown in Eq 1.12.

$$\overline{\Psi}(\overline{C}, a_1, a_2) = \frac{c}{2}(\overline{I}_1 - 3) + \frac{k_1}{2k_2} \sum_{i=4,6} \{e^{[k_2(\overline{I}_i - 1)^2]} - 1\}$$
Eq 1.12

To characterize the material constants, several experimental efforts were carried for the modeling of human aorta and the atherosclerotic plaque [73,77,98–101]. Labrosse *et al.* conducted biaxial and pressurized vessel test for modeling the anisotropic hyper-elastic constitutive equation for human ascending, descending, and abdominal aorta [77]. The human aorta was found to have directional preference for the case of aortic dissection [100] and the damage of tissue is accumulated in collagen fibre network [98]. Additionally, Choudhury *et al.* concluded that among the diseased human aorta, the patients with dilated BAV could have the thinnest aortic wall with greatest collagen composition and significantly less elastin [101].

### 1.4 In Silico Investigation of Aneurysm Biomechanics

As discussed previously, it would be necessary to investigate the hemodynamics in ATAA in additional to the biomechanics of aortic wall given that shear stress due to the pulsatile blood flow plays an important role in the disease progression of an aneurysm. High shear stress could lead to an overexpression of CTGF released by platelets and CTGF overexpression would lead to aortic smooth muscle cell apoptosis, which is the signature of media layer degradation in ATAA. Finite element simulations have focused on the investigation of aneurysm wall stress in patient-specific modeling using data either from computed tomography (CT) imaging or MRI [22,24–26,97,102]. Studies focused on the analysis of the aortic wall stress with the use of anisotropic hyperelastic arterial wall modeling [22,97], geometrical correction for zero blood pressure [24], aortic root displacement [25], and aneurysm expansion prediction [26].

Aortic wall	Previous work	Authors
model		
Isotropic Linear Elastic	Single layer cerebral aneurysm model with isotropic hyper	Torii <i>et al</i> .[81]
	elastic model resulted in smaller maximum displacement	
	Non-uniform aortic wall resulted in greater wall stress	Scotti et al.[82]
	AAA analysis before and after endovascular stent graft	Li and
	implantation	Kleistreuer[83]
	Multi-layer arterial wall stress distribution analysis	Gao et al.[84]
	Turbulent pulsatile flow in multi-layer aorta	Khanafer and
		Berguer[103]
Isotropic Hyper Elastic	Stent deployment in a stenotic artery using Mooney-Rivlin	Schiavone et
	model	al.[88]
	Influence of stent struct thickness using Ogden model	Zahedmanesh and
		Lally[90]
	Stent-aortic wall interaction in coronary sinus using Ogden	Pham <i>et al</i> .[91]
	model	
	TAA laminar-turbulent transition modeling with Mooney-	Tan <i>et al</i> .[104]
	Rivlin model	
	Aneurysm rupture potential	Raghavan and
		Vorp[105]
	Blood flow characteristics and thoracic aortic geometry	Suito <i>et al</i> .[106]
	using FSI with neo-Hookean model	
	ATAA comparing bicuspid and tricuspid aortic valve	Pasta <i>et al</i> .[107]
	Local stiffening of an aortic coarctation	Taelman et al.[108]
Anisotropic Hyper Elastic	Axisymmetric thick wall aorta for ascending thoracic,	Labrosse et al.[77]
	descending thoracic and abdominal aorta	
	AAA fluid-solid-growth remodeling model	Grytsan et al.[97]
	AAA rupture risk	Rissland et al.[109]

 Table 1.1: Summary of Recent Biomechanical Modeling and Analysis on Stents and Aorta

The accurate hemodynamic analysis in the cardiovascular system is heavily dependent on the appropriate interaction modeling between blood and blood vessels; therefore, accurate models for blood rheology and vessel structures are necessary to account for blood flow distributions and aortic wall stresses. Several key previous works are summarized in Table 1.1. Although debates are ongoing regarding the effectiveness of different computational approaches between computational fluid dynamics (CFD) and FSI methods for the investigations of aortic biomechanics [110], the motions of blood vessel induced under physiological pulsatile blood pressure by FSI approach would have different flow distributions than predicted by CFD approaches [111,112]. The prediction from CFD would capture important hemodynamic features, including flow velocity and shear stress, which are significant to pathological evaluations [113-116]. Specifically, these CFD investigations focused on the effect of non-Newtonian models on patient-specific geometry [113], hemodynamics of patient-specific dissection [114], geometrical influence on hemodynamics [115], as well as the flow in a rtic arch [116]. Their analysis has concluded with findings pointed to patient-specific flow patterns that were affected by geometries as well as blood pressure. The effects of different non-Newtonian models applied to patientspecific geometry were investigated and it was concluded that the Newtonian model underestimates WSS prediction [113].

Given the importance in WSS, the FSI approach that couples CFD and structural mechanics for modeling blood vessel expansion (Windkessel effect) should be used toward accurate hemodynamic predictions. Both FSI-CFD comparison studies by Reymond *et al.* and Crosetto *et al.* concluded that there was a WSS overestimation from the simulations without the inclusion of the aortic wall [112,117]. There were multiple FSI studies conducted for modeling cardiovascular system in the past decade. Each of them had a slightly different approach in hemorheological and structural modeling. Earlier FSI studies focused on the assessment of multilayer aortic wall biomechanics [103,118,119]. Gao et al., constructed idealized 3D Newtonian models for the hemodynamics comparison between non-aneurysm and aneurysm model with aortic wall properties assumed as three isotropic linear elastic layers (intima, media, and adventitia) [119]. Similarly, Khanafer and Berguer's three-layered isotropic linear elastic aorta model provided insights into peak wall stress in the media layer [103]. The FSI method has also been used recently in the modeling in ATAA geometrical characteristics [106], ATAA with BAV and TAV [107], abdominal aortic aneurysm growth evolution [97], and local stiffening [108]. While the studies utilized the advanced material model for the aortic wall (isotropic hyperelastic [106–108] and anisotropic hyperelastic models [97]), the blood was assumed to be a Newtonian fluid. As mentioned earlier, WSS prediction is one of the most important biomechanics predictors in ATAA, and an FSI model with Newtonian fluid would result in a WSS underestimation [113]. Interestingly, as all the results implied a geometrical dependence in hemodynamic distributions and helical flow development, the quantitative relationship between geometry and hemodynamics is to be further developed for better model predictions and correlations such that the analysis can be translated toward to clinical practice. Nevertheless, for an FSI modeling, the boundary velocity conditions (3D MRI, 1D MRI, fully developed, and plug flow) prescribed in the model would also have a significant influence in time-averaged WSS distributions and oscillatory shear index, which would affect the predicted outcome [120].

The hyperelastic models for characterizing the aortic wall are used to determine the biomechanical response under physiological loading conditions. Tan *et al.* investigated the mechanics and hemodynamics of TAA using the single layer isotropic hyperelastic Mooney-Rivlin model [104], with material constants taken from the experimental work on AAA [121]. The use of laminar-

turbulent transition model concluded a 13% lower time-averaged WSS and significantly higher turbulence intensity in the FSI model than the rigid wall model [122]. On the other hand, Raghavan and Vorp conducted another study on the rupture potential of AAA with freshly excised tissue [105]. They concluded that AAA wall stress would only vary 4% if the material parameters used from Mooney-Rivlin constitutive equation were within 95% confidence intervals [105]. This suggests that the use of mean value from sample population might be sufficient for patient-specific modeling [105]. For advanced numerical simulation, Grytsan *et al.* have modified the anisotropic arterial wall model and accounted for AAA remodeling under the additional consideration of elastin degradation and adaptation of collagen fibres [97]. The model considered the hemodynamic changes with the progression of AAA enlargement but without the connection between WSS and AAA remodeling [97]. The time-averaged WSS was not meaningfully influenced by the arterial wall motion due to pulsatile blood flow unless the investigation of instantaneous WSS was considered [29]. Since the magnitude of WSS would affect endothelial cell alignment [123] and potentially cause blood cell damage [40], a coupled fluid and structure study on WSS is of considerable value given that the local blood recirculation or unbalanced homeostasis could also lead to aneurysm rupture [28] [124].

### 1.5 Investigations on Artificial Aortic Valve and Bicuspid Aortic Valve

FSI analysis has also been used for the investigations of aortic heart valves [125–130]. While CFD study can be used to study bileaflet mechanical heart valve (BMHV) with prescribed particle image velocimetry (PIV)-measured leaflet motion [131] and localized flow features in a patient-specific aorta [132], the FSI method can provide further analysis in the simulation of heart valve where the blood flow would influence leaflet motion and vice versa. Early FSI works related

to the current study include a 2D hemodynamic investigation of an artificial heart valve with subaortic stenosis [133], an FSI model using a 2D dynamic mesh with experimental validation [134], a 2D FSI model investigating vortices generation of a defective mechanical heart valve [135], a 3D FSI BMHV simulation over a range of Reynolds numbers [136], as well as 3D symmetric BMHV analysis [137]. Recent BMHV modeling in 3D using FSI method was achieved by several groups including the integration of anatomical ascending aorta [138], assessing thrombus potential with shear stress [139], and the assessment of BMHV hemodynamics [140,141]. Additionally, an FSI study focusing on BMHV's implant angle suggested angle dependency on the blood flow [142], and the use of the lattice-Boltzmann method could provide detailed hemodynamic analysis [127,143]. The accuracy of the FSI method in a 3D BMHV simulation was validated with PIV measurements by Guivier-Curien *et al.* [144].

It was discussed previously that the hemodynamics studies of ATAA have shown development of secondary flow structures in ascending thoracic aorta using 4D MRI, especially for the case where BAV were presented [55,65,66,145]. Kimura *et al.* conducted CFD modeling on patient-specific BAV hemodynamics evaluations under various diseased valve configurations [145]. Their study focuses on the distributions of WSS in the enlarged ATAA with BAV using the combination of MRI data and CFD. The patients with BAV had abnormal helical flow distributed in ATAA while TAV patients had no such abnormality [65]. Additionally, Kimura *et al.* CFD results showed a clear streamline distributed helically from across the thoracic aorta with concentrated WSS distributions located on the superior side of ATAA [145]. Similar comparative studies conducted by Shan *et al.* and Meierhofer *et al.* also confirmed TAV cases would result in different WSS distributions than BAV cases [55,65]. The three 4D MRI studies provide significant insights toward to the hemodynamic distributions for diseased aorta coupled with diseased valve

and suggest hemodynamics parameters be used as risk indicators for patient management [55,65,145]. However, even with the rich evidence regarding the effect of WSS in ATAA patients, a well proposed hemodynamic risk factor for patient assessments and management is yet to be developed. By utilizing the similar FSI approach used in modeling BMHV, it would be possible to extend the study of ATAA and couple the investigation with BAV.

## 1.6 Blood Rheology and Blood Clot Formation

## 1.6.1 The use of rheological models in numerical investigations on aortic flow

The Newtonian and non-Newtonian rheological models are used in the CFD and FSI hemodynamical modeling of arteries, aneurysms and heart valves and the current FDA (Food and Drug Administration) guideline on CFD simulations for a medical device does not specify the requirement for the hemorheological model [146]. As the red blood cell deformability, blood cells' volume fraction and hematocrit, and the concentration of cholesterol and triglycerides could all affect the blood viscosity [147–149], the shear thinning behavior of blood plays key role in hemodynamics assessment in cardiovascular system.

The Newtonian model, which assumes a constant blood viscosity, would result in an underestimated WSS value. Mejia *et al.* concluded that the use of the non-Newtonian Carreau-Yasuda model yielded in higher WSS distributions than the Newtonian approximation in the stented section of the artery, resulting in differences in stress and velocity distributions [150]. There are different non-Newtonian fluid models for characterizing complex fluids that have flow behavior depending on shear rate and other physical influences. The widely adopted non-Newtonian relationships for modeling the hemodynamics of ATAA are the Carreau [113,151–154], the Casson, the Quemada [83,155], and the power-law models. These rheological models

predict blood viscosity based on shear rate and the Quemada model has included the hematocrit as an additional modeling variable. Two comparative CFD analyses on patient-specific aortic modeling with multiple rheological models (including Newtonian, Carreau, Carreau-Cross, Casson, Cross, Power Law, and K-L model) concluded although hemodynamics similarities existed between different non-Newtonian models, the non-Newtonian models would significantly affect the results and the Newtonian model would not be sufficient for predicting shear stress [113,156]. The use of non-Newtonian modeling of blood flow was also conducted on BMHV for hemolysis prediction, and diastolic flow in coronary arteries and near-hinge microflow [157,158].

# 1.6.2 Rheological characterizations of blood coagulation and clot formation

Heparin anticoagulation is commonly used to prevent blood clotting during surgeries and to treat thromboembolic diseases [159,160]. One of the common adverse side- effects associated with heparin therapy is bleeding [159]. Reversal of heparin anticoagulation activity is needed after surgical procedures such as the cardiopulmonary bypass to prevent excessive bleeding [161–163]. Currently, protamine is the only clinically available heparin antidote, however, associated with severe limitations and adverse effects [161,164]. Protamine has a very narrow therapeutic window; excess protamine has an inherent anticoagulant effect [165,166]. Protamine activates complement, induces fibrinolysis [167], causes lung-injury after heparin reversal [168], and is only partially effective against low molecular weight heparins (LWMHs) and other heparin derivatives such as fondaparinux [164]. To circumvent the limitations of protamine, researchers are in active search for alternate antidotes with an improved safety profile that works against all the clinically used heparins [169–171].

The dynamics of blood clot formation during heparin neutralization could provide important information regarding the clot stabilization and effectiveness of the neutralization strategy. This may also provide information regarding the potential of re-bleeding after heparin reversal. Thromboelastography (TEG) and rotational thromboelastometry (ROTEM) are conventionally used for providing such information. However, the fixed low oscillatory frequency and oscillatory displacement used by TEG and ROTEM only supply a limited range of conditions to study the clot formation dynamics during anticoagulant reversal. As TEG provides less sensitivity at the beginning of the measurement, a more accurate and generalized evaluation under physiologically relevant conditions could provide additional insights regarding the clot formation dynamics during an anticoagulation reversal and may provide important clues for more accurate and precise management of this therapy. The rheological characterization of the blood clot formation with a higher sensitivity and additional measurement parameters could unravel such information to aid the current practice.

Rheological characterization is one of the widely used methodologies to analyze the global static and dynamic behavior of the non-Newtonian, viscoelastic fluids, including blood and blood clot [172–178]. Although steady viscometry measurement has been used to determine the viscosity of the coagulating blood under different shear rates [179], the use of small amplitude oscillatory shear (SAOS) rheometry provides additional viscoelastic properties measurement by describing the gelation point[172,177], the storage and the loss modulus (G' and G'') [175], and the change in complex modulus (G\*) [176]. The advantage of rheometry using a standard rotational rheometer is that an adjustable oscillatory frequency under a controlled oscillatory amplitude within the linear viscoelastic range can be used. Providing an oscillatory shear within the linear viscoelastic range would be one of the critical control parameters since fibrin gel is known to experience strain hardening under nonlinear oscillation [180–182]. Additionally, shear stress and normal force measurements can be made to provide further details on the physical characteristics of the testing

material. The normal force measurements can be directly linked to the contraction of the blood clot, which was correlated to different cardiovascular diseases and could be used as a potential bleeding disorder biomarker [183,184]. The time evaluation of the blood clot's storage modulus was captured for investigating the coagulation dynamics and the microstructure of the blood clot under a constant oscillatory frequency and within the linear viscoelastic range [175,176,185]. Other methods for assessing blood coagulation and the viscoelasticity of blood clot including the dynamic ultrasound elastography [186] for assessing storage and loss moduli, and the laser speckle rheology for correlating activated partial thromboplastin time, prothrombin time, and functional fibrinogen levels to the conventional coagulation assessment[187].

The use of rheology has also been extended in extensive investigations on fibrin crosslinking in platelets storage conditions [188], clot formation with zinc [189], and mechanical structure of fibrin polymerization [190]. Additionally, a rheological study on the structure of biological gels and polymers revealed the generation of negative normal force under oscillatory shear [180,181,191]. The contractile force generated by the fibrin gel under oscillation was suggested to be related to the crosslinking structure of the clot under nonlinear deformation, which led to strain hardening on blood clots [180–182]. To relate the rheological measurements to the structure of biological gels, it was shown that the storage modulus had a significant increase with an oscillatory amplitude above 15% under a constant small oscillatory frequency of 0.16 Hz (1 rad/s), which suggested strain hardening, while the storage modulus remained relatively independent of oscillatory frequencies [182].

#### **1.6.3** Blood coagulation in aortic aneurysm

Although rare, intravascular coagulation in thoracic and abdominal aortic aneurysms could occur as firstly reported by Fine *et al.* [192]. Typically related to disseminated intravascular

coagulation (DIC), aneurysm-induced DIC was reported in the literature [193-197]. As DIC progresses, the consumption of the coagulation factors increases and leads to an increase in clotting time and excessive bleeding. In addition to chronic bleeding disorder and a consumptive coagulopathy, the aneurysm-induced DIC should return and maintain normal coagulation characteristics after aneurysm repair as suggested by Siebert and Natelson [198]. Due to the abnormalities on blood clotting and excessive bleeding, DIC was suggested to be treated with an anticoagulant such as heparin prior to the aneurysm repair [197]. However, contradicting findings on the use of heparin to treat DIC were summarized in the literature [199]. An in-depth and accurate method on the assessment of blood coagulation and blood clot formation would further assist in the screening of DIC for preoperative treatment since only 4% (three out of 76) of the aortic aneurysm patients revealed their clinical relevance [194]. Blood coagulation and thrombus formation also occur during the EVAR [200-202] and aortic dissection [203,204]. With thrombocytopenia as a potential risk factor for EVAR, Nienaber et al. reported the development of DIC due to endovascular leakage [200]. On the other hand, EVAR was shown to enhance thrombin activation comparing with open surgical repair, potentially due to the contact between blood and endovascular stent graft materials [201]. The blood coagulation and partial thrombus formation in the false lumen of an aortic dissection also played a critical role in the patients' mortality rate and aneurysm growth [203,204]. Furthermore, it was shown that a high, nonephysiological, shear stress could induce platelet activation as well as receptor shedding; therefore, adverse event of thrombosis and bleeding could occur at the same time [205].

# 1.7 Research Motivations

The motivations for the current study was initiated from the lack of in-depth biomechanical and hemodynamical understandings of aneurysm progression under the influence of hypertension. Given that the hemodynamics, aside from other known biological factors such as genetics, plays a key role in aortic wall degradations and thrombus formation, it is critical to investigate the interactions between the blood flow and the aneurysm structure. The balance, or the imbalance, between the blood pressure and the arterial wall stress can influence the disease progression.

In addition to how blood pressures affect the distributions of stress experienced by the aneurysm, the bicuspid aortic valve is another key factor for ascending thoracic aortic aneurysm due to the abnormal blood flow generated by the diseased aortic valve. It is also important to investigate the impact of varying hemorheological characteristics on the blood flow through the aortic valve and aortic valve dynamics, which would result in a significant change in the downstream hemodynamics within the aortic sinus and the ascending thoracic aorta. The studying on the complex interactions between the aortic valve – hemodynamics and the hemodynamics – ascending thoracic aortic aneurysm would offer substantial values not only to engineering the artificial heart valves and the endovascular stent grafts but also to patient monitoring and management.

Furthermore, any change in blood flow hemodynamics would result in a change in flow shear stress distributions. It is understood that an abnormal high shear stress distribution would lead to further development and progression of an ascending thoracic aortic aneurysm and thrombus formation. On the other hand, low shear endothelial stress could also trigger inflammatory response resulting atherosclerosis [206]. More importantly, thrombosis would form during the surgical treatments of ATAA, either traditional open surgeries or endovascular deployment of stent grafts, and could also form during the event of aortic dissection. To account for the dynamics of thrombus formation in the biomechanical investigation of ATAA, it would be critical to first study the process of blood coagulation from the initialization to propagation and to stabilization. The characterization of the process of blood coagulation would, therefore, be able to be integrated into the established biomechanical investigations on the ascending thoracic aortic aneurysm and the aortic heart valve.

## **1.8 Research Objectives and Thesis Outline**

The overall roadmap for this dissertation was to first establish an accurate biomechanical model for the ascending thoracic aortic aneurysm. Following closely with regards to the leading risk factors for thoracic aortic aneurysm, the influences of blood pressure under hypertension, the changes in arterial wall stress, and the effects of hematocrits on the wall shear stress distribution were studied. Next, as the bicuspid aortic valve is also considered as an important risk factor for the progression of ascending thoracic aortic aneurysm, a realistic aortic valve model integrated with the sinus of Valsalva was thus developed. Finally, to account for the formation of thrombus potentially due to surgical repair, blood cell damage under excessive shear rate, or aortic dissection, hemorheological investigations were conducted to establish the foundation of blood coagulation dynamics. This leads to the specific research objectives listed as follows:

The first objective was to evaluate the biomechanical response of the ascending thoracic aortic aneurysm under the influence of various hemodynamic conditions, as presented in Chapter 2. Specifically, the current study:

- provides relevant insights to clinically examination by constructing an accurate and robust fully coupled FSI numerical model based on the physiological hemodynamics conditions and anisotropic hyperelastic arterial wall.
- assesses the influence of aortic arterial wall stress, hemodynamics of blood flow, and wall shear stress with patient-relevant geometries due to the change in blood pressures and hematocrits

The second objective was to extend the fully coupled FSI approach to analyze the hemodynamics of a bileaflet mechanical heart valve and the change in hemorheological characteristics due to the variation in hematocrit, as presented in Chapter 3. Specifically, the current study:

- constructs the fully coupled FSI numerical model using physiological hemodynamics conditions for bileaflet mechanical heart valve validated using particle image velocimetry
- evaluates the influence of non-Newtonian shear thinning blood rheology in the biomechanics of the artificial heart valve and extended the investigation under different hematocrit values

The third objective was to study the dynamics of blood clot formation and the interactions of the anticoagulation reversal agents using small amplitude oscillatory shear rheometry, as presented in Chapter 4. Specifically, the current study:

- characterizes the time evolution of the measured storage modulus and the complex viscosity values such that the relationship could be used toward to the existing numerical model for modeling the blood clot formation in ATAA and heart value
- investigates the dynamics of blood clot formation emphasized on unfractionated heparin (UFH) reversal by protamine and recently reported non-toxic universal heparin reversal agent UHRA-7 in human whole blood under different oscillatory frequencies and antidote concentrations

# Chapter 2: Hemodynamics Assessments of the Ascending Thoracic Aorta Aneurysm

## 2.1 Introduction

To operate or not to operate, that's the question. Current guideline for treating thoracic aortic aneurysm recommends a surgical treatment for an aneurysm based on the diameter of the aneurysm sac, in addition to other risk factors such as gender, genetics, smoking, and history of hypertension [5,9]. However, each aneurysm behaves differently and could potentially evolve into an aortic dissection or an aneurysm rupture before the aneurysm reaches the surgical threshold. Studies from CT, MRI, and CFD have revealed that the anatomy of a specific ascending thoracic aortic aneurysm could alter the flow pattern from a smooth laminar flow from the heart into a helical flow. On the other hand, a high velocity blood flow discharging from the heart into a ascending aorta due to a pathological aortic valve, such as bicuspid aortic valve [55,65,145], could induce a concentrated high wall shear stress distribution generated by the blood flow against the aortic wall, which leads to further tissue degradation and aneurysm progression. High blood flow velocity generated by a diseased aortic valve would also result in high fluid stress creating further complications.

Therefore, there is a need to further study the fundamental biomechanics of an ascending thoracic aortic aneurysm regarding the mechanical interactions between the hemodynamics of the blood flow and the structural mechanics of the aneurysm, especially under hypertension. The additional insights from the current biomechanical investigations could potentially be further developed for predicting the progression of a thoracic aortic aneurysm.

# 2.2 Method

## 2.2.1 Patient-specific geometries

Anonymous patient data exemplifying different geometrical characteristic of ATAA and measured blood flow velocity were examined in detail. Data extraction from these cases was approved by the Institution's Research Ethics Board. Specifically, three patient cases were selected: case 1 with similar ascending thoracic aorta dilation near the aortic sinus and the brachiocephalic artery (BCA), case 2 with a greater dilation near the BCA, and case 3 with a greater dilation near the aortic sinus. Each case was evaluated with a normal blood pressure (120/80 mmHg) and a hypertensive blood pressure (160/90 mmHg) for a total of six simulations. The measurements for ATAA geometries and blood flow velocities were conducted with Philips iE33 xMatrix-DS ultrasound system with Philips S5-1 broadband sector array transducer.

Table 2.1: Measured key geometrical factors from the echocardiogram in three cases

	Inlet Diameter [mm]	Outlet Diameter [mm]	Inlet Velocity [cm/s]
Case 1	45	44	160
Case 2	42	53	436
Case 3	48	40	389.3

Three idealized ascending aortae (Figure 2.1) were constructed using data collected from the echocardiograms after the aortic valve and before BCA (Table 2.1). The radius of curvature of the modeled ATAA was approximated to be 55 mm from the center of vessel based on [116]. The modeled outlet was assumed to be 80 degrees from the horizontal, or 10 degrees off the vertical axis, prior to BCA for all three cases. The off-plan curvature of the current models was neglected due to small vertical distance. The aortic wall was modeled as a single, 2.59 mm, intact arterial layer based on the study of Weisbecker *et al.* [98]. Given that ATAA dimensions were measured directly from patients, the geometrical model was pre-calibrated and the final model dimensions would match the measured values. The calibrations of the models were necessary mainly to comply with the measured aortic diameters such that the expansion of modeled outlet would be accounted for.



Figure 2.1: Computational models of idealized ascending aorta based on patient-specific parameters

A simple optimization procedure was utilized for calibrating the final geometry described as follows. A model was firstly computed with normal physiological conditions using minimum blood pressure of 80 mmHg and peak patient-specific flow velocity over 1 sec, or 125% of one cardiac cycle. The computational model would be calculated based on minimum blood pressure and provide a conservative estimate for arterial wall expansion when exposed to hypertension condition. The difference in aortic diameter at the model outlet between the measured and computed values was calculated. The model outlet was modified according to the difference calculated from previous step. Finally, a second model was constructed and recomputed using the identical procedure and reiterated if necessary. The selection of final geometry was determined when the diameter of model outlet was within the echocardiogram's accuracy of  $\pm 1$ mm.

# 2.2.2 Constitutive model

ATAA was modeled with constitutive equations based on the work of Holzapfel *et al.* [76] and Weisbecker *et al.* [98]. The strain energy density function  $\overline{\Psi}$  (Eq 2.1) for evaluating the strain energy stored for material deformation is the summation of the isotropic (neo-Hookean) and anisotropic (collagen fibres) component. The anisotropic portion of the strain energy density function accounts for two symmetrical collagen fibre groups that reinforcing the vessel under blood pressure. While the invariants  $\overline{I}_4$  and  $\overline{I}_6$  are the squares of stretches along the two fibre directions, the material parameters were prescribed based on experimental data [98], where  $\overline{I}_i$  are the invariants and k<sub>i</sub> are material parameters in Eq 2.1. Furthermore, in order to compute the aortic wall deformation Cauchy stress tensor  $\boldsymbol{\sigma}$  was calculated based on Eq 2.2 by Piola transformation.

$$\overline{\Psi} = \frac{k_3}{2}(\overline{l_1} - 3) + \frac{k_1}{2k_2} \sum_{i=4,6} \{e^{[k_2(\overline{l_i} - 1)^2]} - 1\}$$

$$\sigma = J^{-1}FSF^T$$
Eq 2.2

Where *J* is the volume ratio (or det(F)), *F* is deformation gradient, and  $S = 2 \frac{\partial \overline{\Psi}(C)}{\partial C}$  is the second Piola-Kirchhoff stress tensor, and *C* is Cauchy-Green deformation tensor

Based on the constitutive model [76,98], current ATAA models were also assumed to have two symmetrical collagen fibre groups aligned under a predefined crossing angle for the fibres' directions. A curvilinear system was firstly calculating the main path of the collagen fibres along ATAA. The crossing angle for the fibres was secondly imposed due to the radius of curvature after the calculation of the main path (Figure 2.2). During the time-dependent analysis, the main fibre path would change due to arterial deformation; therefore, current fully coupled approach recomputed the direction of fibres for each time step to account for cyclic loading (Figure 2.2). The anisotropic hyperelastic ATAA was modeled with a density of 1100 kg m<sup>-3</sup>, an initial bulk modulus of 1000 MPa, isotropic material parameter of  $\mu = 0.017$  MPa, anisotropic material parameters of k<sub>1</sub> = 0.56 MPa and k<sub>2</sub> = 16.21, and fibre crossing of  $\theta = 51^{\circ}$ [98]. Since current ATAA models were modeled with single unified aortic wall, the median values of the single intact thoracic aorta properties were applied to current constitutive equations as reported by Weisbecker *et al.* The median values of the material properties for characterizing the aorta model was use as the fifty percentile to account for the physiological variations between different individuals.



Figure 2.2: Schematic representation of the collagen fibres distribution at initial condition (left) and at peak systolic blood pressure (right)

The dynamics of blood flow was modeled with incompressible Navier-Stokes equations with the equations for fluid continuity (Eq 2.3) and momentum (Eq 2.4) shown below. Blood flow was assumed to be within laminar region with a density of 1060 kg m<sup>-3</sup> and a constant viscosity of 0.0035 Pa-s. Finally, to compute the interaction between the deformation and stress normal the boundaries where fluid and structure interacted, Cauchy stress was equated to the pressure and viscous terms in Navier-Stokes (Eq 2.5)

$$\nabla \cdot \mathbf{V} = \mathbf{0}$$
 Eq 2.3

$$\rho \frac{DV}{Dt} = -\nabla p + \eta \nabla^2 \mathbf{V} + \rho \mathbf{g}$$
 Eq 2.4

$$\boldsymbol{\sigma} \cdot \boldsymbol{n} = (-\nabla \boldsymbol{p} + \eta \nabla^2 \mathbf{V} + \rho \boldsymbol{g})$$
 Eq 2.5

Where **V** is blood velocity in [m/s], P is pressure in [Pa],  $\rho$  is blood density  $[kg m^{-3}]$ ,  $\eta$  is viscosity in [Pa s], g is gravity in  $[m s^{-2}]$ , and n is the normal vector.

As the Newtonian model assumes the blood has uniform viscosity independent from the shear rate generated by the blood flow, the Carreau model (Eq 2.6) for blood viscosity was used to assess the impact on the biomechanical characterizations when the shear-thinning behavior of blood was included. The constants used in Carreau model are well established widely accepted for the modeling of normal blood at body temperature. The Carreau model's modeling parameters are viscosity at zero shear rate,  $\eta_0$  (0.056 Pa s), the viscosity at infinite shear rate,  $\eta_{\infty}$ , (0.0035 Pa s), the relaxation time,  $\xi$  (3.313s) and the power-law index,  $n_{Carreau}$  (0.3568).

$$\eta(\dot{\gamma}) = \eta_{\infty} + (\eta_0 - \eta_{\infty}) [1 + (\xi \dot{\gamma})^2]^{\frac{(n_{Carreau} - 1)}{2}}$$
 Eq 2.6

The use of the Carreau model provides a realistic shear thinning behaviour of blood for hemodynamic modeling; however, the model lacks the portability to translate into clinical settings. As an alternative model, the Quemada model (Eq 2.7) characterizes blood's shear thinning properties by incorporating the haematocrit as one of its modeling variables. The degree of shear thinning can therefore be easily adjusted by changing the haematocrit values. Additionally, the Quemada model accounts for red blood cells' critical shear rate at agglomeration.

$$\eta = \frac{\eta_{plasma}}{\left(1 - \frac{Htc \cdot k_{eq}}{2}\right)^2}, \text{ and } k_{eq} = \frac{k_0 + k_{\infty} \cdot \sqrt{\dot{\gamma} / \dot{\gamma}_c}}{1 + \sqrt{\dot{\gamma} / \dot{\gamma}_c}}, \qquad \text{Eq 2.7}$$

Where  $\eta_{\text{plasma}}$  is the viscosity of blood plasma in [Pa s], Htc is the hematocrit in [%],  $k_0$  and  $k_{\infty}$  are the maximum volume fraction at zero and infinite shear rates,  $\dot{\gamma}$  is the shear rate in [s<sup>-1</sup>], and  $\dot{\gamma}_c$  is the critical shear rate in [s<sup>-1</sup>] for erythrocytes agglomeration

# 2.2.3 Numerical methods

A finite element model of idealized human ATAA using patient-specific data was created with COMSOL Multiphysics® (V5.2, Stockholm, Sweden). The ATAA model utilized a fully coupled fluid-structure interaction method with laminar Newtonian blood and an anisotropic hyperelastic nearly incompressible aortic wall. The current FSI method and modeling procedures were developed and upgraded from our previously FSI study [135]. Fully coupled method was necessary to account for the close interactions between pulsatile blood flow and ATAA deformations. The simulations were conducted in 3D using parallel sparse direct solver MUMPS

(MUltifrontal Massively Parallel Sparse direct Solver) with a relative error less than 1e-3. The model inlet of ATAA was applied with a relative motion fixed while the model outlet was applied with a free sliding boundary where only normal displacements were constrained along the crosssectional plane.

The internal aortic wall was the interaction boundaries for computing structure displacement due to fluid pressure and vice versa. The model inlet and outlet of ATAA were applied with measured velocity and pressure conditions. Peak velocities measured from the echocardiograms and a normotensive pressure of 120/80 mmHg and a hypertensive pressure of 160/90 mmHg were applied. The velocity boundary was imposed with time-depended fully developed velocity profile. The boundary profiles were firstly normalized according to the profile published by Bürk et al. [27] and Vasava et al. [116] and then scaled to the measured peak values from the echocardiogram (Figure 2.3 and Figure 2.4). Finally, five cardiac cycles (0.8s each or 75 beats per minute) were simulated and the last (5<sup>th</sup>) stable cycle, from 3.2s to 4.0s, was taken for analysis to account for numerical instability and errors from initial conditions.



boundary with peak velocity of 1.6 m/s

Figure 2.3: Velocity profile at the aortic inlet Figure 2.4: Blood pressure profile at the aortic outlet with normal and hypertensive distribution

## 2.2.4 Mesh convergence study

Mesh convergence studies were carried out to verify current simulations were independent from domain discretization. Blood flow velocity magnitude at three temporal instances at peak systole (at 3.3s), mid systole (at 3.4s), and end systole (at 3.5s) during the simulated fifth cardiac cycle were analyzed using the hypertensive scenario for conservative analysis. The average crosssectional velocities were taken at the midpoint between inlet and outlet. Four mesh configurations were iterated for to conclude a configuration with solution convergence within 1%. The combination of tetrahedral and brick elements was employed in order to account for boundary layer and radius of curvature. A predefined variable, Degree of Freedom (DOF), was used for correlating mesh elements and the computational requirement. DOF is defined by the multiplication of the total number of elements' nodes by the number of dependent variables required to be solved for.

The velocity magnitude verse total DOF (the product of dependent variables and the total number of mesh elements) per mesh configuration at three time steps during the systolic phase was determined (Figure 2.5). This ensured that not only the solution was mesh independent spatially but also temporally. The computed velocity magnitude showed insignificant variation with a DOF above 1.8e5 (Figure 2.5). All subsequent models constructed inherited the identical mesh configuration and treatment used in mesh conversion study to maintain consistency.



Figure 2.5: Velocity magnitude vs degree of freedom for different time step. The *dotted lines* indicated  $\pm 1\%$  in averaged solution from the last two meshes

# 2.3 Results

### 2.3.1 Ascending thoracic aorta hemodynamics

To visualize the hemodynamics of ATAA, 3D velocity streamline plots were created for investigating the flow pattern, especially at peak systolic period of 3.3s (Figure 2.6). Half of the aortic wall was masked to display blood flow distribution. Briefly, case 1 (Figure 2.6(a, d)) had an approximately equivalent ATAA dilation at the inlet, after the aortic sinus, and outlet, before BCA. Case 2 (Figure 2.6(b, e)) had a greater dilation at the outlet and case 3 (Figure 2.6(c, f)) had a greater dilation at the inlet. Blood flow hemodynamics were affected by the unique geometrical as each of the case presented a certain degree of helical flow and vortices due to the anatomical curvature.



Figure 2.6: 3D velocity streamline at peak systolic phase of 3.3s for normotensive (a, b, c) and hypertensive blood pressure (d, e, f) for the modeled cases

A moderate level of vortices can be observed for case 1 with blood flow roughly distributed at the outlet while case 3 showed flow acceleration at the outlet due to its narrower outlet diameter than inlet. Case 2, on the other hand, revealed a significant amount of vortices with high-velocity blood flow exiting near the superior side of the aortic arch. The inferior side of the aortic arch for case had only minimum amount of blood distributed. Interestingly, the magnitude of the evaluated Von Mises stress, which will be discussed in detail in a later section, tended to have a higher stress concentration near the inferior side of the aortic arch. Other hemodynamic developments, including vortices distributions, velocity magnitudes, and aortic wall expansions, had minor differences when compared between normal and hypertensive blood pressure scenario. The minor variations were expected since the applied pressure conditions were the only differences while geometry, peak velocity, and wall properties remained the same.

To further examine the distribution of velocity for each case, central cross-sectional velocity contours (XY plane) and mid cross-sectional velocity contours (YZ plane) were plotted in Figure 2.7 and Figure 2.8, respectively. Results for both blood pressure conditions at peak systole and end diastole were plotted. As discussed, the velocity distributions were similar during the peak systolic period. The peak flow velocity under normal blood pressure for case 1, 2 and 3 was 1.7 m/s, 4.56 m/s, and 6.56 m/s, respectively. In comparison, the peak velocity magnitude under hypertensive blood pressure for case 1, 2 and 3 had a minor decrease with value of 1.64 m/s, 4.48 m/s and 6.11 m/s. This is likely due to the increase in vessel expansions under higher blood pressure. The velocity contours also confirmed that the flow velocity was much lower at the inferior side of the aortic arch, shown in Figure 2.7(a, g), Figure 2.7(c, i), Figure 2.7(e, k). Specifically for case 2, the low-velocity region was caused by significant flow recirculation and reversed flow near the outlet of ATAA. Similarly, case 1 and case 3 both have affected by the flow

recirculation during peak systolic phase. The flow distributions at the end-diastolic phase, on the other hand, had similarity across all cases with the maximum velocity magnitude approximately between 0.2 m/s to 0.27 m/s. Each case had some variations in flow distributions. Specifically, case 1 and case 2 had significant recirculation flow dominating ATAA while the recirculating flow for case 3 had resolved to leave a low-velocity vortex at the center of the domain.



Figure 2.7: Velocity contour at the central cross section of ascending thoracic aorta at peak systolic phase under normotensive (a, c, e) and hypertensive(g, i, k) blood pressure and end diastolic phase under normotensive(b, d, f) and hypertensive(h, j, l) blood pressure



Figure 2.8: Velocity contour at the middle cross section of ascending thoracic aorta at peak systolic phase under normotensive (a, c, e) and hypertensive(g, i, k) blood pressure and end diastolic phase under normotensive(b, d, f) and hypertensive(h, j, l) blood pressure

## 2.3.2 Maximum wall shear stress (WSS)

Three components of shear stress were individually analyzed. Maximum shear stress along the inner aortic wall surface was calculated and plotted in time (Figure 2.9). Overall, WSS magnitude were all below 600 dPa for all cases and pressure conditions and case 1 showed relatively smaller WSS magnitude due to lower peak velocity. However, as smaller velocity 45
magnitudes were observed for hypertensive scenarios, WSS magnitudes analyzed were larger for normotensive scenarios. In addition, not all WSS components had noticeable difference between normotensive and hypertensive conditions.

	Case 1		Case 2			Case 3			
WSS Component	YZ	XZ	XY	YZ	XZ	XY	YZ	XZ	XY
Peak Systolic Difference	8.4%	11.4%	2.4%	15.9%	2.6%	7.3%	2.3%	8.0%	10.2%
Average Difference	13.4%	6.1%	4.2%	14.2%	12.6%	5.7%	5.7%	7.8%	9.5%
Maximum Difference	40.5%	27.8%	13.6%	50.8%	54.9%	36.9%	17.2%	27.5%	34.7%

Table 2.2: Summary of the difference in maximum WSS between normal and hypertensive pressure conditions

The differences in WSS magnitudes for all cases under both pressure conditions are summarized in Table 2.2. Combining the results presented in Figure 2.9(a) and (d), all cases had small WSS variances when blood pressure increase from normotension to hypertension condition. The least significant difference in WSS was found in case 3. Looking at the WSS components, the YZ component for both case 1 and 2 has relatively similar difference while case 3 had a larger difference in the XY component. The maximum difference in WSS during peak systolic period were 11.4% for case 1(XZ), 15.9% for case 2(YZ), and 10.2% for case 3(XY).

120/80 mmHg

160/90 mmHg



Figure 2.9: Maximum wall shear stress over one cardiac cycle for shear stress components under normotensive (a, b, c) and hypertensive (d, e, f) blood pressure

# 2.3.3 Arterial wall deformation

As the diameter of an ATAA is one of the key risk factors, the deformations and expansions were investigated in detail. Specifically, ATAA diameters at the mid-stream and modeled outlet were calculated. The average diameters were computed by approximating the cross-sectional area at each location to be circular. The relative expansions at each time instance were then calculated based on the aortic diameter at the beginning of the cardiac cycle. Again, the analysis started at the beginning of the fifth cardiac cycle (3.2s) to avoid any influence from initial solutions. The results for ATAA expansions at the mid-stream and the modeled outlet are presented in Figure 2.10. The position of the mid-stream is defined at the halfway through the ATAA between aortic inlet and outlet.

 Table 2.3: Summary of the percent difference in aortic wall expansion under normal and hypertensive blood

 pressure for three cases at the mid-stream and the outlet of ATAA

Percent difference	Case 1		Case 2		Case 3	
in arterial wall expansion	Mid- Stream	Outlet	Mid- Stream	Outlet	Mid- Stream	Outlet
Cyclic average	23.6%	36.6%	34.4%	69.4%	19.5%	118.7%
Systolic average	38.5%	65.8%	62.0%	132.6%	26.9%	227.9%
At peak systole	51.8%	53.8%	164.8%	511.8%	0.1%	112.5%

The percent difference of the expansions was calculated and averaged for the fifth cardiac cycle at the mid-stream and the outlet of ATAA, summarized in Table 2.3. For all cases, the cyclic average at the outlet had a higher wall expansion than at the mid-stream with an approximate

increase of 55%, 100%, and 500% for case 1, 2, and 3, respectively. As expected, the aortic wall has larger expansion during systolic phase under a hypertensive blood pressure (Figure 2.10). The percent difference, which increased with respected to the increase of blood pressure, for the systolic average over cyclic average were approximately 71%, 86% and 65% for cases 1, 2, and 3, respectively. However, the thoracic aorta did not have positive expansion at all instance, such as the cases shown by case 2 (Figure 2.10 (b), (e)) and the thoracic outlet of case 3 (Figure 2.10 (f)). Specifically in case 3, it is suspected that due to its geometrical configuration, where the thoracic outlet is much smaller than the thoracic inlet, the outlet diameter contracted during systolic phase under pulsatile pressure while the mid-stream diameter expanded (Figure 2.10 (f)).

At peak systole of 3.3s (Table 2.3), the aortic wall expanded significantly under a hypertensive condition. Case 1 had relatively similar difference at the mid-stream (51.8%) and outlet (53.8%) of the ATAA. The largest difference among the three cases in aortic wall expansion between two blood pressure conditions was found in case 2. At peak systole, the percent differences in wall expansion between two blood pressure conditions were three times greater at the outlet (511.8%) then at the mid-stream (164.8%). On the other hand, the aortic wall expansion virtually remained unchanged at mid-stream for case 3 under difference was found at the aortic outlet (112.5%).



Figure 2.10: Arterial wall expansion at the mid-section of ascending thoracic aorta and thoracic aortic outlet for case 1 (a, d), case 2 (b, e), and case 3 (c, f)

To further quantify the aortic wall expansion, the cyclic strain of given ATAA was calculated based on the diameter of ATAA at peak systole and end diastole. Specifically, the circumferential cyclic strain ( $\epsilon_{00}$ ) is defined as one-half of the ratio of the square of aortic circumferences (C<sub>s</sub>, the systolic circumference and C<sub>d</sub>, the diastolic circumference) minus one, as defined by Morrison *et al.*[207], and shown in Eq 2.8. It was approximated that the cross section of the ATAA was roughly circular; therefore, the circumferential cyclic strain was calculated based on the diameter of the aorta (D<sub>s</sub> and D<sub>d</sub> in [mm]) at any given time. One potential factor that could affect the estimation of a cyclic strain of aortic wall would be the wall thickness as it would change under stress and deformation. However, as found in a current model, the change in aortic wall thickness was small compared to the change in aortic diameter and thus was neglected in strain analysis. The systolic and diastolic diameters were analyzed with the maximum systolic aortic diameter and minimum diastolic aortic diameter such that a conservative estimation could be made.

$$\varepsilon_{\theta\theta} = \frac{1}{2} \left( \frac{C_s^2}{C_d^2} - 1 \right) = \frac{1}{2} \left( \frac{D_s^2}{D_d^2} - 1 \right)$$
 Eq 2.8

<b>E</b> 00	Case	e 1	Case	e 2	Case 3	
- 00	Mid-stream	Outlet	Mid-stream	Outlet	Mid-stream	Outlet
Normotensive	2.56	2.55	1.90	2.00	4.73	2.23
Hypertensive	3.73	3.88	3.03	3.20	4.75	3.49
% Increase	46%	52%	60%	60%	0%	56%

 Table 2.4: Circumferential cyclic strain for three modeled cases under normotensive and hypertensive

 condition at mid- ascending thoracic aorta and outlet

The circumferential cyclic strain for all three modeled cases at two locations and under two blood pressure conditions were summarized in Table 2.4. On average, the strain at the mid-stream of ATAA was 3.45 whereas the strain at the outlet was slightly less with a value of 2.89. For all locations and pressure conditions, except for mid-stream in case 3, the circumferential cyclic strains were 55% greater on average under hypertensive blood pressure. The results from current strain analysis with three modeled ATAA were in agreement with the results published by Morrison *et al.* [207], who showed an average strain value of  $3.4\pm1.5$  at the outlet location of current study.

# 2.3.4 Arterial wall stress

The Von Mises stress was used in order to evaluate the aortic wall stress for different cases. Due to aortic wall deformations and expansions, it was expected that higher stress level would be found for the cases where ATAA was experiencing hypertensive pressure. The Von Mises stress distributions along the aortic wall at peak systolic phase is displayed in Figure 2.11 and the 3D plots. As discussed earlier, stress buildup can be observed on the inferior side of the aortic arch. Note that the stress distributions for case 2 were more smoothly distributed than the other two cases with lower stress magnitude. On the contrary, case 3 revealed the highest stress level for both normal (Figure 2.11(c)) and hypertensive (Figure 2.11(f)) scenarios. Again, it was hypothesized that the geometrical differences in aortic wall dilation were the key factors affecting the aortic wall stress distribution.



Figure 2.11: 3D von Mises stress distribution within ascending thoracic aorta at peak systolic phase of 3.3s for normotensive(a, b, c) and hypertensive(d, e, f) blood pressure

The further quantitative analysis in the total surface area under a threshold Von Mises stress of 250kPa was presented in Figure 2.12. All three cases have an increase in wall stress under hypertensive blood pressure. Specifically, for case 1, the high-stress region, where the surface area is greater than 250kPa, was increased from 2% to 28% or an increase of 255%. More surprisingly, the high-stress region for case 2 was increased by a dramatically of 2900% with high-stress area increasing from 2% to 63%. Although case 3 also had an increase in high-stress region under hypertension, the increase was only 5%. However, the high-stress region for case 3 under the normotensive blood pressure was much higher than the other two cases. The high-stress region covered 88% of the total inner aortic surface for case 3.



Figure 2.12: Surface area (in percent) along the inner arterial wall at peak systole of 3.3s

# 2.3.5 The effect of hematocrit on the biomechanics of an ATAA

While the Newtonian analysis presented above demonstrated the influence of increasing blood pressure on the biomechanics of the ATAA, it would be necessary to further investigate the effect of hematocrits, or the volume fraction of red blood cells, as the blood viscosity increases with the increase in hematocrits. To begin the investigation, a sensitivity analysis on case 1 and 2 were conducted using the Carreau model for modeling the shear thinning rheological behavior of blood. This would provide an examination with regards to the influence of including the non-Newtonian shear thinning behavior of blood to any changes to the ATAA biomechanics that were obtained using the Newtonian analysis.

Table 2.5: Average percent difference in maximum WSS between normotension and hypertension

% Difference		Case 1		Case 2			
	YZ	XZ	XY	YZ	XZ	XY	
Newtonian	13.4	6.1	4.2	14.2	12.6	5.7	
Carreau	9.7	5.8	3.1	8.4	13.7	5.7	

The sensitive analysis began by investigating the difference in the maximum WSS between the normotension and hypertension scenario with the use of the Newtonian and Carreau model (Eq 2.6). Table 2.5 summarized the difference, in percentages, of all three components of the maximum WSS for the two cases investigated. Differences were found in both cases between the two rheological models used. Specifically, the difference in the maximum WSS between the two blood pressure scenarios suggested an overall higher variation in shear stress predicted by the Newtonian model than the Carreau model.

However, the use of the Carreau model predicted a smaller difference in maximum WSS for almost all components except the XZ component in case 2. A full analysis of maximum WSS for all six components is shown for the fifth cardiac cycle simulated using the Carreau model (Figure 2.13). The magnitudes of WSS for case 2 were much higher than case 1, similar to the prediction made by the Newtonian model. This would be due to a higher blood inlet velocity to start with for case 2. However, while in case 1, the maximum WSS for both the YZ and XZ components were relatively smaller than the YX component, the case 2 had a higher maximum WSS in the XZ and YX components. This may suggest that in addition to the upstream blood flow velocity, the geometry of an ATAA had additional influence on the elevated maximum WSS. This information would be potentially useful for investigating blood cell damages under shear flow and/or thrombus formation. Finally, the use of the Carreau model had an insignificant effect on the structural responses of the ATAA. It was found that the average differences in aortic expansion under the cardiac cycle were less than 1% for both blood pressure scenarios between two rheological models. There were only minimal differences in blood flow distribution and wall stress distribution when the Carreau model was employed.

Given the inclusion of shear thinning blood rheology would have a significant influence on the shear stress prediction, it would be worth to examine how the hematocrit could affect the biomechanics of an ATAA. As the Quemada model (Eq 2.7) captures the shear thinning behavior of blood, any region with a lower shear rate within the aneurysm would lead to higher blood viscosity. As a result, there would be differences in the shear stress distribution between normotension and hypertension, as well as between the hematocrits.



Figure 2.13: Components of maximum wall shear stress under hypertensive scenario for Case 1 and Case 2 with the Carreau model

 Table 2.6: Maximum WSS magnitude at peak systole for the hematocrit of 27% and 44% under normotension

 and hypertension

	Case 1	Case 1	Case 2	Case 2	Case 3	Case 3
	27%Htc	44%Htc	27%Htc	44%Htc	27%Htc	44%Htc
Normotension [dPa]	86.6	143.9	248.9	449	320.8	640
Hypertension [dPa]	79.1	132.3	238.7	442.9	295.3	585



Figure 2.14: Viscosity versus shear rate predicted by the Quemada model for different hematocrits (hollow lines refer to viscosity value after 100 s<sup>-1</sup> using secondary axis on the right)

The maximum WSS at peak systole for the two hematocrits simulated is summarized in Table 2.6 with the corresponding viscosity values for a hematocrit of 27% and 44% shown in Figure 2.14. Overall, there was an approximate 8% decrease in maximum WSS under hypertension for Case 1 and 3, and the decrease in WSS for Case 2 was smaller at 4.1% and 1.4% for 27% and 44% hematocrit (Htc.), respectively. The maximum WSS magnitude increased dramatically with the increase in hematocrit for all cases regardless of the blood pressure conditions. The approximate increase of WSS due to the increase of hematocrit, as shown in Figure 2.15, is 40% (Case 1), 45% (Case 1) and 50% (Case 3).



Figure 2.15: Maximum wall shear stress magnitude over one cardiac cycle under normo-tension for three cases between two hematocrits of 27% and 44%

To better visualize the distribution of WSS and high-light the increase of stress with higher hematocrit, the contour plots for all cases are shown in Figure 2.16 for normo-tension and in Figure 2.17 for hypertension. The overall distributions of the elevated WSS for all cases are consistent. With the increase in hematocrit, the shear stress propagates to the upstream from the anterior and posterior side of the ATAA. Given that the blood cells and endothelial layers might respond to the elevated shear stress including shear induced platelet aggregation and thrombosis, the difference in patients' hematocrit values combining with the ATAA's anatomical configuration could be an additional assessment factor during an evaluation. In addition to the WSS distributions included in Figure 2.16 and Figure 2.17, the von Mises stresses within the arterial wall were also plotted. There was a significant increase in the stress distribution under the hypertensive condition; however, the variations between the hematocrits were minimum. The distribution of the von Mises stress along the internal arterial wall surface can be assessed by a threshold of 0.25 MPa. Note the increase in the arterial wall stress due to the increase in blood pressure and the increase in wall shear stress due to the increase in hematocrit.



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### 2.4 Discussion

## 2.4.1 Arterial wall motion

We have made several novel observations in this FSI study that included the aortic wall and blood flow. First, we found significant differences occur in aortic wall deformation in hypertensive compared to normotensive blood pressure conditions. Second, the motion of ATAA was heavily influenced by the unique geometrical characteristics exhibited of an aortic aneurysm. Specifically, since the aortic diameter dimension was relatively similar for case 1, the aortic wall expanded at the mid-stream and the outlet followed relatively the same trend. This was expected since the ATAA for case 1 was not geometrically converged or diverged toward the downstream and the blood flow was steady without significant flow separation as shown in Figure 2.7.

In case 2, where the ATAA outlet was dilated, the diameter of the aorta decreased for normotensive condition during the beginning of systolic phase for both the mid-stream and the outlet. On the other hand, the aortic diameter increased as expected during systolic period under the hypertensive condition. Additionally, case 2 showed an unsteady aortic wall expansion during one cardiac cycle for both blood pressure conditions. Initially, the decrease in aortic diameter for the normotensive scenario seemed to be contradictory results; however, current analysis only considered the change in aortic diameter under pulsatile pressure while the translation of the aorta under pressure was not considered in the deformation calculation. This case, the current deformation analysis would focus on the aorta's expansion under normotensive and hypertensive blood pressure. Of course, from our computed models, the ATAA would have both expansion as well as upward translation during systolic phase. The model from case 2 would translate upward under systolic period by approximately 3mm, which would be twice than arterial wall expansion. Similarly, the vertical translation for case 1 and case 3 was approximately 1 mm and 2 mm, respectively.

Finally, given that the geometrical configuration for case 3 was the opposite of case 2, the behavior of aortic wall motion from case 3 was expected to be different than case 2. Referring back to Figure 2.10, it was evidential that the diameter of ATAA increased at the mid-stream for both blood pressure conditions but the aortic diameter decreased at the aortic outlet. This was likely due to the fact that case 3 was tapered at the aortic outlet and the increase in blood pressure during systolic phase caused the midstream of the ATAA to expand first while the outlet contracted due to continuous solid domain. Combining the finding of ATAA translation and expansion, case 1 had moderate aortic expansion at the midstream and aortic outlet with minimum vertical aortic translation. Case 2 had minimum aortic expansion at both the midstream and aortic outlet with minimum vertical aortic translation. Case 3 has maximum wall expansion at the midstream and maximum wall reduction at the aortic outlet with moderate vertical aortic translation.

#### 2.4.2 Arterial wall stress

Our analysis contributed novel insights into the location of aortic wall stress in aortic aneurysm. For the analysis of aortic wall stress, the current model's predictions agreed with the general argument that a higher stress distribution would be generated with higher blood pressure at the wall boundary. However, aortic wall stress distribution would be different and affected by the geometrical configuration of the ATAA. Specifically, the location where the high concentrated wall stress located varies for each case under normotensive and hypertensive blood pressure. Based on stress analysis from Figure 2.11, the elevated wall stress for case 1 under normotensive condition was 27.3 mm from the inlet of ATAA. Comparing with the hypertensive condition for case 1, the high-stress region migrated to 18.5 mm from the inlet, or 8.8mm closer. Similarly, the

high-stress region for case 2 was 15.1mm closer to the inlet under the hypertensive condition, with the region located at 35.2 mm and 20.1 mm away from the inlet for normotensive and hypertensive conditions, respectively. However, for case 3, mostly likely due to a much higher wall stress distribution than the other two cases, the high-stress region was only 2.1 mm closer to the inlet with a region located at 16.6 mm and 14.5 mm away from the inlet for normotensive and hypertensive and hypertensive conditions, respectively.

The stress distribution of the ATAA wall also revealed some characteristics that was specific to each case. With wall stress value agreeing with published results [22,24–26,97,102], at peak systolic period and under normotensive condition, case 1 had slightly higher distribution for the high stress region, where the area with wall stress that's greater than 250kPa, compared against to case 2. On the other hand, under peak systolic period and hypertensive condition, the increase in high stress region was significantly greater in case 2 then in case 1. This increase in elevated wall stress distribution suggested that case 2 could be affected much more under hypertensive blood pressure and careful monitoring in blood pressure might be necessary. As for the wall stress distribution of case 3, it was shown that the high stress regions were much higher than case 1 and case 2 for both normotensive and hypertensive blood pressure. This is because the area with high stress distribution in case 3 was already 88% of the inner ATAA under normal blood pressure. This suggested that case 3 should require more frequent evaluations in aneurysm progressions.

Based on the aortic wall motion and predicted wall stress, we observed that the unique geometrical characteristic from various aortic diameters would have dramatic influences in the biomechanics evaluations of an ATAA. The geometrical configurations of ATAA could potentially be one of the risk criteria in patient managements and decision makings, especially during the initial evaluation stage. For example, if a patient is seen with an ATAA with a larger

aortic diameter before BCA then the aortic diameter measured distally to the aortic sinus (case 2), then this patient would potentially require additional, more active, monitoring and managements in hypertension. Furthermore, if a patient is seen as the opposite of the previous (case 3), then a more urgent management in ATAA treatment might be necessary.

## 2.4.3 Hemodynamics

We found that the distribution of blood flow was similar for each case with minor difference in vortices generation. At peak systolic period, flow separation and significant vortices could be seen in case 2. This was due to a larger aortic outlet as well as high inlet blood velocity over the nature curvature of the ATAA. Similarly, there were also blood recirculation for case 1 and case 3 near the inferior side of the aorta. Due to the tapered aortic outlet for case 3, blood flow accelerated and velocity magnitude was much higher at the aortic outlet than the prescribed inlet velocity. At end diastole period, blood recirculated within the ATAA and vortices generation could be seen in both Figure 2.7 and Figure 2.8. The area at the inferior side of the ATAA, where blood velocity was lower at peak systolic period due to flow separation, was experiencing relatively higher velocity at the end diastole period due to flow recirculation.

Looking at the shear stress distributions at the inner wall of ATAA, the two shear stress components (XY, and XZ) with larger maximum WSS magnitude were evident (Figure 2.18) under hypertension. Regardless of the geometrical configurations, the distributions of WSS were similar across three cases. More specifically, the WSS in XY component were concentrated at the outlet on the superior and inferior side whereas the WSS in XZ component were concentrated at the anterior and posterior side of the ATAA. As for the magnitude of WSS, it is clear that all cases were predicted to have a WSS magnitude that was above the normal value of 15 dPa [123]. This

was expected since the results are using physiological parameters obtained from real patient cases with ATAA under hypertensive conditions. Additionally, given that the exposure time for high WSS can also affect how cells and tissue get damaged, the evaluations and predictions using the calculated WSS values on tissue damage and aneurysm rupture are still ongoing. In our current cases, WSS distributions were more or less symmetrically distributed. Patient-specific geometry could potentially provide additional information on the specific area where WSS concentrated and where cells and tissues experienced accumulative high shear stress and could result in cell damages. This is an additional analysis which is part of our future planned work.

## 2.4.4 Hematocrits

In addition to the change in wall stress and WSS due to the change in blood pressure conditions, the investigation on changing hematocrits also yielded some interesting results. Specifically, the effect of blood pressure and hematocrit on ATAA biomechanics seemed to be independently affecting the arterial wall stress and the wall shear stress. Under the same blood pressure scenario, the increase in hematocrit only increase WSS but not arterial wall stress. While the arterial wall stress distribution seemed to be relatively the same between the Newtonian and the non-Newtonian modeling, the WSS showed a stronger dependency under the influence of blood's shear thinning behavior during modeling. As a high WSS distribution is one of the biomechanical factors that could promote the development of an aneurysm, future investigations utilizing computational methods should account for the non-Newtonian characteristics of blood.

XY Component





(a) Case 1















Figure 2.18: 3D hypertensive wall shear stress distribution in dPa(dyne/cm2) within ascending thoracic aorta at peak systolic phase of 3.3s for XY component (a, b, c) and XZ component (d, e, f)

## 2.4.5 Clinical applications

Current blood pressure management for patients with aortic aneurysm focuses on blood pressure target values and recognizes the magnitude of the size of the aortic aneurysm. The results of this study suggest an additional approach. Our findings in the hypertensive state were that the greatest amount of aortic expansion, the greatest peak wall shear stress and the greatest increase in high wall stress distribution, all occurred in the case with the aortic outlet diameter greater than the inlet diameter. This finding suggests that patients with this kind of ascending aortic aneurysm need much more vigorous antihypertensive drug treatment in order to lower blood pressure to a target lower than patients whose aorta at the sinuses (inlet) is larger than the diameter of the ascending aorta at a more distal location (outlet). The data in the present study need clinical application. Longitudinal studies on aneurysm progression as an outcome variable should be conducted based on inlet and outlet diameter, the degree of aortic expansion, wall shear stress and percentage of stress in the ascending aorta. The effect of antihypertensive treatment strategies on aortic wall expansion and wall stress warrant future clinical trials.

#### 2.4.6 Layer-specific arterial wall models

As the biomechanical properties of intima, media, and adventitia, differ from each other, it would be interesting to elaborate on the current ATAA models with a single unified aortic wall into layer-specific models. As discussed in [103,118] using the three-layer models, the arterial wall stress distributions changed across each layer of the aorta. The potential of aortic wall buckling and collapsing due to the instability of the stress generated from the blood flow under specific conditions may lead to the progression of aneurysms and dissection [118]. The modeling procedure for creating the layer specific ATAAs remained nearly identical to the unified layer ATAAs including the geometrical pressurization optimization as discussed above. The modifications in

ATAA geometry were made to create a computational domain for each layer using the measurements by Weisbecker *et al.* [98]. Instead of a unified aortic wall thickness of 2.59 mm, the intima, media, and adventitia have a thickness of 0.48 mm, 1.18 mm, and 0.93 mm, respectively. Subsequently, the orientation of the fibres was depended on each aortic wall layer (Figure 2.19). The medial values of the anisotropic material parameters were also used:  $\mu_{int} = 0.034$  MPa,  $k_{1,int} = 4.34$  MPa,  $k_{2,int} = 13.32$ ,  $\theta_{int} = 46.5^{\circ}$ ,  $\mu_{med} = 0.028$  MPa,  $k_{1,med} = 0.14$  MPa,  $k_{2,med} = 11.90$ ,  $\theta_{med} = 38.4^{\circ}$ ,  $\mu_{adv} = 0.020$  MPa,  $k_{1,adv} = 0.39$  MPa,  $k_{2,adv} = 6.79$ , and  $\theta_{adv} = 52.3^{\circ}$  [98]. In order to evaluate the influence of the three-layer models, Case 1 and Case 2 were studied using identical boundary conditions.



Figure 2.19: Schematic representation of the fibre orientations for the multi aortic wall layer model (black – intima, blue – media, yellow – adventitia).

The preliminary results suggested the averaged von Mises stress experienced the aortic wall layer was the greatest within intima as shown in Figure 2.20. The averaged wall stress peaked at approximately 0.8 and 0.6 MPa in intima for Case 2 under normotension and hypertension, respectively. A decrease of approximately 50% in the averaged wall stress can be seen between the intima and media layer. Interestingly, adventitia and the exterior surface of the ATAA experienced an almost insignificant amount of averaged wall stress comparing to intima during the cardiac cycle. Additionally, under the identical hemodynamical boundary conditions, Case 2 experienced slightly higher averaged wall stress than Case 1, suggesting a pure influence from the aneurysm anatomy. Due to the significant increase in the stress experienced by intima, the previous usage of 0.25 MPa threshold for the evaluation of the high-stress region was no longer applicable and a new threshold level would be required. In terms of blood flow velocity and wall stress distributions, the contours of the results were plotted in Figure 2.21. Aside from the intima layer now sustained the most stress, the influence of hypertension on the wall stress followed the similar trend as seen previously: both Case 1 and Case 2 experienced an increased wall stress distribution.



Figure 2.20: Averaged von Mises stress along the arterial wall for multilayer arterial wall models – (a) Case 1 and (b) Case 2 under normotension (solid line) and hypertension (hollow line)



Figure 2.21: Multilayer arterial wall models at peak systole under normotension and hypertension for Case 1 and Case 2 - (a, b) contour of velocity streamline distributions, (c, d) contour of von mises stress distributions in the arterial wall

### 2.4.7 Study limitations

We have constructed accurate FSI models for the ATAA with an anisotropic arterial wall that considered the properties of the arterial wall focusing on its collagen component. Three different ATAAs were modeled using geometrical and physiological parameters measured from patient data, which were geometrically different from each other. There are several assumptions and limitations that warrant discussion. First, the ascending thoracic aorta was modeled with uniform wall thickness and was passive without active muscle activation and aneurysm remodeling, which would be an important aspect of the future study on the interaction between the hemodynamic stresses and the aortic wall deformation/motion. Although the orientations and directions of collagen fibres were coupled with solid mechanical motions under pulsatile flow, the crosslinking angle for the fibres was configured as a constant. The assumption of constant collagen fibre angle was made since it would be difficult, if not impossible, to obtain patient-specific time depended on fibre angle for each model. The properties of the aorta would also depend on the section of the artery as well as the progression of the disease. As discussed in the ATAA pathogenesis, fluid-induced shear stress would influence endothelial cells and could potentially lead to arterial inflammation under non-physiological shear stress. The extended interactions between aortic wall stiffening, blood vessel deformation, and hemodynamics will need to be addressed in future studies. The patient geometries also neglected the in-plane curvature that could potentially introduce additional vortices and affect the overall hemodynamics and aortic motion. However, we believed that this simplification would not have a major effect on the hemodynamics in the ascending aorta, which we studied, except if the computational domain was extended to cover the aortic arch and/or descending thoracic aorta.

# 2.5 Conclusion

The current computational method utilized realistic anisotropic aortic material properties with fully coupled fluid-structure interaction for robust and repeatable hemodynamic and biomechanical analysis. These methodologic computations could be useful to aid clinical assessments. The current study found that while the overall blood velocity distributions were similar between normotensive and hypertensive conditions, there were considerable differences in the maximum WSS. Our model predicted significant and novel changes in arterial wall deformation when blood pressure changed from normotensive to hypertensive conditions. The models successfully predicted the circumferential cyclic strain and demonstrated that elevated blood pressure also caused the high-stress region to migrate much closer to the thoracic aorta inlet near the aortic root. Finally, wall stress analysis at the internal layer of the ascending thoracic aorta, showed that the region with high concentrated wall stress increases dramatically under hypertension. Based on the geometrical configuration of ascending thoracic aorta, our current modeling technique provides insights regarding the motion and wall stress distribution of the ascending thoracic aorta. The next step for our investigation is to introduce additional geometrical parameters that are unique in ATAA and expand our modeling to wider population for validating our predictions.

# Chapter 3: The Influence of Hematocrit on the Hemodynamics of Artificial Heart Valve

## 3.1 Introduction

As the bicuspid aortic valve affect the development and progression of ATAA due to the change in biomechanical and hemodynamical stress distributions, conducting the analysis on heart valve would provide the additional information and the foundation for future investigations on ATAA. As the left ventricle, regulated by the mitral and the aortic valves, is subjected to the highest mechanical loads, most disorders of the heart initiate here [208]. The most commonly affected heart valves in a diseased heart are the mitral and the aortic valves responsible for 34% and 44% of morbidity, respectively [209,210]. Based on the recent American Heart Association and American College of Cardiology guideline for managing patients with heart valve disease, the mechanical heart valve is considered for patients under 50 years old without the constraints of receiving anticoagulation [211]. The decision for a mechanical or bioprosthetic valve for patients between 50 and 70 years old would be patient-depended due to the devices' own disadvantages [211,212].

Therefore, the objective of this study is to analyze the hemodynamics and valve mechanics of a bileaflet mechanical heart valve and investigate the hemorheological characteristics under the change of hematocrit. The fully coupled FSI approach was used to model the hemodynamics and valve dynamics. PIV experiments were conducted with *in vitro* benchtop model using ViVitro Pulse Duplicator by the Department of Mechanical Engineering from the University of Victoria to verify and validate the FSI models. The influence of hematocrit on the fluid shear stress in the current analysis may provide further understanding from the biomechanics perspective and contributing towards to the future patient managements and patient-specific modeling of prosthetic heart valves.

### 3.2 Method

## **3.2.1** Experimental system

To validate the numerical model, physiologically relevant test conditions were applied with phase-resolved velocity measurements using particle image velocimetry (PIV) (Figure 3.1). A commercially available, 23 mm BMHV with a tissue annulus diameter / internal diameter (TAD/ID) of 18.5 mm (Figure 3.2), was used as the test model. ViVitro pulse duplicator was used to assess the performance and function of prosthetic heart valves under simulated cardiac conditions. An acrylic test chamber (Figure 3.3), that represented a simplified model of the ascending section of a human aorta, was used to allow flow visualization around the aortic valve. Experiments were conducted at nominal conditions in accordance with ISO 5840-2:2015 [213]. A simulated heart rate of 70 beats/min (corresponds to a cardiac cycle with a period T = 860 ms) was applied with the target cardiac output of 5.5 l/min and the mean aortic pressure of 100 mmHg. The duration of the systolic phase was approximately 35% of the cardiac cycle period. The tests were conducted at a temperature of 37° C. The working fluid, in the current experiment, was a mixture of glycerin and water in the ratio of 40:60 that had a dynamic viscosity of 3 mPa·s and a specific gravity of 1.1 at 37 °C.

The PIV system included an Nd:YLF dual cavity laser (22.5 mJ/pulse at 1 kHz and a wavelength of 527 nm). Silver-coated hollow glass spheres (mean diameter of 14  $\mu$ m and specific gravity of 1.3) were used as seeding particles. The Stokes number of the tracer particles was equal

to  $0.7 \times 10^{-3}$ , which indicated that the particles were sufficiently small to accurately follow the flow [214]. Photron Complementary Metal Oxide Semiconductor (CMOS) camera was used to capture the seeding particles within the flow. Images were collected in the central plane as shown in Figure 3.1. The camera was set to operate at  $1024 \times 1024$  pixels under a field of view of 70 mm x 30 mm, resulting an image resolution of 17 µm/pixel and an average of 2-pixel seeding particles. Imaging sampling rate was 100 Hz with a time interval between the frames in a pair of 500 µsec. Davis 8.1.3 software (LaVision Inc.) was used to correct optical distortions due to the edge curvature of the test chamber. The collected images were processed using a multipass cross-correlation algorithm with a final interrogation windows of 16 pixels × 16 pixels using 50% overlap.

The typical error in the calculated particle displacement for PIV correlation algorithms of this kind is of the order of 0.1 pixels [215,216]. There were also measurement artifacts near wall boundary resulting in decrease experimental measurement certainties. The sources of error could potentially result from insufficient treatment in data collection near the wall [122] or a bigger seeding particle sized used in the current study [217]. Based on the 16×16 pixel window used for correlation, a conservative estimate of 5% error excluding the wall in true displacement can be assumed [218]. Therefore, the data near the wall boundary was excluded during numerical model validation.



Figure 3.1: Schematic illustrating DPIV test set-up used in the current experiment (Image courtesy of ViVitro Labs Inc.)



Figure 3.2: Schematic of bileaflet valve (left A) and the orientation of the valve (right B) with respect to the left coronary artery (LCA), the right coronary artery (RCA) and the noncoronary cusp (NCC) (Note that the PIV Data Acquisition Plane is shown with dashed lines)

Figure 3.3: Acrylic test chamber with geometrical specifications (dimensions in mm)

# 3.2.2 Governing equations

The blood flow was modeled by the incompressible Navier-Stokes equations with the equations for fluid continuity (Eq 3.1) and momentum conservation (Eq 3.2) shown below. Flow is assumed to be within the laminar regime as the Reynolds number, approximately at 6,300 for

the current study, is less than the calculated critical oscillatory Reynolds number, approximately 9,000 calculated based on the criterion by Ohmi and Iguchi, where the critical Reynolds number is a function of oscillatory frequency, pipe radius, and kinematic viscosity [219]. The laminar flow assumptions also agree with various studies in the analysis of BMHV [138–140]. Additionally, the blood flow is assumed to be incompressible with negligible gravitational force. The interactions between blood flow and valve leaflet were computed with the coupling equation (Eq 3.3). Cauchy stress tensor,  $\sigma$ , was calculated based on the pressure and the viscous terms from the momentum equations from Navier-Stokes. Finally, the von Mises stress used to evaluate the leaflet stress is calculated based on Eq 3.4

$$\nabla \cdot \boldsymbol{V} = \boldsymbol{0}, \qquad \qquad \mathbf{Eq} \ \mathbf{3.1}$$

$$\rho \frac{DV}{Dt} = \nabla \cdot (-PI + \tau), \qquad \text{Eq 3.2}$$

$$\boldsymbol{\sigma} \cdot \boldsymbol{n} = (-P\boldsymbol{I} + \boldsymbol{\tau}) \cdot \boldsymbol{n}, \qquad \text{Eq 3.3}$$

$$\sigma_{\nu M} = \sqrt{3\left(\frac{1}{2}tr(\boldsymbol{\sigma}^2) - \frac{1}{3}tr(\boldsymbol{\sigma})^2\right)}$$
 Eq 3.4

where **V** is the fluid velocity in [m/s],  $\rho$  is the fluid density in [kg m<sup>-3</sup>], P is the pressure in [Pa], **I** is the identity tensor, **t** is the viscous stress tensor, n is the unit normal vector, and  $\sigma_{vM}$  is the von Mises stress in [Pa].

The Quemada model was used to account for the non-Newtonian shear thinning behavior of the blood's viscosity under the change of the hematocrit, as shown in Eq 3.5 [220].

$$\eta = \frac{\eta_{plasma}}{\left(1 - \frac{Htc \cdot k_{eq}}{2}\right)^2}, \text{ and } k_{eq} = \frac{k_0 + k_\infty \cdot \sqrt{\dot{\gamma} / \dot{\gamma}_c}}{1 + \sqrt{\dot{\gamma} / \dot{\gamma}_c}}, \text{ Eq 3.5}$$

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where the  $\eta_{\text{plasma}}$  is the viscosity of blood plasma in [Pa s], Htc is the hematocrit in [%],  $k_0$  and  $k_{\infty}$  are the maximum volume fraction at zero and infinite shear rates,  $\dot{\gamma}$  is the shear rate in [s<sup>-1</sup>], and  $\dot{\gamma}_c$  is the critical shear rate in [s<sup>-1</sup>] for erythrocytes agglomeration.

The rheological parameters ( $\eta_{plasma}$ ,  $\dot{\gamma}_c$ ,  $k_0$ , and  $k_\infty$ ) were taken from the study conducted by Marcinkowska-Gapińska *et al.* for the blood rheology measured at body temperature for a patient without anticoagulation intake for a week prior to the measurements [221]. Although these parameters could also be influenced by the hematocrit [222], the four rheological parameters were kept constant for current study with  $\eta_{plasma}$ ,  $\dot{\gamma}_c$ ,  $k_0$ , and  $k_\infty$  equal to 1.28 mPa s, 4.2 s<sup>-1</sup>, 4.01, and 1.77, respectively [221]. Based on Eq 3.4, the shear rate-dependent Quemada viscosity for a wide range of shear rates is plotted in Figure 3.4. To visualize better the shear thinning behaviour at high shear rates, the hollow lines on the right-hand side of Figure 3.4 represent the viscosity above 100 s<sup>-1</sup> with the magnitude in Pa-s labeled on the right vertical axis, as indicated by the black arrow. The degree of shear thinning changes dramatically for shear rates below 10 s<sup>-1</sup>, where a higher hematocrit resulted in a significantly increase in viscosity at a lower shear rate region.



Figure 3.4: Viscosity versus shear rate predicted by the Quemada model for different hematocrits (hollow lines refer to viscosity value after 100 s<sup>-1</sup> using a secondary axis on the right)

# **3.2.3** Computational method

The current numerical models were constructed using COMSOL Multiphysics (V5.2a, Stockholm, Sweden) with parallel sparse direct solver MUMPS (MUltifrontal Massively Parallel Sparse direct Solver). The numerical setup was inherited from the experiment, including the geometrical specifications of the acrylic chamber and the applied physiological pressures. The fully-coupled, 2-way FSI models were built based on the approach from our previous study [135,223], where ALE method was used to calculate the displacement of the valve leaflet under physiological blood pressure. A computational model representing the benchtop experimental setup was built to validate the numerical method with the same geometrical and material properties. The BMHV had a diameter of 23 mm, a leaflet thickness of 0.78 mm, a length of 10.27 mm and a free rotation angle ranging from 25° to 85°. The valve leaflets were assumed to be

isotropic linear elastic with Young's modulus of 30 GPa, Poisson's ratio of 0.3, and a density of 2116 kg/m<sup>3</sup>, similar to the study by Choi and Kim [140]. The computational domain is shown in Figure 3.5. At the inlet and the outlet boundaries, the physiological pressure profiles were applied as same as in the experimental setup, as shown in Figure 3.6. To account for the solution instability due to initial conditions, a total of 8.6 s (ten cardiac cycles) of the diastolic pressure was applied. The fluid-structure interface was specified along with the BMHV surface. The free rotation condition was applied independently to the four valve hinges with angular constraints at 25° to 85°  $\pm 0.001^{\circ}$ . To avoid reaching solution singularity and because of the variations in geometrical scales, the butterfly hinges of an actual BMHV were simplified as simple pin hinges without fluid flow in between. The effect of these geometrical simplifications on the hemodynamics and valve leaflets stress distributions was assumed to be minimal.



Figure 3.5:Computational domain corresponding to the experimental geometry.

Figure 3.6: Physiological blood pressure profiles for the ventricular (inlet) and aortic (outlet) boundary

The computation for the fluid and structure domain was fully coupled with a relative error less than 1e-3. Mesh convergence study was conducted to verify that the solutions were independent of the discretization of the computational domain. Both tetrahedral and brick types of
mesh elements were used to account for a computational boundary and maximize computational efficiency. The average blood flow velocity magnitude along the centerline of the computational domain was analyzed for the first ten cardiac cycles. A convergence was concluded when the difference between the velocities was within 2% for all the time instances throughout the cardiac cycle. Temporal convergence was confirmed at the seventh cardiac cycle.

## 3.3 Results

#### **3.3.1** Numerical results

To validate the FSI model with the PIV experiment, the flow velocity along the PIV data acquisition plane was analyzed. Both the numerical and the experimental models were under the same operating conditions including the matching geometry and Newtonian fluid properties. The locations for validating the blood flow velocities were chosen to be within the aortic sinus at the widest cross-section downstream from the BMHV. These locations corresponded to be approximately at 9 mm, 12 mm and 15mm downstream, measured from the base of BMHV. The velocity profiles at the validating locations were plotted at peak systole of 8.75s and end systole of 8.80s for the comparison between the numerical and the experimental models, as shown in Figure 3.7. The overall difference in flow velocity distributions at three locations and two timesteps was 6.1%, ranging between -6.5% (8.80s, 9mm) to 16.2% (8.75s, 15mm). The absolute difference between the six instances evaluated was 14.6%. Due to the influence of optical distortion from the acrylic chamber, the PIV accuracy for near-wall measurements was reduced; therefore, the velocity distributions were validated slightly away from the acrylic wall approximately 3 mm from each side. The inaccuracy and uncertainties from the measurement arose mainly from the optical artifacts and occurred near the wall. The measurement could have been

improved by refining the interrogation area similar to the work by Nguyen *et al.* [122]. Additional qualitative validations against literature published PIV measurements were therefore conducted in order to provide further support to the existing numerical model. The simulated peak systolic flow distributions within the aortic sinus close to the wall were in qualitative agreement with previous study conducted by Li *et al.* [217]. Furthermore, the leaflet dynamics was in close agreement with the simulated results by Choi and Kim with similar leaflet opening durations and leaflet rebound characteristics[140]. It was therefore concluded that our 3D FSI model was an overall representation of the experimental setup with qualitative validation from literature for flow near the wall boundary.



Figure 3.7: Velocity profile validation at 9 mm downstream from BMHV at peak systolic phase with the dotted and the solid line representing the experimental data and the numerical result, respectively (the long dash lines represented the locations 3mm away from the wall)

## 3.3.2 BMHV hemodynamics

The velocity contours at the central cross-section of the BMHV for the cases with 35% Htc., 40% Htc. and 44% Htc under systolic and diastolic conditions are shown in Figure 3.8(a)-(f). The results at the peak of systolic phase (Figure 3.8(a), (c), (e)) and the end of the diastolic phase (Figure 3.8(b), (d), (f)) were presented for each hematocrit value. In general, all three scenarios yielded similar velocity distributions both in velocity magnitude and direction. The inclusion of non-Newtonian modeling showed minor variations in the distributions of the vortices within the aortic sinus at systole and behind the valve leaflet at diastole due to the blood's shear-thinning behaviour. Additionally, the numerical models retained additional flow features such as recirculatory flow, or the washout characteristics, within the aortic sinus at the systolic phase and behind the valve leaflet at the diastolic phase. Both flow recirculation at systole and diastole were not visible in the experimental result due to the PIV field of view obstruction by the valve housing.

The BMHV generated the distinctive three-jet flow when the valve fully opened. The velocity profiles (Figure 3.9) indicated similarity for all three scenarios at 9mm downstream or the location where experimental validation was conducted. Blood was ejected through BMHV with a maximum ejection velocity of 1.4 m/s at the sides while the recirculatory blood within aortic sinus had a reversed velocity just under 0.3 m/s for all cases.



Figure 3.8: Computed velocity vector fields and contours of velocity magnitude at the central crosssectional plane for peak systole and end diastole under different hematocrit conditions



Figure 3.9: Peak Systolic velocity profiles at 9mm downstream away from BMHV with different hematocrit of 35%, 40%, and 44%

Additionally, the 3D velocity vectors downstream the BMHV were plotted (Figure 3.10) to present the spatial velocity distributions. While the 2D contours in Figure 3.8 clearly mapped the distribution of the velocity jet, additional detail was revealed regarding the spatial orientation of the semilunar blood flow jets from the two sides of BMHV and the elliptical central jet. Flow recirculation due to the expansion of the aortic sinus was also observed at systole (Figure 3.10(a), (c), (e)). At diastole (Figure 3.10(b), (d), (f)), reversed leakage jets passed through the intervalvular space of BMHV. The leaks were more from the sides than at the centre of BMHV, represented by the higher leakage velocity. The instantaneous leakage velocity magnitude reached 4 m/s at the tip of the valve leaflet while the flow velocity slowly diminishing to approximately 1 m/s near the inlet boundary. Note that in both Figure 3.8 and Figure 3.11, the colour legend for blood flow velocity was intentionally capped at 1.6 m/s to better visualize the velocity distribution. Overall, the hematocrit did not influence the region with high flow velocity significantly, but there were differences in the recirculation regions with lower flow velocity.







Figure 3.10: 3D velocity vector plots downstream BMHV at peak systole and end diastole under different hematocrit conditions

## 3.3.3 Shear stress distribution

The maximum shear stress magnitude was analyzed and plotted in Figure 3.11 for the simulated cardiac cycle. The maximum shear stress magnitudes from one cardiac cycle were computed as 1766 dPa, 1935 dPa, and 2698 dPa for 35%, 40%, and 44% Htc. respectively. During the systolic phase, when BMHV fully opened, the maximum magnitude of the shear stress ranged approximately between 60 dPa to 500 dPa. However, during the diastolic phase, when BMHV fully closed with reversed leakage flow, the maximum shear stress reached approximately 2700 dPa for the case with 44% Htc. All three scenarios had similar shear stress distribution in time, yet, maximum shear stresses were significantly lower for the hematocrit of 35% and 40% during the diastolic phase after valve closure.



Figure 3.11: Maximum shear stress magnitude within the computational domain with a different hematocrit of 35%, 40%, and 44%

For the individual component of the shear stress, all three shear stress component, XY, XZ, and YZ, were plotted in Figure 3.12 for peak systole and Figure 3.13 for end diastole. Again, the results for all three cases, 35% Htc. ((a)-(c)), 40% Htc. ((d)-(f)), 44% Htc. ((g)-(i)), were presented. The spatial distributions of shear stress were similar across all considered cases. During the systolic phase (Figure 3.12), the shear stress in the XY direction ((a), (d), (g)) concentrated near the tip of valve leaflet while the shear stress in the XZ direction ((b), (e), (h)) concentrated around BMHV housing. The shear stress in the YZ direction ((c), (f), (i)) concentrated along the valve leaflet surface and BMHV housing. Focusing on the case where hematocrit was 35%, the shear stress in all three components were significantly less than the 44% Htc. case.

On the other hand, the shear stress distribution for the 40% Htc. case was similar, but with smaller magnitude than the 44% Htc. case. The shear stress results at diastole (Figure 3.13) revealed that all three shear stress components concentrated at the leaflet tips and the valve housing. Similar to the systolic phase, the shear stress distributions were similar between the 40% Htc. and the 44% Htc. case with high shear stress less concentrated for the 35% Htc. case. Note again that in both Figure 3.12 and Figure 3.14, the colour legend for shear stress was intentionally capped at 50 dPa to visualize the shear stress distribution.



Figure 3.12: 3D shear stress distribution in dPa (dyne/cm<sup>2</sup>) at peak systolic phase for 35% Htc. (a, b, c), 40% Htc. (d, e, f), and 44% Htc. (g, h, i)



Figure 3.13: 3D shear stress distribution in dPa (dyne/cm<sup>2</sup>) at end diastolic phase for 35% Htc. (a, b, c), 40% Htc. (d, e, f), and 44% Htc. (g, h, i)

## 3.3.4 Valve leaflet dynamics

The motion for both BMHV's leaflets was plotted in Figure 3.14(a) and (b) over one cardiac cycle. All three hematocrit cases predicted similar opening period, approximately 200 ms on average, during systolic phase; however, not all the cases had the same leaflet motions during the opening period. We define the opening period to be the time between the time when the leaflet first reached the maximum opening and the time when leaflet first closed. Specifically, the 40% Htc. case maintained maximum opening throughout the whole systolic phase whereas the 35% Htc. case started the closure immediately after the maximum opening at peak systole was reached. The 44% Htc. model had leaflet 2 (Figure 3.14(b)) maintained at maximum opening while leaflet 1(Figure 3.14(a)) showed slight instability in maintaining valve opening. The 3D views of valve leaflet revealed a concentrated distribution of the leaflet stress near valve leaflet hinges at valve closure (Figure 3.10(b), (d), (f)). Additionally, the maximum Von Mises stress experienced by the leaflets under all cases were below 90 MPa at the time of leaflet closure, which can be seen in Figure 3.8(b), (d), (f) under the cross-sectional plane. This confirmed the durability of a BMHV and its unlikeliness to fail due to simple mechanical stress.



Figure 3.14: Opening angle for the mechanical valve leaflets during one cardiac cycle

## 3.4 Discussion

Since the value of the hematocrit is a readily accessible parameter from a blood test result during clinical evaluations, the integration of the Quemada model into the current FSI analysis on BMHV provided additional insights. Given that the Quemada model is a phenomenological model that characterizes the overall viscosity-shear rate relationship of a system with concentrated disperse particles, whole human blood rheological behaviour could be accounted for based on the hematocrits. The rheological parameters used in the Quemada model could vary over a wide range of hematocrit values; therefore, the current study only considers a narrow but normal range of hematocrits. By analyzing three hematocrit values within the normal range, the influences in the change of hematocrit due to physiological factors can be mapped. We observed an overall decrease in maximum shear stress with the decrease in hematocrit; however, the decrease in shear stress was not linear with respect to the decrease in hematocrit due to the difference in the degree of shear thinning for each hematocrit value. Although the general velocity distribution remained similar between each hematocrit case, the localized recirculatory flow within aortic sinus near the wall had large variations when the hematocrit changed from 35% to 44% Htc. The detail comparisons between the cases with different hematocrit for each of the key physical parameter analyzed in the current study were summarized in Table 3.1.

	35% Htc.	40% Htc.	44% Htc.			
Shear Stress						
Max Shear Stress Magnitude (dPa)	1766	1935	2698			
Difference in Max Shear Stress (%)		9.5%	52.7%			
Time Averaged Shear Stress (dPa)	1006	1061	1437			
Time averaged shear stress difference (%)		5.4%	42.8%			

Table 3.1: Summary of key parameters comparisons between the 35% Htc. case to 40% and 44% Htc. cases

	35% Htc. 40% Htc.		44% Htc.			
Leaflet Motion, Leaflet 1 (Leaflet 2)						
Max opening at (s)	8.747 (8.758)	8.762 (8.762)	8.754 (8.815)			
Min closing at (s)	8.973 (8.973)	8.979 (8.978)	8.977 (8.977)			
Opening duration (ms)	226 (214)	217 (217)	224 (162)			
Leaflet Stress						
Max leaflet stress (MPa)	72.9	88.0	85.5			
Difference in max leaflet stress (%)		20.7%	17.2%			
Time-averaged difference (%)		11.7%	17.3%			

## 3.4.1 The effect of hematocrit on BMHV hemodynamics

The maximum peak velocities were similar for all the cases; however, there were recirculatory/washout flow variations within the aortic sinus. Since the influence of shear rate on the blood's viscosity is greater at low shear rate regime while the value of viscosity reaches a plateau at a shear rate of 100 s<sup>-1</sup> and above, it is not a surprise that the difference in the hemodynamics would be found around the aortic sinus, where flow recirculation occurred. In our earlier work involving the characterization of the rheological properties of whole human blood, we observed a clear increase in the degree of the shear thinning of the blood's viscosity due to the increase of the hematocrit [224]. The viscosity could increase by approximately 32% at a low shear rate if the hematocrit was increased from 43% to 48%. Given that the fluid shear-thinning characteristics would affect the size of vortices generated as well as form secondary asymmetric flow [225], it would be important to consider the effect of these changes in rheological parameters in patient-specific hemodynamics modeling such as heart valves as the changes were not linear with respect with the change of hematocrit.

The maximum shear stress difference between the 35% Htc. case to the others were 9.5% (40% Htc.) and 52.7% (44% Htc.) as the result of a nonlinear change in the degree of shear thinning across the hematocrit values. Time-averaged shear stress (TASS) magnitudes had a similar value

between 35% Htc. and 40% Htc. with a minor increase of 5.4%; however, there was a significant increase of 42.8% in TASS between 35% and 44% Htc. This result suggested that there was a greater influence from the 44% Htc. hemorheological model in TASS predictions. Since the difference in the viscosities at high shear rates was small and that the degree of shear thinning was increased nonlinearly at a low shear rate, our results suggested the importance of considering the hematocrit-depended rheology with performing hemodynamics evaluation in cardiovascular disease. Additionally, Figure 3.11 identified instances where the maximum shear stress went above 1500 dPa for all models. Using a simple estimate for critical shear stress of 1500 dPa to evaluate cell damage [40], the current analysis would suggest blood cell damages due to BMHV regardless the value of hematocrit; therefore, anticoagulant would most likely be necessary for all cases. This result agreed with common practice for patients receiving an aortic valve replacement with a BMHV[226]. Given the wide variation in blood-induced shear stress across the three hematocrit values studied, which are considered as normal values, the patient's hematocrit might have significantly more importance during patient management.

## **3.4.2** The effect of hematocrit on BMHV leaflet motions

In general, the leaflet dynamics predicted in the current study were in good agreement with previous investigations [133,140]. However, due to the change in the hematocrit, the motion of BMHV leaflet was affected by these changes as shown in Figure 3.14 and Figure 3.15. There were variations in the valve opening phase for both valve leaflets given that the valve opened on averaged for 220 ms (35% Htc.), 217 ms (40% Htc.), and 193 ms (44% Htc.). Although the leaflet motions for 35% Htc. and 40% Htc. had a similar performance for both leaflets, the 44% Htc. case had an asymmetric leaflet dynamic resulting in 24.4% reduction in opening duration for one of its leaflets. The first leaflet for the 44% Htc. case had similar opening and closing time to the other

hematocrit cases; however, the second leaflet for the 44% Htc. case reached the maximum opening at a later stage with a similar closing time (Figure 3.15). This result indicated that the 44% Htc. case had the shortest opening period on average while the 35% Htc. case had incomplete leaflet openings (Figure 3.14).



(a) Leaflet opening at systolic phase(b) Leaflet closing at diastolic phaseFigure 3.15: Close-up view at the leaflet motion for Leaflet 2 at (a) peak opening and (b) initial closure

As the motion of the leaflet was simulated based on the forces exerted from fluid flow, these variations in the data set support the need to differentiate modeling properties, as intuitive as hemorheological profiles under different hematocrit, in order to conduct patient-specific simulation and diagnostic more carefully. The asymmetrical leaflet motions and the difference in valve opening duration due to the change of hematocrits further echoes the conclusion by Ternik that the change in the shear thinning behaviour of the fluid could result in flow asymmetry [225]. Additionally, severer leaflet rebounds were found during valve closure (Figure 3.15(b)) with a rebound of 1.4 degrees (44% Htc.) follow by the 0.8 degrees (35% Htc.), and 0.1 degrees (40% Htc.). These variations in leaflet motion due to the change in hematocrit, or the rheological behaviour of blood, warrant future investigations.

Finally, there were also some noticeable differences in Von Mises stress that the leaflets experienced. Similar to the maximum shear stress magnitude evaluated earlier, the 35% Htc. case had the lowest maximum Von Mises stress of 72.9 MPa evaluated but the 40% Htc. case had the highest value of 88.0 MPa, followed by 85.5 MPa (44% Htc.). The time-averaged difference in Von Mises stress was also calculated to be 11.7% (40% Htc.) and 17.3% (44% Htc.) with respect to the 35% Htc. baseline. Although there were differences in structure stress under current FSI investigation in BMHV, these differences in stress evaluation will be more influential for modeling involving biological tissue since the maximum stress in current BMHV would less likely cause simple mechanical failure given the small stress magnitude.

## **3.4.3** Study limitations

There are several study limitation and assumptions that would need to be addressed. Although the BMHV's leaflets were modeled with linear elastic material and their motions were predicted by FSI coupling, the arterial wall was assumed to be rigid without blood vessel compliance. The rigid arterial wall assumption was made not only because of the PIV experimental validations but also served as a study control to isolate the influence of hematocrit in the analysis. Arterial wall compliance would be added as a future extension of the current study for investigating the significance of blood's shear thinning behaviour around the aortic valve. Additionally, since the current simulation was validated using similar validation procedure by the FDA with the use of Newtonian fluid for both the PIV experiment and the simulation [227], the verification of the non-Newtonian simulations could be further conducted experimentally using a shear-thinning blood analog that contains Xanthan gum [228]. Additionally, the hinges in our modeled BMHV were geometrically simplified without applied friction, this simplification was made because the microflow near the leaflet hinges as well as the hinge structural integrity was not the focus in the current study. Finally, the resolution artifact near wall from the PIV prevented accurate near-wall velocity measurements. It is planned to decrease the influence of the artifact by enhancing near-wall treatment as well as decrease seeding particle diameter.

## 3.5 Conclusion

We have constructed the FSI models for simulating the hemodynamics of BMHV that could be integrated to the ATAA models for an aneurysm-heart valve simulation. The BMHV models had experimental validations using PIV measurements excluding the near wall measurement. The measurement near the test chamber wall had some noticeable uncertainties, due to optical artifact and seeding particle size. Therefore, we had to qualitatively verify our simulated results with literature published experimental results. Three models were built with the integration of the shear thinning Quemada model, which contained hematocrit as the controlling parameter. The fully coupled FSI approach used in the current study successfully predicted the hemodynamics and leaflet motion of a BMHV. The inclusion of hematocrit as an additional modeling parameter could provide customized and personalized clinical assessments. The shear stress distribution, on the other hand, had a significant decrease with the decrease in hematocrit. Our results suggested that the distributions of high shear stress during systole were around the valve leaflet surface and housing while during diastole were around the valve housing and the tips of the valve leaflet. Finally, the motion of valve leaflet was affected by the change in hematocrit with the most unstable opening for the lowest hematocrit at 35%. It was found that there was a hematocrit dependence on the hemodynamics of BMHV; therefore, it is important and critical to consider the impact of hematocrit when conducting patient-specific modeling.

# Chapter 4: Rheological Characterization on Blood Clot Formation and Blood Coagulation

## 4.1 Introduction

In order to establish a numerical model regarding the process of blood clot formation that could be integrated into the existing numerical models associated with aneurysm or heart valve, rheological characterization on blood coagulation was conducted. The small amplitude oscillatory shear rheometry characterization for the untreated citrate blood provided the modeling of storage modulus and complex viscosity. The combination uses of different rheological parameters identified the blood's clotting time, coagulation rate, final storage modulus values, and the contractile force. Further, to study the dynamics of blood clot formation and the interaction of the heparin reversal agents, the focus of the current study was extended to analyze the coagulation dynamics between protamine and UHRA (universal heparin reversal agent) under different oscillatory frequencies. The recent development of universal heparin reversal agent (UHRA) showed promising heparin neutralization characteristics; however, further detail analysis on blood coagulation and blood clot formation with UHRA is still required. Different antidote concentrations were evaluated by analyzing several key rheological parameters with further assessments with scanning electron microscopy. The current study revealed the blood clot structure had a significant difference in both the rheological assessment and the microscopic imaging between an oscillatory frequency mimicking low non-physiological heart rate verse a normal heart rate.

## 4.2 Method

## 4.2.1 Ethics approval

Blood collection and the protocols used in the current studies were approved by the Clinical Research Ethics Board of the University of British Columbia, and written consent from donors was obtained in accordance with the Declaration of Helsinki.

## 4.2.2 Heparin reversal agents

UHRA-7 was synthesized following our reported procedure [168,169,229]. Characteristics of the UHRA-7 is given in the supporting information. Protamine from Salmon, Grade IV, histone free (P4005-250MG) was purchased from Sigma Aldrich. Stock solutions of both the reversal agents were prepared in HEPES buffer (pH 7.4, 150 mM NaCl) with a final concentration of 5 mg/mL and

#### 4.2.3 Blood sample preparation

Blood was collected from consented healthy donors at the Centre for Blood Research, the University of British Columbia, into 3.8 % sodium citrated vacutainers. Blood was heparinized using UFH (4IU/mL, final) to closely mimic cardio bypass conditions. Before rheological measurements, protamine or UHRA-7, were added with at least 1-minute mixing time on a mini mixer (Benchmark Scientific). Buffer added citrated blood (to compensate for the dilution caused by heparin and reversal agent addition) was considered as a control for the measurements. Different concentrations of protamine or UHRA-7 were added to evaluate the effectiveness of reversing the anticoagulation properties of UFH. The standard testing concentrations were 50 µg/mL and 100 µg/mL for protamine, 100 µg/mL and 200 µg/mL for UHRA, unless otherwise specified.

#### 4.2.4 Hemorheological measurements

The rheological measurements were conducted within an hour after blood collection with Kinexus Ultra+ rotational rheometer (Malvern Panalytical, Worcestershire, United Kingdom). A standard 60 mm stainless-steel parallel plates system was used for the measurements. The system was enclosed using a thick plastic cover to minimalize evaporation and maintained at a constant temperature of 37 °C. A gap of 1 mm was kept at a constant throughout the measurement between the parallel plate. A full machine torque calibration was performed before each set of the hemorheological measurements. A measurement verification was conducted using general purpose viscosity standards N4 (Cannon Instrument Company, Pennsylvania, USA) at 37 °C after each torque calibration.

To minimalize wall slip from the stainless-steel surface of the parallel plates and reduce plate gap dependency, moisture resistant adhesive backed sandpapers (grit 240, McMaster-Carr) were used for both plates to create a roughen surface similar to the work by Picart *et al.* [230]. Approximately 3 mL of the blood sample was used for each measurement. The experimental sequence began by recalcifying the blood samples. Buffer was added to citrated whole blood, or different reversal agents at different concentrations mixed with heparinized whole blood as described previously [229]. A stopwatch was used to establish the reference time for tracking blood coagulation dynamics after recalcification. A mixing time of 30 seconds was applied to ensure the calcium solution was well mixed with the sample. The recalcified blood sample was then quickly transferred to the parallel plate for measuring its hemorheological characteristics. First, a quick 30-second pre-shear at 221 s<sup>-1</sup> was applied mimicking carotid artery flow, similar to the previous work using steady state viscometry [224]. The purpose of the pre-shear sequence was primarily meant to evenly distribute the blood sample due to the limited amount of time prior to the initiation 101

of blood coagulation. Oscillatory rheometry was then performed under a constant oscillating frequency of 0.5 Hz, 1.2 Hz, and 2 Hz, depending on the testing scenario. As per Rånby *et al.* and Scrutton *et al.* a constant shear amplitude of 5% was used and this range was predetermined to be within the linear viscoelastic range [176,185]. The measured data were recorded with a 2-second interval in order to ensure at least one complete oscillation between each interval. A total of one thousand data points, or approximately half an hour, were measured due to the noticeable influence of sample evaporation under physiological temperature beyond 45 minutes of experimental time. The measurements were repeated for five different donors (N=5).

## 4.2.5 Blood clot preservation and scanning electronic microscope (SEM) imaging

At the end of hemorheological characterization, a blood clot was immediately preserved by carefully removing the sandpaper from the stainless-steel plates without detaching the clots. A slice of the sample was taken in the radial direction in order to examine the global clot structure at multiple radial locations. The clot sample was gently rinsed three times with HEPES buffer then fixed with Karnovsky fixative (2.5% glutaraldehyde and 4% formaldehyde) for at least two hours under room temperature. After clot fixation, the sample was gently washed three times with 0.1 M sodium cacodylate buffer and preserved at 4 °C in the buffer solution until dehydration. The clot samples were brought to room temperature and washed with fresh 0.1 M sodium cacodylate buffer. To allow for better penetration of the 1% osmium tetraoxide staining solution into the clot, a PELCO344I Laboratory Microwave System was used. Then, 1% osmium tetraoxide dissolved in 0.1 M sodium cacodylate buffer was used and allowed to stain in the microwave. The clot sample was washed profusely using distilled water for a minimum of five exchanges and resuspended in 50% ethanol solution. It was left to incubate for 10 minutes at room temperature before subjecting it to the microwave. The dehydration procedure was repeated using 70%, 80%, 90%, and 95% ethanol followed by 100% ethanol three times. Once the sample was fully dehydrated, it was placed in a Tousimis Autosamdri 815B Critical Point Dryer overnight under stasis mode before fully completing the drying process the following day. Finally, the processed samples were mounted on SEM stubs using carbon tape or hot glue and coated in 10 nm of Au/Pd coating (16.38 g/cm<sup>3</sup>) using a Cressington 208HR High Resolution Sputter Coater. Samples were kept in a desiccator until imaging.

The SEM images were taken with Hitachi S4700 and Helios 650 scanning electron microscope. The images were taken at 2 000, 10 000, and 25 000 magnifications. The 10 000 magnification images were used for the assessment of the fibrin fibre network due to the balance between fibrin fibre density and individual fibre resolution. A total of three randomized locations were used for this step. The evaluation of the fibrin fibres was conducted using ImageJ. A minimum of thirty-five measurements of fibrin fibre diameter was taken randomly per imaging location. The maximum and minimum diameter measured were truncated to avoid measurements on indistinguishable fibre twines or broken fibres. At the end of the measurement, a total of one hundred measurements (N=100) were kept for the three locations for the final analysis. The samples were blinded for fibre diameter measurements for ensuring unbiased assessment.

#### 4.2.6 Statistical analysis

The experimental data set was analysed using GraphPad Prism. 2-tailed unpaired t-test were performed for comparing difference between any 2 sample sets. Statistically significance was presented using P value analysis, where a P value less or equal than 0.05, 0.01, 0.001, and 0.0001 were shown using 1 to 4 asterisks, respectively. All the results shown in the figures with error bars are represented as mean ± standard deviation from five different donors.

## 4.2.7 Coagulation dynamics characterization

In order to prepare for integrating the rheological findings on normal whole human blood coagulation to the existing ATAA and artificial heart valve models, the characterization of the blood clot formation would need to be established first. Starting from the previous formulation proposed by van Kempen [231] for characterizing the viscoelastic behavior of blood clot (Eq 4.1), the storage modulus G', which represented the elasticity of the blood clot, can be characterized to express the clot structural evolution in time. This viscoelastic representation of the clot structure was constructed based on the generalized Maxwell model and rheological measurements; however, it missed the aspect of fibrin formation via biochemical reaction. The equation, based on physical measurements of the blood clot's response to small amplitude oscillatory shear, was a piecewise function where the value of G' was set to be zero before the initiation of blood coagulation.

$$G'(t) = G'_{eq} \left( \begin{cases} 0, & \text{if } t \le t_0 \\ 1 - e^{-\frac{(t-t_0)}{t_c}}, & \text{if } t > t_0 \end{cases} \right)^2$$
 Eq 4.1

Where  $G'_{eq}$  represented the equilibrium steady state G' value in [Pa],  $t_0$  represented the delay time for the initiation of the coagulation in [s],  $t_c$  represented the characteristic time for the coagulation dynamics in [s]

On the opposite part of the spectrum, the first-order chemical reaction equation for modeling exponential decay/growth can be modeled using the sigmoidal function, similar to the work proposed by Xu *et al.* [232]. Eq 4.2 characterized the structural development of the blood clot based on the formation of fibrins. Both models characterized the evolution of G' with 104

exponential function suggesting a rapid formation of fibrin after clot initiation; however, Eq 4.2 approximate G' with a continuous function based on first-order chemical reaction relationship.

$$G'(t) = \frac{G'_{eq}}{\left(1 + e^{\left(-\frac{(t-t_{mid})}{k_{coagulation}}\right)}\right)}$$
 Eq 4.2

Where  $G'_{eq}$  represented the equilibrium steady state G' value in [Pa],  $t_{mid}$  represented the midpoint of the sigmodal function in [s], and  $k_{coagulation}$  represented the coagulation formation kinetics in [s]

While modeling the progression of G' during blood clotting provided predictions regarding the evolution of clot formation, the modeling of blood clot's complex viscosity,  $\eta^*$  in [Pa s], would provide significantly more value for the numerical simulations of blood flow involving coagulation, such as thrombus formation due to blood cell damage or endovascular stent graft deployment. Equation 4.1 has been transformed with minimal modification for the use of  $\eta^*$  as shown in Eq 4.3 [231].

$$\eta^{*}(t) = \eta^{*}_{eq} \left( \begin{cases} 0, & \text{if } t \leq t_{0} \\ 1 - e^{-\frac{(t-t_{0})}{t_{c}}}, & \text{if } t > t_{0} \end{cases} \right)$$
 Eq 4.3

However, given that the piecewise function for  $\eta^*$  equals to zero when the time is less than the delay time, this condition would describe blood as inviscid fluid prior to the coagulation initiation and post non-physical constrain to numerical simulations. As the coagulation process could be identified and separated into two processes (initiation and propagation) based on the formation of thrombin [233,234], it is reasonable to also consider a segregated but continuous coagulation progressions during numerical modeling. In the current study, a new continuous function for  $\eta^*$  was proposed phenomenologically based on Eq 4.2 and Eq 4.3. It was first assumed that the functions in the viscoelastic form were dominated during the propagation phase for  $\eta^*$  measurement as shown in Eq 4.4. On the other hand, since the thrombin formed exponentially at the beginning of blood coagulation [235,236], the value of  $\eta^*$  during the coagulation initiation phase was modeled exponentially until the delay time t<sub>0</sub>. Therefore, a second component of the proposed function had a simple exponential form (Eq 4.5) where modeling constant "a", "b", and "c" reflect the magnitude, the rate of blood coagulation initiation, and the power index. Finally, by applying the principle of superposition for coagulation initiation and propagation, Eq 4.6 represented the final continuous formulation for  $\eta^*$  in time.

$$\eta^*(t)_{propagation} = \eta^*_{eq} \left\{ 1 - e^{\left[ -\frac{(t-t_0)}{k} \right]} \right\} + \eta^*(t_0)_{initiation}$$
 Eq 4.4

$$\eta^*(t)_{initiation} = ae^{(bt^c)}$$
 Eq 4.5

$$\eta^*(t) = \eta^*(t|_{t < t_0})_{initiation} + \eta^*(t|_{t > t_0})_{propagation}$$
 Eq 4.6

## 4.3 Results

## 4.3.1 The effect of reversal agent concentrations on blood coagulation dynamics

To provide quantitative analysis on the coagulation dynamics, four rheological parameters were chosen: crossover time, maximum coagulation rate, final storage modulus (G'), and final normal force. Specifically, the point where the values of G' and loss modulus (G'') are crossing and equal in magnitude during a time-dependent evaluation is described as the sol/gel transition point. Similar to the determination of the sol/gel transition point, the gelation point utilized by Evans *et al.* [172,177] was determined as the intersection of the loss tangent under different oscillatory frequencies. The loss tangent is another rheological parameter measuring the ratio of energy lost to the energy stored during oscillatory shear and is calculated as G''/G'. The gelation point was found to have a loss tangent value greater than unity [172,177], which occurred earlier than the sol/gel transition point. Since the exact time for the sol/gel transition point is the most relevant information in the current study, hereafter referred to as the (G' and G'') crossover time for simplicity.

The use of crossover time provides a reference time to identify the initiation of the blood clot formation when G' surpasses G", which would have a higher initial value as the blood behaves more fluid-like with a viscous dominated response. During coagulation, this means the gelation process is advancing and blood is becoming a soft solid. The initial coagulation is characterized by calculating the maximum coagulation rate, which is defined as the tangential slope of which the storage modulus reached the maximum rate of increase. The final storage modulus and normal force are defined as the corresponding value at 2000 second, which is at the end of the experiment.

The hemorheological analysis on G' that characterizes the elasticity of the material would provide direct insights to the global structure of the clot formed at different conditions. As illustrated in Figure 4.1(a), the evolution of G' values from a single donor during one rheologcal experiment was monitored with different reversal agent dosages under 2 Hz. With a similar coagulation pattern, the use of rheometry was able to differentiate how G' varied due to the use of different reversal agents under various concentrations. As seen in this specific case, the use of protamine at a concentration of 100  $\mu$ g/mL would result in a stiffer clot than at a concentration of 50  $\mu$ g/mL, with an approximate difference in G' of 50 Pa. It is also shown that both protamine and UHRA-7 with a concentration of 100  $\mu$ g/mL had similar coagulation dynamics.

The use of crossover time for assessing the initiation of clot formation is shown in (Figure 4.1(b)) for buffer control and UHRA-7 at 100  $\mu$ g/mL, which had a crossover time of 315 sec (5.25 min) and 363 sec (6.05 min), respectively. A shorter crossover time indicates a faster response in the initiation of clot formation. If a crossover time could not be observed during the measurement, it was concluded that therewas no initiation of blood coagulation, as a higher G" value would indicate that blood behaves like a fluid. A situation where no coagulation was detected by the crossover time would be the test with the heparinized blood without reversal agents added.

The rate of coagulation characterizes the growth rate of G', and it was determined by the tangential slope of a polynomial fitting of the experimental data (Figure 4.1(c)). The point where the tangent line passed through was selected at the time when the change in the G' value between two data points of a 2-second interval reached a maximum. This would directly correlate to the formation and the development of fibrin clots as a higher coagulation rate represents a faster transformation from viscous blood to elastic clot.



Figure 4.1: Hemorheological analysis for a single donor tested under 2Hz, (a) effect of varying reversal agent concentrations on the storage modulus (G'), (b) illustration for identifying the crossover time using storage (G') (solid lines) and loss modulus (G") (hollow lines), and (c) illustration for calculating the maximum coagulation rate based on the tangent line (green dash line) passing through the point at the maximum change of storage modulus (G') (purple hollow circle). Note the concentrations of the reversal agents are identified as µg/mL in the bracket shown in part (a) and (b).

Table 4.1: Averaged rheological parameter measurements at an oscillatory frequency of 2 Hz for UFH neutralized with protamine and UHRA-7 under different dosage. Data presented as mean ± standard deviation and n represents the number of donors.

	Crossover	Max Coagulation	G' at 2000s	Normal Force at
(n=5)	Time [s]	Rate [Pa/min]	[Pa]	2000s [N]
Buffer control	331 ± 46	$26.8\pm6.1$	$296\pm39$	$-0.282 \pm 0.063$
Protamine 50 µg/mL	$352 \pm 75$	$19.9 \pm 4.0$	$241 \pm 30$	$-0.231 \pm 0.051$
Protamine 100 µg/mL	$395\pm57$	$23.4 \pm 4.2$	$281 \pm 30$	$-0.280 \pm 0.033$
UHRA-7 100 µg/mL	$372 \pm 55$	22.1 ± 5.8	$267 \pm 41$	$-0.277 \pm 0.050$
UHRA-7 200 µg/mL	390 ± 83	22.3 ± 1.8	$251 \pm 56$	$-0.255 \pm 0.047$

To study the effect of protamine and UHRA-7 concentrations on blood clot formation, the rheological results at an oscillatory frequency of 2 Hz were analyzed and shown in Table 4.1. The buffer control without the addition of UFH is serving as the baseline. The results indicate that in the absence of heparin, blood coagulation initiated the earliest  $(331 \pm 46 \text{ sec} / 5.5 \text{ min})$  with the highest maximum formation rate (26.8 Pa/min). Final G' and normal force magnitude also showed a high strength clot was formed at the end of the experiment.

When UFH was added to the citrate blood then neutralized with protamine at different concentrations, the crossover time increased from  $352 \pm 75$  sec to  $395 \pm 57$  sec (5.9 min to 6.6 min) when the concentration was increased from 50 to 100 µg/mL. Additional tests were conducted for protamine at 200 µg/mL and showed a significant delay in the crossover time of  $519 \pm 176$  sec (8.7 min) (Fig.S1). This result suggested an intrinsic anticoagulation response for a high dosage of protamine at 200 µg/mL and agreed with the conclusion from Meesters *et al.* that the clotting time and postoperative blood loss would increase with the increase in protamine dosage [166]. A 110

shorter/faster crossover time does not guarantee a higher coagulation rate as protamine at 50  $\mu$ g/mL had a relatively fast crossover time of 352 seconds but a slower coagulation rate of 19.9 Pa/min. The crossover time for UHRA 100  $\mu$ g/mL and 200  $\mu$ g/mL were similar with 372 sec and 390 sec (6.2 min and 6.5 min), respectively. Both 100 and 200  $\mu$ g/mL UHRA had comparable coagulation dynamics with the buffer control. Furthermore, the increase in normal force magnitude, or the decrease in the negative normal force, suggest a stronger crosslinking between the fibrin fibres within the blood clot. The normal force in the measurements was a contractive force pulling the parallel plates toward each other under oscillatory motion. Similar behavior was found previously when both biopolymer and agar gelation showed the generation of a negative normal force [180,181].

The rheological parameters were able to indicate the effects of different reversal agent concentrations with respect to the buffer control as shown in Figure 4.2. With respect to control, the clot initiation occurred at a significantly later time for all cases except protamine at 50  $\mu$ g/mL as indicated by the crossover time (Figure 4.2(a)). However, protamine at 50  $\mu$ g/mL had a significant decrease in the maximum coagulation rate (Figure 4.2(b)), the final storage modulus (Figure 4.2(c)), as well as the generation of normal force (Figure 4.2(d)). The optimal dosage for protamine occurred at 100  $\mu$ g/mL under the heparin concentration used as all four rheological parameters showed no significant difference to control. UFH neutralized with UHRA-7 was relatively stable as both 100 and 200  $\mu$ g/mL resulted in no significant difference with respect to control and between the two UHRA concentrations. There was a slight decrease in the final storage modulus value for UHRA-7 at 200  $\mu$ g/mL; however, both UHRA-7 100 and 200  $\mu$ g/mL appeared to effectively neutralize 4 IU/mL of UFH at conditions mimicking cardio bypass surgery conditions.



Figure 4.2: The neutralization of UFH by protamine and UHRA-7 at different concentrations under an oscillatory frequency of 2Hz in human whole blood. 4 IU/mL of UFH was added to citrated whole blood which was followed by the neutralization with reversal agents at concentrations ranging from 50 µg/mL to 200 µg/mL. Coagulation was then initialized by introducing CaCl<sub>2</sub> with a final concentration of 0.011 M into the neutralized blood. (a): the crossover time evaluated at the time when G' and G" had the same value, (b): the maximum coagulation rate evaluated at the point when the change in G' reached maximum, (c): the G' value at 2000 seconds of the experiment, (d): the normal force value at 200 second (note that the axis is inverted since a negative normal force was generated during coagulation).

Altogether, there is a clear trend in the dynamics of coagulation when heparinized blood was neutralized by protamine and UHRA-7 when the concentrations of the reversal agents were increased. An increase in the concentration of protamine from 50  $\mu$ g/mL to 200  $\mu$ g/mL resulted in a decrease in the G' value (Fig.S1) while an increase in the concentration of UHRA-7 from 100 to 200  $\mu$ g/mL did not significantly affect the final G' value compared with respect to the buffer control. The global trend in G' indicated that the effectiveness of UFH neutralization by protamine diminishes with an increased concentration while the effectiveness by UHRA-7 sustained with an increased concentration. A significantly low G' value at the end of the rheological measurement indicated a weak or an incomplete blood clot formation.

We further investigated the microstructure of the clot using electron microscopy to determine the correlation between rheological measurements and clot structure. As per our knowledge, this is the first study reporting the clot microstructure after rheological measurements at physiological heart rate conditions. Representative SEM images are shown in Figure 4.3. The diameter of the fibrin fibres from different clots is also shown in Figure 3. It was revealed that while there was no significant difference in the fibre thickness between either UHRA-7 100 or 200  $\mu$ g/mL, the fibres were significantly thicker for the heparinized blood neutralized by protamine at both concentrations. On average, the fibre diameter for buffer control sample was approximately 99 ± 18 nm; however, the averaged fibre diameter for protamine neutralized samples was 156 ± 28 and 195 ± 35 nm for protamine 50 and 100  $\mu$ g/mL, respectively.



Figure 4.3: Scanning electron microscope images of blood clot formed after the UFH neutralization by protamine and UHRA-7: (a) buffer control, (b) protamine 50 μg/mL, (c) protamine 100 μg/mL, (d), UHRA 100 μg/mL, (e) UHRA 200 μg/mL, and (f) measured fibrin fibre diameter from the clot structure (N=100).

## 4.3.2 The effect of oscillatory frequency on coagulation dynamics

Three oscillatory frequencies of 0.5, 1.2, and 2 Hz were applied to understand the frequency dependence on blood coagulation dynamics upon heparin neutralization by reversal agents. The 1.2 and 2 Hz settings were designed to mimic physiological heart rate of 72 and 120 beats per minute while the 0.5 Hz setting was designed to mimic the non-physiological heart rate of 30 beats per minute based on previously reported values in literature [185]. The assessments under these oscillatory frequencies' settings differentiated from the clinical use of TEG or ROTEM as their application frequency is at around 0.2 Hz. Only protamine and UHRA-7 at 100  $\mu$ g/mL were selected for the investigation of oscillatory frequencies due to the complete neutralization of UFH anticoagulation activity based on the analysis of reversal agent concentration (Figure 4.2).

Table 4.2: Averaged rheological parameters for buffer control, protamine 100  $\mu$ g/mL, and UHRA-7 100  $\mu$ g/mL at an oscillatory frequency of 0.5 Hz, 1.2 Hz, and 2 Hz. Data presented as mean  $\pm$  standard deviation and n represents the number of donors.

		Crossover	Max Coagulation	Storage Modulus at	Normal Force at
(n=5)		Time [sec]	Rate [Pa/min]	2000 sec [Pa]	2000 sec [N]
0.5 Hz	Buffer control	$272 \pm 25$	$29.8 \pm 5.5$	363 ± 28	$-0.416 \pm 0.103$
	Protamine 100 μg/mL	$336 \pm 96$	27.8 ± 7.3	322 ± 41	$-0.315 \pm 0.040$
	UHRA-7 100 μg/mL	$324\pm47$	$24.8 \pm 4.5$	304 ± 26	$-0.295 \pm 0.043$
1.2 Hz	Buffer control	281 ± 17	22.5 ± 2.6	$296 \pm 24$	$-0.270 \pm 0.038$
	Protamine 100 μg/mL	367 ± 41	$16.8 \pm 5.1$	$240 \pm 50$	$-0.247 \pm 0.046$
	UHRA-7 100 μg/mL	344 ± 47	$19.9\pm2.9$	$258 \pm 20$	$-0.243 \pm 0.043$
2 Hz	Buffer control	$300 \pm 40$	23.3 ± 4.0	283 ± 20	$-0.261 \pm 0.011$
	Protamine 100 μg/mL	403 ± 56	20.5 ± 2.4	261 ± 21	$-0.266 \pm 0.024$
	UHRA-7 100 μg/mL	381 ± 69	$20.7 \pm 4.6$	264 ± 30	$-0.275 \pm 0.035$

Table 4.2 presents the averaged rheological parameters for buffer control and heparin neutralized with 100 µg/mL of protamine and UHRA-7 under the excitation frequency of 0.5, 1.2, and 2 Hz. Increasing the frequency slightly prolonged the crossover time. With the increase in oscillatory frequency to 1.2 Hz from 0.5 Hz, showed a significant decrease in the maximum coagulation rate can be seen for the buffer and protamine sample. The decrease in the averaged normal force magnitude due to the increase in oscillatory frequency for the buffer control was also pronounced. For the buffer control, a much higher normal force value, by an approximately 54%, was measured at the non-physiological frequency of 0.5 Hz. Likewise, the results for protamine and UHRA also followed the same trend with a higher averaged normal force at a lower frequency. Based on these averaged values for assessing the whole human blood's coagulation behavior, not only the formation of the clot was affected but also the final clot strength was weaker under physiological excitation conditions.

Table 4.3: Fibrin fibre diameters of blood clot formed after UFH neutralization by protamine and UHAR-7 sheared at an oscillatory frequency of 0.5, 1.2, and 2 Hz. Data presented as mean ± standard deviation and n represents the number of fibre measurements.

(n=100)		Diameter [nm]		Diameter [nm]		Diameter [nm]
Buffer control		$103 \pm 8$		$112 \pm 13$		$111 \pm 11$
	0.5					
Protamine 100 µg/mL		$139 \pm 22$	1.2 Hz	$142 \pm 21$	2.0 Hz	$137 \pm 19$
	Hz					
UHRA-7 100 µg/mL		$101 \pm 9$		$111 \pm 14$		$110 \pm 15$

SEM images were taken for the buffer control, protamine 100  $\mu$ g/mL and UHRA-7 100  $\mu$ g/mL samples under three oscillatory frequencies as shown in Figure 4.4 for the buffer control (Figure 4.4(a, d, g)), protamine (Figure 4.4(b, e, h)), and UHRA (Figure 4.4(c, f, i)) after the samples were sheared at 0.5 Hz, 1.2 Hz, and 2 Hz under 10,000 times magnification.

To further provide a quantitative analysis regarding the microstructure of the fibrin fibre network, the diameter of a total of one hundred fibrin fibres (n) were sampled at three different locations. The averaged measurement for the diameters of the fibrin fibre is summarized in Table 4.3 for each oscillatory frequency. The averaged fibre diameter for the buffer control sample was 103, 112, and 111 nm after a frequency of 0.5, 1.2, and 2 Hz, respectively. There was no significant difference in the fibre diameters between the buffer control and UHRA-7 samples under all three frequencies tested; however, the protamine neutralization resulted in significantly thicker fibrin fibres than the buffer control and the heparinized blood neutralized with UHRA-7 (Figure 4.4(i-iii)).

When examined the influence of oscillatory frequencies on fibrin diameter, the buffer control and UHRA-7 samples showed a significant difference between the low non-physiological frequency of 0.5 Hz to both 1.2 and 2Hz (Figure 4.4(iv, vi)). Specifically, the measurements showed a thinner fibre was formed at a low frequency while there was no significant difference between the two samples previously sheared at a physiological mimicking frequency of 1.2 and 2 Hz. In contrast, there was no significant difference in the measured fibre diameter across the three oscillatory frequencies for the protamine samples (Figure 4.4(v)).


Figure 4.4: Scanning electron microscope images for blood clot sheared previously under an oscillatory frequency of (a-c) 0.5 Hz, (d-f) 1.2 Hz, and (g-i) 2 Hz for buffer control, protamine 100 µg/mL, and UHRA-7 100 µg/mL, respectively. The diameters of the fibrin fibre were measured and analysed to compare (i-iii) the influence of protamine and UHRA-7 with respect to buffer control, and investigate (iv-vi) the effect of changing oscillatory frequencies.

Overall, there was no significant difference in crossover time between the frequencies for buffer control, protamine, nor UHRA-7 (Figure 4.5(a)). This suggested that the initiation of the coagulation was not affected by the change in oscillatory frequencies. In terms of maximum coagulation rate, there were differences. The coagulation rate decreased with increasing in oscillatory frequency for both buffer control and protamine (Figure 4.5(b)). The maximum coagulation rate assessment of UHRA-7 did not seem to be affected by the oscillatory frequencies.

The final G' value at the end of the experiments at 2000 second (Figure 4.5(b)) showed a significant decrease when oscillatory frequencies were changed for buffer control, protamine, and UHRA-7. The results suggest a decrease in final clot strength due to the increase in oscillatory frequency from the non-physiological frequency of 0.5 Hz to the physiological frequency of 1.2 and 2 Hz. The generation of normal force (Figure 4.5(d)) followed the same relationship of maximum coagulation rate assessment. Furthermore, there were no significant differences for all rheological parameters evaluated between 1.2 Hz and 2 Hz.



Figure 4.5: The influence of oscillatory frequency to the neutralization of UFH. (a): the crossover time, (b): the maximum coagulation rate, (c): the final G' value, and (d): the final normal force

# 4.3.3 The time evolution of storage modulus (G') and complex viscosity ( $\eta^*$ )

The measurements conducted on the untreated buffer control samples were analyzed under 2 Hz. The rationale for selecting the 2 Hz buffer control was threefold. First, the frequencies of 1.2 and 2 Hz represented and mimicked a physiological heart rate of 72 and 120 beats per minute. Second, it was shown that the rheological parameters were statistically insignificant between the measurements conducted under 1.2 and 2 Hz (Figure 4.4). Third, more measurements were

conducted under 2Hz for the evaluation of reversal agent concentrations and a total of 16 datasets were used here for the characterization of blood clotting dynamics.

	<i>G'<sub>eq</sub></i> [Pa]	$t_0[s]$	$t_c[s]$
Viscoelastic (van Kempen) Eq 4.1	307 ± 35	348 ± 69	415 ± 59
	G' <sub>eq</sub> [Pa]	$t_{mid}[s]$	<i>k</i> [s]
Biochemical (sigmoidal) Eq 4.2	286 ± 38	856 ± 98	205 ± 19

 Table 4.4: Averaged formulation parameter for viscoelastic and biochemical modeling for blood coagulation

 dynamics. Note that one standard deviation from the averaged values were presented.

Starting with the time-dependent evolution data of G', both the viscoelastic (van Kempen) and biochemical (Sigmoid) models were used to characterize G', as presented in Figure 4.6, with the averaged modeling parameters summarized in Table 4.4. All the modeling parameters for the buffer control samples tested under 2 Hz were presented in Table A.1.1. A quick reference to the buffer control experimental data (Table 4.1), the crossover time of  $331 \pm 46$  seconds and the final G' value of  $296 \pm 39$  Pa from the experiment were in agreement with the viscoelastic model's to of  $348 \pm 69$  seconds and G'<sub>eq</sub> of  $307 \pm 35$  Pa. The G'<sub>eq</sub> value ( $286 \pm 38$  Pa) predicted by the biochemical model was also similar in value to the measurement.

The characterizations for a single sample fitting using the two models were plotted Figure 4.6(a) with the averaged fitting on all buffer control samples under 2 Hz shown in Figure 4.6(b) using the modeling parameters summarized in Table 4.4. Comparing against the experimental measurements (Figure 4.6(a)), the viscoelastic formulation resulted in a closer agreement in predicting the dynamics of blood clot formation after the delay time. Both formulations did

represent the experimental data of G' after the initiation phase at the beginning of the measurements; however, noticeable divergence in G' prediction could be observed around approximately 350 seconds when modeled using the sigmoidal function. The viscoelastic formulation by van Kempen constrained the G' value at zero before the delay time resulting in a closer overall prediction but without providing a smooth projection at the beginning of blood coagulation as seen in Figure 4.6(b). The inflection point from the sigmoid function could be seen at approximately 850 and 1000 seconds in Figure 4.6(a) and (b), respectively.



Figure 4.6: The time evolution of the storage modulus predicted by the viscoelastic response (van Kampen) and the biochemical response (Sigmoidal). (a) A typical data set fitted with both models, (b) the averaged fitting from all the buffer blood sample under 2 Hz

Table 4.5: Averaged modeling parameters for the proposed formulation (Eq 4.6) characterizing complex viscosity  $\eta^*$ 

$\eta^*_{eq} [Pa * s]$	t <sub>0</sub> [min]	t <sub>c</sub> [min]	a[mPa * s]	b [c/min]	c [ - ]
$26.3\pm2.6$	7.7 ± 1.3	$11.5 \pm 2.7$	$13.4 \pm 4.0$	$0.00587 \pm 0.00235$	$3.24\pm0.26$

The analysis of the modeling of blood's complex viscosity using Eq 4.6 was summarized in Table 4.5. Table A.1.2 summarized the modeling parameters for each buffer control sample tested under 2 Hz. The predicted averaged steady-state complex viscosity ( $\eta^*_{eq}$ ) was 26.3 ± 2.6 Pa-s versus the averaged final complex viscosity value ( $\eta^*$ ) of 23.6 ± 3.1 Pa-s from the rheological measurements. The delay time ( $t_0$ ) with an average value of 462 ± 78 second (7.7 ± 1.3 minutes) from the model was significantly longer than the averaged crossover time from rheological measurements. The proposed complex viscosity based on Eq 4.6 had an excellent fit to the experimental data as presented in Figure 4.7. As one can see from Figure 4.7(b) under a logarithmic scale, the modeled blood viscosity captured the viscosity during the initiation phase at the beginning of the measurement accurately.



Figure 4.7: Predicted complex viscosity in time using Eq 4.6 on a single measured data set under (a) linear scale and (b) logarithmic scales for clarity

# 4.4 Discussion

### 4.4.1 Rheological investigations on heparinized whole human blood

It is anticipated that the combined use of the four rheological parameters along with the morphology and the clot microstructure provided a better assessment of anticoagulant reversal. The current rheological investigation demonstrated its potential to differentiate the overall blood coagulation dynamics for protamine and UHRA neutralization of heparin under various concentrations and oscillatory frequencies using four rheological parameters – the crossover time, the final G' value, the maximum coagulation rate, and the normal force. We were able to distinguish several key significant differences for the rheological parameters analyzed between the protamine and UHRA-7 neutralized samples. The clot microstructure obtained from electron microscopy analysis from these samples also validated the heparin neutralization and provide a link between the rheological parameters.

The use of SASO rheometry in the current study for assessing the dynamic of blood coagulation resulted is in close agreement with previous published measurements on control clots in terms of the final G' values and the overall evolution characteristics of G' as shown in [177,231]. The final values of G' were used to assess the stiffness of the blood clots as it was previously demonstrated the usage of G' for the assessment of coronary artery disease patients [237] and pulmonary embolism [238]. Similar to the usage of G' values from the literature, our analysis revealed the measured G' values were significantly higher at an oscillatory shear frequency of 0.5 Hz than either 1.2 or 2 Hz (Figure 4.5). This suggested the blood formed a less stiff clot under an oscillation mimicking physiological heart rate. Furthermore, the UFH neutralization investigation showed UHRA-7 neutralized heparin accordingly as the final G' value showed a no significant decrease for UHRA-7 at different concentrations with respect to buffer control. There was no significant 124

difference for the maximum coagulation rate nor the generation of normal force between buffer control and UHRA-7 (Figure 4.2). There was also a significant increase in the final G' values and the maximum coagulation rate under a low oscillatory frequency of 0.5 Hz, suggesting a stiffer and faster blood clot formation due to less physical disturbance during coagulation. The current finding might have a potential conflict on TEG/ROTEM data [168,229] as their oscillatory shear are conducted at even lower frequencies. The statistical insignificance from the frequency analyses suggested the blood clotting assessment conducted at a physiological excitation frequency could result in a more robust evaluation in large arteries.

We related the fibrin fibre diameter to excitation shear frequencies based on the visualization on blood clot structure using SEM. The measured fibre diameters, as presented in Figure 4.4, showed a significant increase between an oscillatory frequency of 0.5 and 1.2 Hz, and 0.5 and 2 Hz for both the buffer control and UHRA-7 samples. The protamine neutralized clots, however, did not result in any significant differences in fibre diameters with respect to the change in frequencies. The protamine neutralized clots did show a significantly thicker fibrin fibre diameter compared to the buffer control. This suggested the protamine formed a weaker fibrin network [239], as a thicker fibre diameter did not result in higher stiffness from the rheological assessment. Additionally, a clot with thicker fibrin fibres would lysed faster than a clot with thinner fibres [240]. There were no significant differences for the fibrin fibre diameters between the buffer control and the UHRA-7 neutralized UFH samples (Figure 4.2) for the final G' values, the maximum coagulation rate, and the measured normal force. Together with the usage of the crossover time, the current rheological assessment provided a more comprehensive coagulation dynamic evaluation for UHRA-7. Further verified with the SEM visualization, our current analysis demonstrated that the use of UHRA-7 to neutralize UFH would not only preserve blood clot structure but also provide 125

comparable coagulation dynamics with respect to the buffer control. It is also worth to mention the rheological measurements and the SEM measurements correlated well for UHRA-7 in the sense that the final G' values and the measured normal force values yielded with no significant differences with respect to buffer control, while the measured fibrin fibre diameter also showed no significant difference.

Protamine, on the other hand, did not have an aligned conclusion between the rheology and SEM. Although protamine showed no significant difference for G' and normal force, the measured fibrin fibre was thicker than buffer control. Similarly, it was not able to differentiate if the fibrin fibre was thicker when the blood clot was undergoing lower oscillatory frequency of 0.5 Hz, with rheology detected a significant decrease in G' at the physiological frequencies. This discrepancy found in the protamine neutralized heparinized blood suggested that there were additional factors other than fibrin fibre diameter were influencing the rheological measurements (Figure 4.5(c)). This is a correlation with Ryan *et al.* that the blood clot's network stiffness depended on both the fibre diameters and branchpoint concentration [175].

We further analyzed the normal force generated by the blood clot during the process of coagulation (Fig.S2). The increase in the normal force magnitude, which provides a negative tensile force contracting the clot sample, was an indication of an increase in fibrin fibre crosslinking orthogonal to the direction of the shear [180,191]. As summarized by Williams *et al.*, there were correlations between different cardiovascular diseases and the contraction of blood clot [183]; therefore, a viscoelastic assessment of the blood clot with contractile/normal force as an additional measuring parameter could contribute further understanding. The contractile force generated by platelets, measured with microfluidic devices by Myers *et al.*, was shown to be a potential biomarker for

bleeding disorders [184]. Under the current rheological measurements, a proper neutralization of UFH using protamine and UHRA-7 resulted in similar contractile/normal force generated by the blood clot comparing against the buffer control as presented in Table 4.1 and Figure 4.2. Based on the previous investigation on the structure of compacted blood clot by Cines *et al.*, the generation of the contractile/normal force by the platelets and fibrin(ogen) was required for a tightly packaged blood clot by the blood cells [241]. Given that the rheological results concluded a no significant difference between the buffer control and UHRA-7 on the final G' value, the maximum coagulation rate and the measured normal force, all three rheological parameters were feasible for determining the neutralization state of UFH under different concentrations of antidotes (Figure 4.2). Protamine 50  $\mu$ g/mL, on the other hand, showed a decrease in the generated contractile/normal force of -0.231  $\pm$  0.051 N than a force of -0.282  $\pm$  0.063 N generated by the buffer control. Combining both rheological characteristics (Table 4.1) that the final G' vale and the maximum coagulation rate were significantly less than the buffer control, the current rheological analysis concluded a suboptimal neutralization for protamine 50  $\mu$ g/mL.

Finally, the use of the crossover time in the current study differed from the gelation point found with the use of the lost tangent [172,177]. As we have shown an influence from a low oscillatory frequency affecting the coagulation behavior from the current rheological measurements, the use of crossover time provided an independent assessment under a constant oscillatory frequency and shear amplitude. The simple use of crossover time in the current study still demonstrated its potential. The use of the crossover time successfully predicted the intrinsic anticoagulation effect from the high concentration of protamine as the crossover time was significantly longer for both protamine 100 and 200  $\mu$ g/mL during UFH neutralization. A supratherapeutic amount of protamine administrated would result in an extended activated clotting time as discussed 127

previously [165,242]. However, in the current analysis, a shorter crossover time was not necessary in sync with a lower final G' value, a slower rate of clotting or a smaller generated normal force, suggesting a faster initiation of clotting did not result in a faster propagation of clot formation. The rheological result suggested the initiation of coagulation process was decoupled and the formation of blood clot could be separated into two processes as typically seen in literature [233,234]. The production of thrombin during blood clot propagation could, therefore, be correlated to the rate of increase in G' values observed by the rheological measurements (Fig.S3). Additionally, the increase in protamine concentrations would decrease the generation of thrombin through factor V inhibition [243].

### 4.4.2 Characterization of the coagulation dynamics for normal human blood

Using Eq 4.1 and Eq 4.2 to characterize the evolution of G' during coagulation, both models resulted in a reasonably well fit to the current experimental rheological data for buffer control samples oscillated under 2 Hz frequency. The viscoelastic model proposed by van Kempen captured the initiation phase of G' better than the sigmoid model; however, the major limitation for the viscoelastic model was the constraint of zero value in G' during the time prior to the delay time. The viscoelastic model provided a great tool for predicting the time-dependent structure development of the blood clot during the propagation phase as well as the steady-state G' value. On the other hand, if one would like to apply the relationship for numerical modeling, which is one of the current interests, the limitation of the viscoelastic model would introduce modeling difficulty. Given both Eq 4.1 and Eq 4.3 were piecewise and constrained G' and  $\eta^*$  to zero prior to the delay time, utilizing the viscoelastic formulation would result in inviscid flow during the blood clot's initiation phase.

To translate the rheological measurements on the process of blood coagulation to the numerical modeling of ATAA and the aortic valve, Eq 4.6 was proposed for modeling the evolution of the blood clot's complex viscosity under oscillatory shear. The proposed timedependent formulation for the complex viscosity of blood clot was phenomenologically modeled based on the rheological measurements. The current equation linearly combined the initiation and the propagation phase of blood coagulation, which were separated by the delay time. The predicted averaged complex viscosity,  $\eta^*_{eq}$ , from Eq 4.6 resulted in similar steady state viscosity value measured at the end of the rheological experiments on average. However, the delay time,  $t_0$ , from the model did not correlate with the crossover time from the rheological measurements as the delay time occurred at a significantly later time. During numerical analysis, once the coagulation was deemed feasible, the proposed model could then apply the modification of blood's viscosity. The continuous and a single transition nature of the proposed equation provided the ease of integration to the current numerical models on aneurysms and heart valves. The major limitation for Eq 4.6 was that the evolution of blood clot only considered clot formation under constant shear rate; therefore, any destruction of the blood clots due to the variable shear rate would not be captured.

### 4.4.3 Limitations

There are some limitations and restrictions from the current study that warrant discussion. First, there was only a limited time window that the donated blood did not show significant variations, which could be distinguished by the rheometer; therefore, a limited number of tests were conducted per day. To account for this experimental time constraint, the donors donated on multiple days to ensure blood sample integrity. Subsequently, a buffer control measurement was conducted for each donation. Additionally, the effect of sample evaporation was pronounced after approximately 45 minutes of experimental time; therefore, the measurement was terminated earlier at 2000 second to ensure the blood clot formation reached steady state based on the measured G' value under normal circumstances. As the result, the current study can only investigate the clot formation but not fibrinolysis. Finally, although statistical differences for fibrin fibre diameters and rheological analysis were evident even from the small number of donor recruited in the current study, additional donors will be required for clinical investigations and a good representative of overall population.

### 4.5 Conclusion

The current study utilized small amplitude oscillatory rheometry to characterize the coagulation dynamics of whole human blood. UFH was added to the blood samples that mimic cardio bypass surgical conditions followed by the neutralization of protamine and UHRA under various concentrations. Given the accurate and precise control of oscillatory frequencies and shear amplitude, two physiological frequencies were used, in addition to a low non-physiological frequency, to assess the coagulation dynamics. It was found in the current study that an optimal dosage for protamine was at 100 µg/mL when neutralizing UFH at 4 IU/mL; however, incomplete coagulation occurred for protamine at 200 µg/mL. UHRA-7, on the other hand, demonstrated a high safety dosage tolerance of 100 and 200 µg/mL without interfering with the coagulation and microstructure of blood clots. The four rheological parameters in combination with the clot microstructure provide a more accurate description of coagulation dynamics and the anticoagulant neutralization efficiency. The study for the first time compared the rheological evaluation of heparin neutralization of clinically used protamine and antidote in development, UHRA-7. The experimental results were used toward to the characterization of coagulation process with

relationships found in the literature for G' and a newly proposed continuous formulation for  $\eta^*$  that could be easily integrated to the existing numerical models on ATAA and heart valve.

# **Chapter 5: Conclusions**

To summarize all the work completed in this dissertation, a concluding section on the contributions is firstly recapped following by a recommendation section on the future work that can be conducted to extend from the current study. To the best of our knowledge, the current work differentiates itself from the previous studies in literature by formulating the anisotropic hyperelastic properties of the thoracic aortic wall into the fully coupled fluid-structure interaction models using patients' echocardiogram measurements regarding the diameters of the aneurysms and peak blood flow velocities. The additional use of hematocrit values in the analysis of ATAA under both normotension and hypertension also provided a unique aspect of biomechanics for potential future clinical evaluations. The continued usage of hematocrits for the biomechanical and hemodynamical investigations of bileaflet mechanical heart valve also provided further clinical values in artificial heart valve designs and patient managements, which were both currently undervalued and overlooked. The characterization of thrombus formation under physiological heart rates with rheological assessment also provided the necessary modeling parameters for both clinical and biomedical assessment for the patients and future numerical thrombosis modeling. Finally, the evaluations on the effectiveness of two different anticoagulation reversal agents provided a clear picture for optimal drug dosages for neutralizing heparin products during surgical setting.

# 5.1 Summary of Results

In the current work, the biomechanics and hemodynamics of ATAA have been numerically investigated with the focus on patient-relevant measurements on the geometrical characteristics of an aneurysm and peak blood flow velocity using echocardiogram. As presented in Chapter 2, the existing fully coupled FSI model provided an accurate and robust prediction based on the physiological hemodynamics conditions and anisotropic hyperelastic arterial wall. To further provide clinical insights due to the different hematocrit each patient has, the models were extended using non-Newtonian shear thinning Quemada model. It was found that the aneurysm wall stress distribution significantly depended on blood pressure condition and the aneurysm's geometrical characteristics, but the wall stress distribution remained relatively independent from the change in hematocrit. On the other hand, the influence of hematocrit was primarily on the wall shear stress generated by the blood flow and the wall shear stress was indeed another risk factor for aneurysm progression.

To extend the current ATAA investigation, another set of FSI model was built for the examination on bileaflet mechanical heart valve as presented in Chapter 3. This model was built because a bicuspid aortic valve is another the main risk factor for the initialization and development of an ATAA. This fully coupled FSI model validated with PIV measurements provided another detail evaluation on the influence of hematocrit to the artificial heart valve. The hemodynamic analysis on the heart valve due to the change in hemorheological characteristics and the degree of shear-thinning of blood was conducted. This work provided additional supporting information that there were influences of varying hematocrits on not only the shear stress distributions but also the leaflet motion of the artificial heart valve.

Furthermore, to investigate the dynamics of thrombus formation of whole human blood and the influence of anticoagulation reversal agents, small amplitude oscillatory rheometry measurements were performed under physiological heart rates as presented in Chapter 4. Due to the potential of thrombus formation either due to surgical operations, aortic dissections, or blood cell damages, the current *in vitro* work evaluated not only the coagulation under normal circumstance but also the coagulation under the influence of anticoagulation reversal agents. These rheological characterizations of the dynamics of whole human blood coagulation provided additional insights on the initialization of blood clot formations. With the combination use of rheological parameters (the clot's initiation time, the formation rate, the final clot strength, and the contractile force), the structure of the blood clot was correlated to SEM visualizations between the frequencies and reversal agent concentrations tested. The current work successfully identified the potential anticoagulation effect from the overdose of protamine, which is an anticoagulation reversal agent. Moreover, the rheological measurements for the coagulation dynamics on the untreated citrated blood were fitted with the characteristic equations from literature.

### 5.2 Key Contributions

The contributions from the current work are listed as follows:

• An accurate and robust fully coupled FSI model was constructed for anisotropic ascending thoracic aortic aneurysm models with focuses on the biomechanical and hemodynamical evaluations using three semi-idealized ATAA cases under normotension and hypertension, as well as low and normal hematocrit.

- The current ATAA models were unique in the way that the models provided relevant clinical insights and foundations for patient specific ATAA managements by relating the aneurysm diameters, hypertension, and hematocrits through biomechanical analysis.
- An experimentally validated fully coupled FSI model was constructed for a bileaflet mechanical heart valve with focuses on the hemodynamical and the aortic valve dynamics assessments regarding the hematocrit influence on the flow and stress distributions.
  - The current BMHV models distinguished itself with literature by systematically evaluate the biomechanics of the artificial heart valve with the non-Newtonian shear thinning blood under the influence of the hematocrits.
- A whole human blood rheological characterization using the combination of four key rheological parameters was performed on the study of the dynamics of blood clot formation emphasized on unfractionated heparin reversal by protamine and recently reported non-toxic universal heparin reversal agent UHRA-7.
  - The combination usage of four rheological parameters from the small amplitude oscillatory shear rheometry with the clot microstructure under SEM was the first in the literature, based on my best knowledge, to accurately characterize coagulation dynamics and the anticoagulant neutralization efficiency.

# 5.3 Future work

The current work has established several foundations for further advance biomechanical modeling and simulation of ascending thoracic aortic aneurysm initializations and progressions. A step-by-step advancement could be visualized by combining each section of the current work one by one. A relatively easy future implementation using the current FSI model on ATAA could be to extend into full patient-specific anatomy by reconstructing from CT scan images. This would offer a more realistic prediction and deliver a personalized assessment on the ascending thoracic aorta based on clinical evaluations. Additionally, a newly published technique to assess the anisotropic material properties of a patient's ascending thoracic aortic aneurysm from CT scans shows a promising step towards to a fully patient-specific management [244]. Following the creation of a patient-specific ATAA would involve with prescribing distinct anisotropic hyperelastic properties for intima, media, and adventitia layer of the aorta.

Furthermore, as the bicuspid aortic valve is one of the risk factors for ATAA, the next step would be to merge the aneurysm model with the heart valve model for a fully coupled ascending aorta system that includes an aortic valve, a realistic aortic sinus, and an ascending thoracic aortic aneurysm. The integration of a diseased or an artificial aortic valve to the investigation of ATAA progression would provide significant clinical value regarding the influence of hemodynamics on the aortic wall stress and shear stress distributions, which is also known to stimulus tissue degradation under abnormal high values.

With the characterization of thrombus formation dynamics, the coupled ascending aorta system could integrate the rheological characterization to assess the potential of initialization of thrombus first and modeling the dynamics of thrombus formation once initialization is deemed possible. Not only the rheological characterizations could be used directly in a surgical setting to

assess the coagulation behaviour of a patient but could also be used to simulate the potential thrombosis events occur due to further disease progression or device implantations. The potential work on the numerical assessment of thrombus could involve in an ascending thoracic aortic aneurysm advancing into an aortic dissection as well as endovascular stent graft implementations. Both scenarios would encourage the formation of thrombus due to tissue injuries and stagnation of blood flow.

Additionally, several important tasks could be conducted in the future to address some limitations experienced in the current study. There will be a need to verify the patient-specific ATAA simulations using experiments. PIV measurements using patient-specific silicone phantoms constructed using Sylgard 184 can be conducted with non-Newtonian shear thinning working fluid for visualization and validation purpose. The silicone phantoms can also be used to study endovascular stent graft deployment and flow diverting characteristics. Studies on the complications with endovascular stent grafts, including stent graft migrations, collapsing, and endovascular leakage can be performed. An extended silicone phantom including the aortic annulus, aortic sinus, ascending thoracic aorta, and the aortic arch can also be fabricated for the coupling the experimental study with BAV and artificial heart valves. Finally, the current study on blood coagulation in aneurysms will benefit significantly with *in vitro* cardiovascular flow experiments using platelet rich plasma or fibrinogen solution to assess the blood clot formation. All these experiments will provide additional verifications and validations to the numerical simulations and the rheological measurements to support the limitations of the current study.

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## Appendix

## Appendix A Supplemental Material for Rheological Characterization

## A.1 Modeling Parameters

Table A.1.1: Moo	leling parameters for	storage modulus	s (G') with al	ll the buffer	control sample	es under 2 Hz
using Eq 4.1 and	Eq 4.2					

Viscoelastic (van Kempen)			Biochemical (Sigmoidal)			
<i>G'<sub>eq</sub></i> [Pa]	<i>t</i> <sub>0</sub> [s]	$t_c[s]$	<i>G'<sub>eq</sub></i> [Pa]	t <sub>mid</sub> [s]	<i>k</i> [s]	
317	327	328	304	172	744	
292	411	466	268	193	961	
245	434	444	223	204	962	
253	450	523	226	220	1078	
360	303	314	348	165	705	
365	423	315	341	213	843	
351	358	290	336	193	740	
293	428	288	273	213	812	
271	388	339	255	193	820	
349	380	320	332	205	793	
304	398	346	285	200	838	
288	500	334	259	227	921	
298	496	309	269	226	893	
284	455	391	259	215	934	
326	375	278	309	195	748	
318	522	288	287	244	902	

Table A.1.2: Modelling parameters for complex viscosity ( $\eta^*$ ) with all the buffer control samples under 2 Hz using Eq 4.6

$\eta^*_{eq} \left[ Pa * s \right]$	t <sub>0</sub> [min]	t <sub>c</sub> [min]	a[mPa * s]	b [c/min]	c [ - ]
26.12	6.72	8.14	16.15	0.00501	3.388
24.80	9.68	11.17	14.61	0.00348	3.119
22.36	10.07	13.90	21.35	0.00488	2.915
23.08	10.47	13.84	21.06	0.00483	2.771
28.57	6.72	7.10	11.02	0.00658	3.443
31.89	6.71	11.63	10.28	0.00255	3.686
27.89	6.79	8.22	9.14	0.00904	3.254
23.96	7.01	11.27	9.96	0.01122	3.135
22.41	7.44	10.02	16.76	0.00716	3.140
29.23	7.06	9.34	9.98	0.00739	3.141
26.11	7.29	10.70	9.98	0.00313	3.515
26.29	7.46	15.06	14.26	0.00787	2.999
26.63	7.21	14.96	15.05	0.00496	3.398
26.27	8.16	13.87	15.10	0.00484	2.909
25.75	6.74	9.10	9.74	0.00731	3.436
28.73	7.01	15.05	10.02	0.00374	3.509



Figure A.2.1: The neutralization of UFH by different Protamine and UHRA-7 dosages under an oscillatory frequency of 2Hz. Protamine 200 µg/mL data are presented and showed the intrinsic anticoagulation effect when protamine overdosed. (a): the crossover time, (b): the maximum coagulation rate, (c): the final G' value, (d): the final normal force magnitude



Citrate - Protamine(50) - Protamine(100) - Protamine (200) - UHRA-7(100) UHRA-7(200)

Figure A.2.2: Single donation results under 2Hz on the generated normal force during blood clotting for protamine and UHRA-7 neutralized heparinized whole human blood. Note the decrease in the force magnitude for protamine 200 µg/mL and 50 µg/mL towards to the end of the measurement.



Citrate - Protamine(50) - Protamine(100) - Protamine(200) - UHRA-7(100) UHRA-7(200)

Figure A.2.3: Single donation results under 2Hz for the rate of change in G' value during coagulation. A significant delay in the increase rate of G' can be seen for protamine 200  $\mu$ g/mL. The maximum rate of change was lower for both protamine 50 and 200  $\mu$ g/mL. It's also worth to mention that the time when maximum rate of change in G' occurred was used as the time to calculate the tangent line through the value of G' for the determination of maximum coagulation rate.