Understanding and Modeling Pathways to Thrombosis

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John Seligson
University of Central Florida

UNDERSTANDING AND MODELING PATHWAYS TO THROMBOSIS

by

JOHN M. SELIGSON

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Thesis Chair: Alain Kassab, Ph.D.

ABSTRACT

Intra-vessel thrombosis leads to serious problems in patient health. Coagulation can constrict blood flow and induce myocardial infarction or stroke. Hemodynamic factors in blood flow promote and inhibit the coagulation cascade. Mechanically, high shear stress has been shown to promote platelet activation while laminar flow maintains plasma layer separation of platelets and endothelial cells, preventing coagulation. These relationships are studied experimentally, however, physical properties of thrombi, such as density and viscosity, are lacking in data, preventing a comprehensive simulation of thrombus interaction. This study incorporates experimental findings from literature to compile a characteristic mechanical property data set for use in thrombosis simulation. The focus of this study's simulation explored how thrombi interact between other thrombi and vessel walls via Volume of Fluid method. The ability to predict thrombosis under specific hemodynamic conditions was also a feature of the data collection. Using patient specific vessel geometry, the findings in this study can be applied to simulate thrombosis scenarios. The possible applications of such a simulation include a more precise method for estimation of patient myocardial infarction or stroke risk and a possible analysis of vessel geometry modification under surgery.

DEDICATION

To my sister,

for your love and support,

bringing joy and laughter to my world

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CHAPTER ONE: INTRODUCTION

Thrombosis is a topic of much importance. As the circulatory system is vital for human health, any blockage formed by a thrombus can cause major issues, including fatality. Modern medicine sought to control coagulation via drugs such as warfarin. Such drugs present new problems of gastrointestinal bleeding and intercerebral hemorrhage, due to the inhibition of necessary coagulation (Kirklin et al. 18). In Kirklin's and his colleagues' studies, clot formation was seen in the application of a left ventricular assist device (LVAD), where the inflow bearings, inflow cannula, and outflow graft at spots of drastic change in direction were potential thrombus sites (Kirklin et al. 18). Noticing the problem being caused by mechanical application, it follows that a solution towards controlling thrombosis lies in understanding the mechanical aspects of thrombus formation. This can be done by studying how thrombi form, the hemodynamic factors that promote thrombosis, and thrombus mechanical properties. In understanding what a thrombus is and what triggers it, a computer model can be made to simulate patient specific blood flow, showing where, how, and when a thrombus would generate. Such a method would highly influence the medical field and further equip medical specialists, giving patients facing thrombotic issues a greater chance.

CHAPTER TWO: THROMBUS FORMATION

In order to stop blood loss in the event of vessel injury, the body must create a "plug." When a break in the vessel arises, platelets activate, adhering to collagen fibers in the damaged endothelial cells, and produce pro-coagulant factors leading to the conversion of the plasma protein, prothrombin, to the enzyme, thrombin. This enzyme also produces factors that create more thrombin, which convert inactive fibrinogen present in blood to fibrin. Multiple fibrin lay down to create a network or "mesh" in which red blood cells fill, creating a sufficient plug for leakage prevention (Campbel 911-912). When these factors influence clot formation inside the vessel instead of outside or in the vessel wall, the formed clot is considered a thrombus.

With a thrombus being formed in an intra-vascular location, the locations to analyze are inside veins and arteries, from the vessel wall to the center of the blood flow. When platelets rest and bind to proteins on the vessel wall causing platelet activation and adhesion, as well as enzyme factor VIIa binding with receptors on endothelial cells, thrombin is formed. This thrombin also causes platelet activation and fibrinolysis (Xu et al. 237). The first of these two mechanisms, the activation of platelets, uses glycoproteins to bind to other platelets and constituents. The second, fibrinolysis, recruits red blood cells to create a mesh, and contributes to the structure of the clot ("Medical Physiology" 446B). The first mechanism mentioned is known as white thrombus, while the second is known as red thrombus. On the vascular wall and in blood are constituents which play roles in anti-thrombotic and pro-thrombotic states based on when clots need to form ("Medical Physiology" 446C). For anti-thrombotic cases, endothelial cells line the vascular wall and produce anticoagulant factors. If these cells are damaged or removed due to injury, blood cells come into contact with pro-coagulant factors and thrombosis

occurs (“Medical Physiology” 446C). For pro-thrombotic cases, unusual shear can cause platelets to activate. On top of this, according to Shadden, in areas of low velocity such as the wall of the vein which also contain activated platelets lead to platelet adherence and coherence (Shadden and Hendabadi 473).

Two pathways must be considered for thrombosis. The intrinsic pathway deals with blood interacting with negatively charged surfaces or glass, followed by interaction with clotting factor XII and other factors. The extrinsic pathway deals with blood interacting with damaged cells, being exposed to tissue factor III, followed by interaction with clotting factor VII. Both of these pathways cause procoagulent factors to “activate” which starts a chain of reactions towards a common pathway terminating at formed thrombus (Medical Physiology 446E). To illustrate how all of the factors orchestrate the formation of a thrombus, the following figure displays the thrombosis cascade.

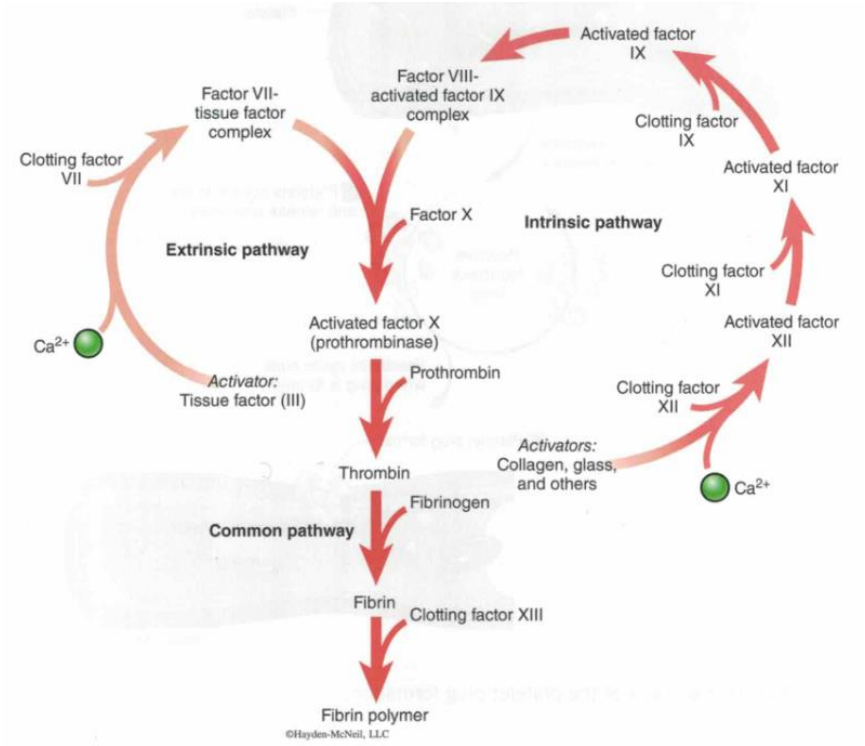

Figure 1: Summary of Blood Clotting Mechanisms (Lopez 294)

CHAPTER THREE: HEMODYNAMIC FACTORS PROMOTING THROMBOSIS

There are several conditions in which the environment of vessel blood flow is pro-thrombotic. A German physician, Rudolf Virchow, studied the subject of thrombosis approximately one hundred fifty years ago. Though it was not proposed by him, a generalization of hemodynamic factors were proposed and named after the physician, now known as Virchow's Triad (Bagot and Roopen 180). The three factors consist of the flow of blood in the vessel, the type and amount of constituents in the blood, and injury to the endothelial wall (Kiyomura et al. 216). Regarding blood flow, abnormal fluid dynamic features such as turbulence and stasis promote thrombosis. Normally, under laminar flow, a layer of plasma, moving slower than regular blood flow, separates the constituents of blood from the endothelial wall. In the case of non-laminar flow, the plasma layer can be ripped away, allowing platelets to touch the endothelial wall and start pro-coagulant factors. Another unwanted situation, static blood flow keeps coagulant factors in one location, preventing fresh, "inactivated" blood along with anti-coagulant factors from diluting or replacing the pro-coagulant factors (Kiyomura et al. 216). Concerning blood constituents, a high density of red blood cells can promote the formation of a thrombus. An increase in hematocrit, or the volume percentage of red blood cells, can raise the endogenous thrombin potential (ETP). Horne's study provided that as hematocrit percentage rose from 0% to 60%, the maximal thrombin concentration rose from zero to up to 78 nanomoles per liter while the time to reach maximal thrombin concentration fell from 20 minutes to as low as 7.5 minutes. This data can be seen in Horne's figure below.

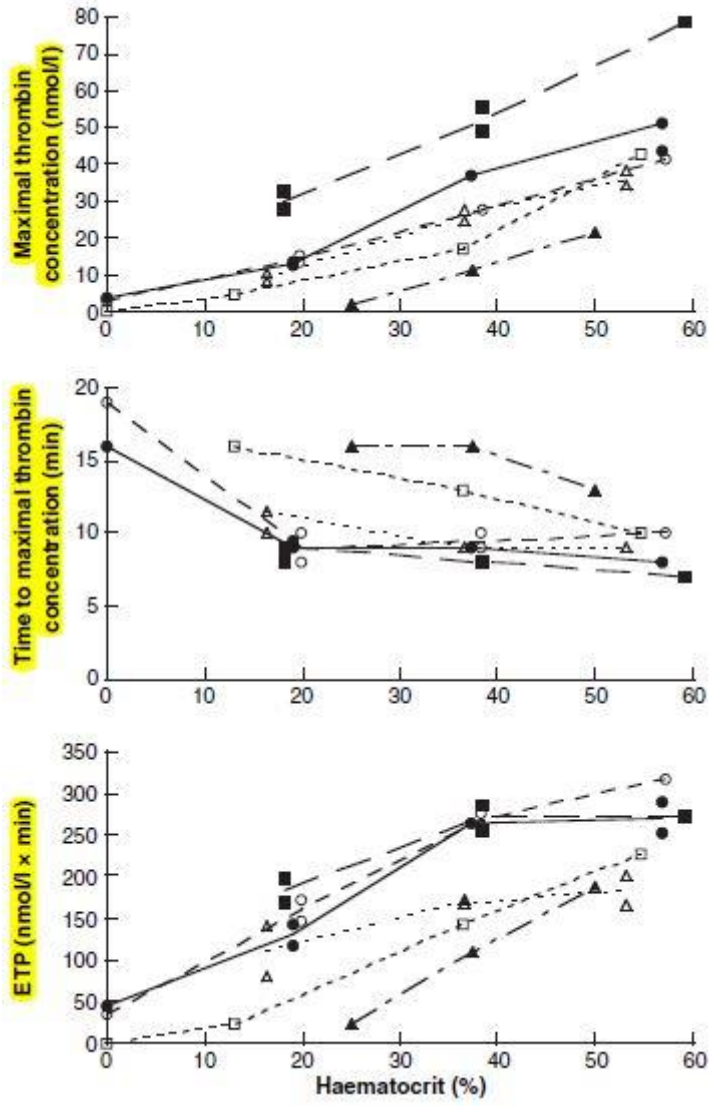

Figure 2: Maximal Thrombin Concentration (Top), Time to Maximal Thrombin Concentration (Middle), ETP (Bottom) vs. Hematocrit (Horne et al. 405)

The procedure was done by taking red blood cells from blood samples and sedimenting them by centrifugation at 2000 g for 10 minutes. Lipidated tissue factor and $CaCl_2$ was added to promote clotting (Horne et al. 405). In support, Kiyomura's study reported a value for hematocrit above 51% poses risk for stroke (Kiyomura et al. 217). This suggests that at a certain red blood cell density, a thrombus is more likely to form. Understanding that turbulence might cause an

increase in red blood cell density, a relationship between shear stress and hematocrit might exist. This relation could be utilized in a computer model to show the formation of a thrombus. Finally, in terms of endothelial injury, platelets can be activated when exposed to substances in damaged endothelial cells such as collagen, resulting in adherence of the platelets to the damaged location (Kiyomura et al. 217).

Another trigger for thrombosis can mechanically be represented as a function including high shear stress for a period of time (Shadden and Hendabadi 467). In a study by Chesnutt, multiple values of critical shear stress, the stress required to activate a platelet, were considered. Several studies compiled by Chesnutt had resulted in critical shear stress values ranging from 2.3 – 32.0 N m^{-2} for whole blood and 1.5 – 12 N m^{-2} for platelet rich plasma. However, the study indicated that, *in vitro*, high shear stress of 7.5 – 14 N m^{-2} as well as low shear stress of 1.5 – 3 N m^{-2} lead to platelet activation (Chesnutt and Han 12). These two ranges could be used as the upper and lower bounds for pro-thrombotic conditions, relating to high shear stress and stagnation in blood flow. However, from the pathways stated above, it is obvious that thrombi do not form instantaneously. To model such an action would sacrifice the reliability of the outcome. From the same study, Chesnutt used a relationship for critical shear rate, the rate in which platelets are activated. The relationship is such that $\dot{\gamma} = {\tau}/{\mu_b}$, where $\dot{\gamma}$ is the critical shear rate (s^{-1}), τ is the critical shear stress (N m^{-2}), and μ_b is the viscosity of the fluid, in this case, whole blood (kg m^{-1} s^{-1}) (Chesnutt and Han 6). In the creation of a computer model as mentioned below, this equation could be implemented using the range of critical shear stress to be $\tau = (1.5,3) \cup (7.5,14)$ N m^{-2}.

CHAPTER FOUR: THROMBUS PROPERTIES

A thrombus constantly interacts with blood constituents, vessel walls, and other thrombi. It is beneficial to understand the mechanical properties of a thrombus including its density, viscosity, and restitution to help understand the characteristic behavior of a free floating thrombus. According to how fibrin forms the structure of the clot, the properties will vary. However, the level of hematocrit in the blood relates to fibrinogen density in the blood. With low hematocrit, high amounts of fibrinogen are present and increase the viscoelastic modulus of the thrombus (Huang, Chen, and Shih 042901-1).

Density

The volume, mass, and subsequently the density of a thrombus was quantified in a study by Baker-Groberg where noninterferometric quantitative phase microscopy (NI-QPM) was used to determine mass and Hilbert transform DIC (HT-DIC) microscopy was used to find volume. The study used three surfaces with differing makeup on which to promote aggregation of platelets and test the properties of the resulting white thrombi: fibrillar collagen, fibrillar collagen +0.1 nM tissue factor (TF), and fibrillar collagen +1 nM TF. These surfaces contain immobilized extracellular matrix proteins, which helps to determine platelet formation under shear flow. NI-QPM involves Brightfield imaging of cells which have weak scattering and low absorption of illuminating light. Thickness and density fluctuations cause phase lags in the transmitted waves, which can be related to the axial variation of wave intensity. Once the phase is mapped to the axially integrated mass density image, the total mass can be determined by the summation of the area of the projected mass density image (Baker-Groberg, Phillips, and McCarty 016014-1). HT-DIC uses spatial frequency space multiplier operators, producing symmetric image features.

With the addition of low frequency components, edges of specimens in the DIC image cubes can be detected. This HT-DIC method was determined to be valid for samples above 0.11 μm in diameter (Baker-Groberg, Phillips, and McCarty 016014-2).

Using these two methods to find mass and volume of a sample of thrombi, a statistical analysis was performed for the data Baker-Groberg collected and resulted in three average values, with standard deviation, for thrombi: 0.03 ± 0.002 pg μm^{-3} for collagen, 0.04 ± 0.004 pg μm^{-3} for collagen +TF (0.1nM), and 0.07 ± 0.003 pg μm^{-3} for collagen +TF (1nM) (Baker-Groberg, Phillips, and McCarty 016014-3). The displayed data can be seen below.

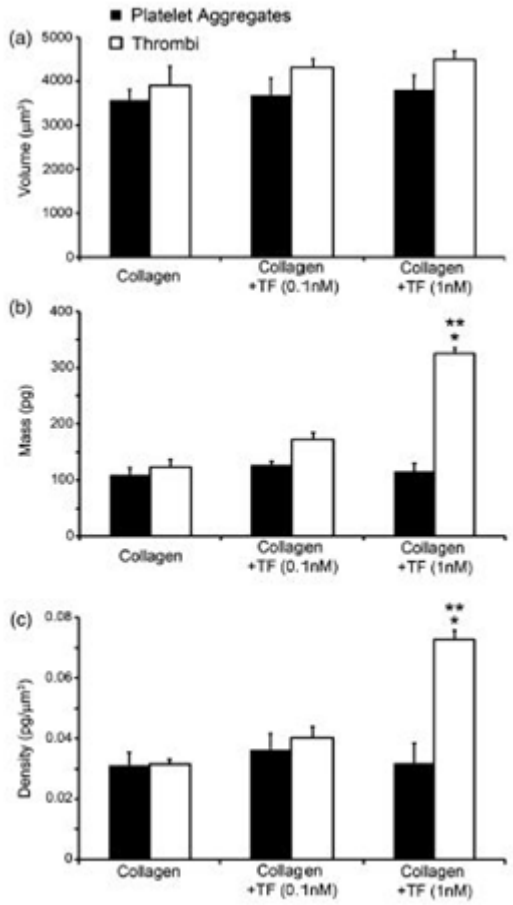

Figure 3: Volume (Top), Mass (Middle), Density (Bottom) of Thrombi (Baker-Groberg, Phillips, and McCarty 016014-3)

Another study by Nahirnyak investigated the density of venous white thrombi by a combination of fluid displacement method and laboratory scale. The method was conducted for 202 clots from 28 human participants and resulted in an average clot density of $(1.08\pm0.02)x10^3$ kg/m^3 (Nahirnyak, Yoon, and Holland 3768, 3771). As thrombi are composed of several different constituents in whole blood, the density of thrombi are more likely to share a similar density to whole blood. This density is consistent with the density of whole blood as mentioned

later in this study. The data from Baker-Groberg was still used in the computer model to understand how such a low density would affect the interaction of thrombi.

Viscosity

In a study done by Huang, the method of shear-wave dispersion ultrasound vibrometry (SDUV) was used to analyze mechanical properties of thrombi. Tissue vibration induced shear waves are caused by an ultrasound beam at a certain focal point. The shear wave propagation speed in the tissue is then found by a second ultrasound transducer which detects shear wave phase changes per distance. The results of the SDUV showed viscosity of the thrombus to be 0.42 ± 0.01 kg m^{-1} s^{-1} at 3% hematocrit, 0.39 ± 0.02 kg m^{-1} s^{-1} at 20% hematocrit, and 0.29 ± 0.02 kg m^{-1} s^{-1} at 40% hematocrit (Huang, Chen, and Shih 042901-6). Concerning input into a computer model, the average human male and female has 45% and 40% hematocrit, respectively. Though it depends on the patient for a patient specific model, the use of 0.29 kg m^{-1} s^{-1} for the viscosity of a thrombus is reasonable for normal conditions.

Restitution

The thrombus to thrombus and thrombus to vessel wall interaction is important to analyze, governing whether or not a thrombus will "stick" or "bounce off" in either interaction. Due to the absence of experimental data to support the evaluation of thrombus restitution, this study employed the use of a computational fluid dynamics (CFD) model using the two properties listed above in a 2D flow field. A thrombus with an initial velocity at a specific angle of incidence to the wall before collision will result in an opposite velocity after collision, relatable to restitution. Observance of the computer simulation can provide a theoretical thrombus to wall restitution coefficient. Another simulation involving multiple thrombi colliding can provide a

theoretical thrombus to thrombus restitution coefficient. The implementation of these simulations can be seen in chapter five, however, the results were limited by the modeling method. The modeled thrombi were simulated as fluid with densities and viscosities mentioned above. When simulating a thrombus moving toward the vessel wall, the momentum of the drastically less dense thrombus could not overcome the flow of whole blood. Therefore, a restitution coefficient regarding thrombus to vessel wall could not be obtained. The nature of fluid modeling also made each thrombus collide in a perfectly inelastic nature, only showing a restitution coefficient of 1. In conclusion, modeling thrombi as fluid is not sufficient for restitution coefficients.

Shear to Break Free Vessel Wall Thrombi

It is important to understand the shear stress involved in breaking off a thrombus formed on the wall of the vessel. In a computer model, the shear caused by blood flow may cause the thrombus to shear off and enter the flow, resulting in downstream complications. In the same study performed by Huang mentioned above, the use of SDUV resulted in the findings of the shear modulus for a thrombus. The findings are as follows: 641.4 ± 76.3 Pa for 3% hematocrit, 402.7 ± 66.2 Pa for 20% hematocrit, and 196.8 ± 58.4 Pa for 40% hematocrit (Huang, Chen, and Shih 042901-6). Using the same logic put forward in the viscosity report above, 196.8 Pa is reasonable for use in the computer model.

Thrombus Properties Compilation

A collective table of hemodynamic properties of thrombi was made including the values mentioned above. It should be noted that the studies that produced the properties focused on white thrombi, formed by platelet activation. The collective properties used in this study's simulation can be used in future thrombus simulations.

Table 1: White Thrombus Properties Compilation

	Collagen	Collagen +TF (0.1nM)	Collagen +TF (1nM)	Source
Density (pg µm-3)	0.03 ± 0.002	0.04 ± 0.004	0.07 ± 0.003	Baker-Groberg, Phillips, and McCarty 016014-3

	3% hematocrit	20% hematocrit	40% hematocrit	Source
Viscosity (kg m-1 s-1)	0.42 ± 0.01	0.39 ± 0.02	0.29 ± 0.02	Huang, Chen, and Shih 042901-6
Vessel Wall Separation Shear (Pa)	641.4 ± 76.3	402.7 ± 66.2	196.8 ± 58.4	Huang, Chen, and Shih 042901-6

CHAPTER FIVE: THROMBOSIS MODEL

A computer model can be made, incorporating the physical properties of thrombus and thrombosis triggers, to simulate the formation of a thrombus. As mentioned above, the critical shear stress for platelet activation is assumed to be $\tau = (1.5,3) \cup (7.5,14)$ N m^{-2}. The relationship $\dot{\gamma} = {}^{\tau}/_{\mu_b}$ can dictate the rate at which thrombi are formed. Berzi analyzes granular-fluid mixtures with the "solids" being represented by spheres for simplicity (Berzi 547). Though thrombi are not spherical, for simplification purposes, a sphere model is a good average shape representation. The movement of the thrombus can be modeled, and when colliding with the vessel wall with sufficient energy transfer, the model can simulate vessel wall damage, causing thrombus spheres to form, stuck to the wall. Additionally, as mentioned above, negatively charged surfaces trigger thrombosis. Based on the correct amount of shear in the fluid at a specific location, the model can simulate the thrombus from both damaged and negatively charged surfaces breaking off and joining the flow. For the purposes of this study, only thrombi interaction was modeled to prove validity of thrombus properties and explore possible characteristics of thrombi. A unique approach of modeling the thrombi as liquid with the given properties includes the deformable nature of thrombi.

Whole Blood properties

In order to model thrombi as fluid interacting with whole blood, whole blood properties must first be collected. The values for density and viscosity of whole blood were be utilized in the model to generate realistic flow. A study performed by Trudnowski analyzed blood contributed by six women and 19 men of good health and ages ranging from 29 to 58 years. Taking the samples before lunch, 10 ml of whole blood was taken and separated into 2 ml

volumetric flasks. Weighing the samples at 4 ºC and 37 ºC, the relative density to water was 1.0621 for 4 ºC and 1.0506 for 37 ºC, both featuring a 95% confidence interval (Trudnowski, Raymond, and Rico 615). This study incorporates 1050.6 kg/m^3 as whole blood density for the purposes of the thrombus simulation shown below. As for the average viscosity of whole blood, Windberger's study performed Haemorheology by LS30 viscometers for whole blood. The viscometer was set at 0.7, 2.4, and 94 s^{-1} shear rates at 37 ºC. Electromagnetic measurements of mechanical strain by whole blood viscosity on the inner cylinder of the viscometer correlated to the whole blood's viscosity (Windberger et al. 432). The results of Windberger's study gave whole blood viscosity of 39.584 mPa s for 75th percentile (Windberger et al. 434). Blood at low shear rates acts as a non-Newtonian fluid, as shown in the plot below.

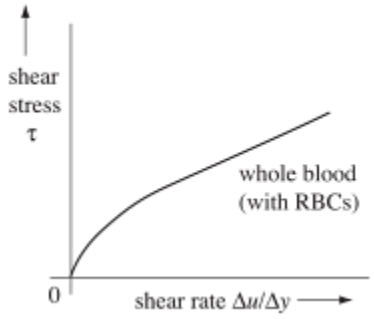

Figure 4: Shear Stress vs. Shear Rate of Whole Blood (Christensen 35)

A Newtonian fluid acts exhibit a linear relationship for a plot of shear stress versus shear rate. However, the red blood cells in whole blood cause a non-linear curve at low shear rates, varying the viscosity with flow rate (Christensen 35). The whole blood viscosity from Windberger's study was reported at a low shear rate of 0.7 s^{-1}. The viscosity decreased to 5.996 mPa s at a shear rate of 94 s^{-1} (Windberger et al. 434). Though 39.584 mPa s is large and only for

the non-Newtonian range, the value was still chosen for the simulation to observe how thrombi would interact with such conditions.

Cardiovascular Induced Flow

In the model of blood flow, parameters need to be set to dictate the nature of the flow. In other words, the amplitude and characteristic of pressure caused by the heart can be employed in the model. For the purposes of relating this study's findings to LVAD applications, the Aorta was chosen as the blood vessel of interest. According to Lopez-Ojeda, systolic pressure of the Aorta is 100mmHg, while the systolic velocity is approximately 0.11 m/s (Human Physiology 135).

Modeling method

Star CCM+ is a CFD program which employs several different methods regarding the dynamic interaction of gasses, fluids, and solids. A fundamental method is known as the Volume of Fluid (VoF) method. VoF is a numerical modeling method which is concerned with the boundary layer between two fluids, and in this case, the thrombus is assumed to be a fluid with the densities and viscosities mentioned above. Bo's study describes the method well. VoF was originally intended for incompressible fluids, but was later modified to compressible fluids. In order to account for mixed phase flow, specific material particles with equilibrium of both pressure and velocity and advecting specific entropies with the flow are seen as distanced from each other by volume. More precisely, a computational cell consists of a volume fraction (a mixture of different fluids) developed for half a time step, creating a reconstructed planar interface at that cell. This is for constant thermodynamics. This reconstruction produces an interface normal which positions the planar interface according to the separate fluid volumes.

The quantity of the individual fluid materials fluxing in the computational cells is then predicted concerning the local flow velocity and the reconstructed interface. A second order Godunov scheme is then used with the previously calculated quantities to improve the numerical fluxes. Now, each computational cell has a single set of mass fluxes including the momentum and energy fluxes. Thus, this result is intrinsically conservative (Bo and Grove 114).

According to Baraldi's study, the VoF function, C, describes the volume fraction of the reference phase between the two fluids where C = 0 refers to fluid one, C = 1 refers to fluid two, and $0 \leq C \leq 1$. VoF involves two steps: VoF interface reconstruction and VoF advection. The interface reconstruction requires a piecewise linear interface calculation. To construct the computational cell, the interface normal and the interface location must first be computed. VoF advection involves the Eulerian implicit-Eulerian algebraic-Lagrangian explicit algorithm (Baraldi, Dodd, and Ferrante, 324-325).

Simulation

Using the VoF code in Star CCM+ to model two phase liquid interaction, several different flow scenarios were simulated. The first simulation attempted was to cause a collision between a thrombus and the vessel wall. The geometry and fluid dynamic environment was modeled as systolic conditions in the aorta. The height of the 2D tube was 3 cm.

Figure 5: Thrombus to Wall Collision Attempt

The volume fraction is shown as blue for whole blood and red for thrombus. The simulated solution time was 0.13 seconds. The thrombus had an initial velocity at 45 degrees to the horizontal. As seen in the figure above, the thrombus never reached the wall. Understanding that the density of thrombi is much less than that of whole blood, the thrombus in this simulation did not have enough momentum to overcome the whole blood flow. Another simulation was performed with unrealistic initial velocity of the thrombus. This was done in order to force collision with the wall.

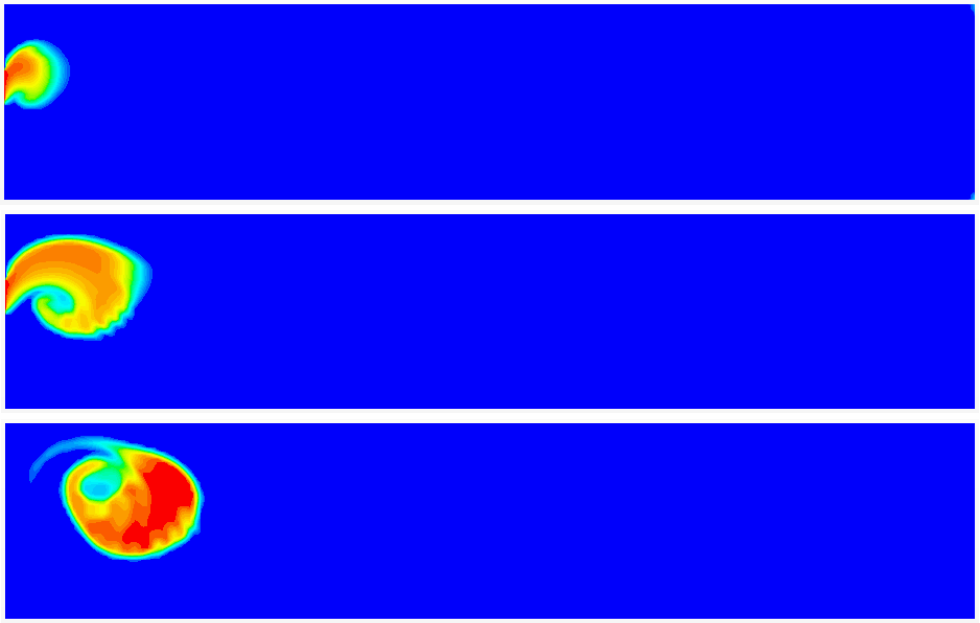

Figure 6: Fast Thrombus to Wall Collision Attempt

The simulated solution time was 0.09 seconds. With an initial velocity of 2 m/s at a 45 degree angle from the horizontal, the thrombus is sheared by the whole blood flow and does not collide with the wall. As indicated earlier in this study, restitution coefficients for thrombus to wall interaction were unable to be quantified by the method of modeling thrombi as liquid. Next, a simulation was run with two thrombi colliding in the flow.

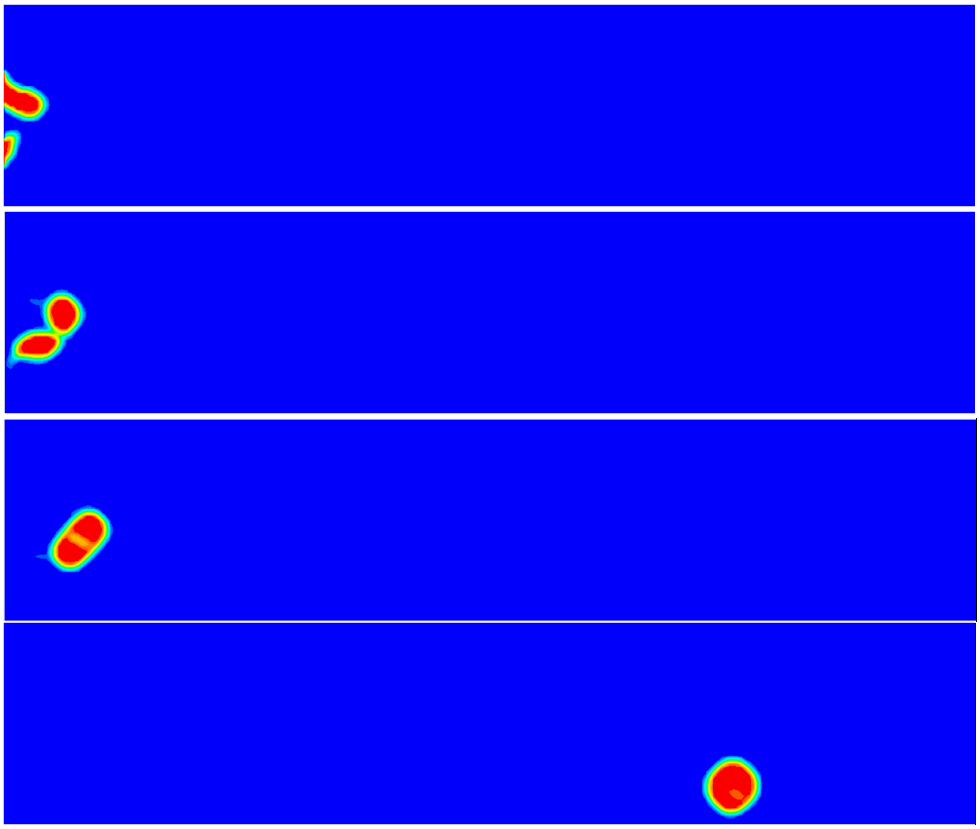

Figure 7: Thrombus to Thrombus Collision

The simulated solution time was 0.84 seconds. The two thrombi collide at an offset and show inelastic collision. The result of the offset collision made the combined thrombus drift towards the bottom wall, however, the thrombus continued on the same path as the whole blood flow and never collided with the wall. See the appendix for thrombus to thrombus collision with no offset, a simulated solution time of 0.24 Seconds. The liquid thrombus modeling method ensures inelastic collision due to the surface tension of the two fluids. However, this method can be useful for early stage thrombosis as the physical property is a solid-fluid mixture. The final simulation incorporated an arbitrary geometry of the aorta branching. This geometry was to observe the interaction of multiple thrombi with the liquid thrombus modeling method.

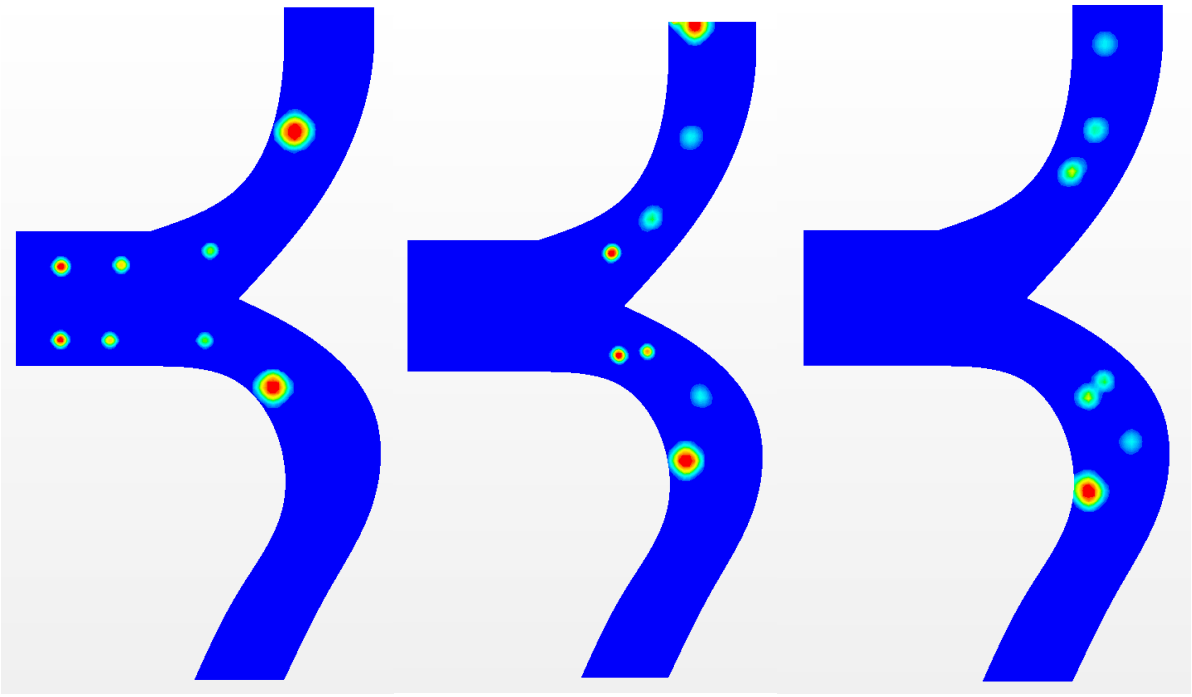

Figure 8: Branching Geometry Thrombus Interaction (Part 1)

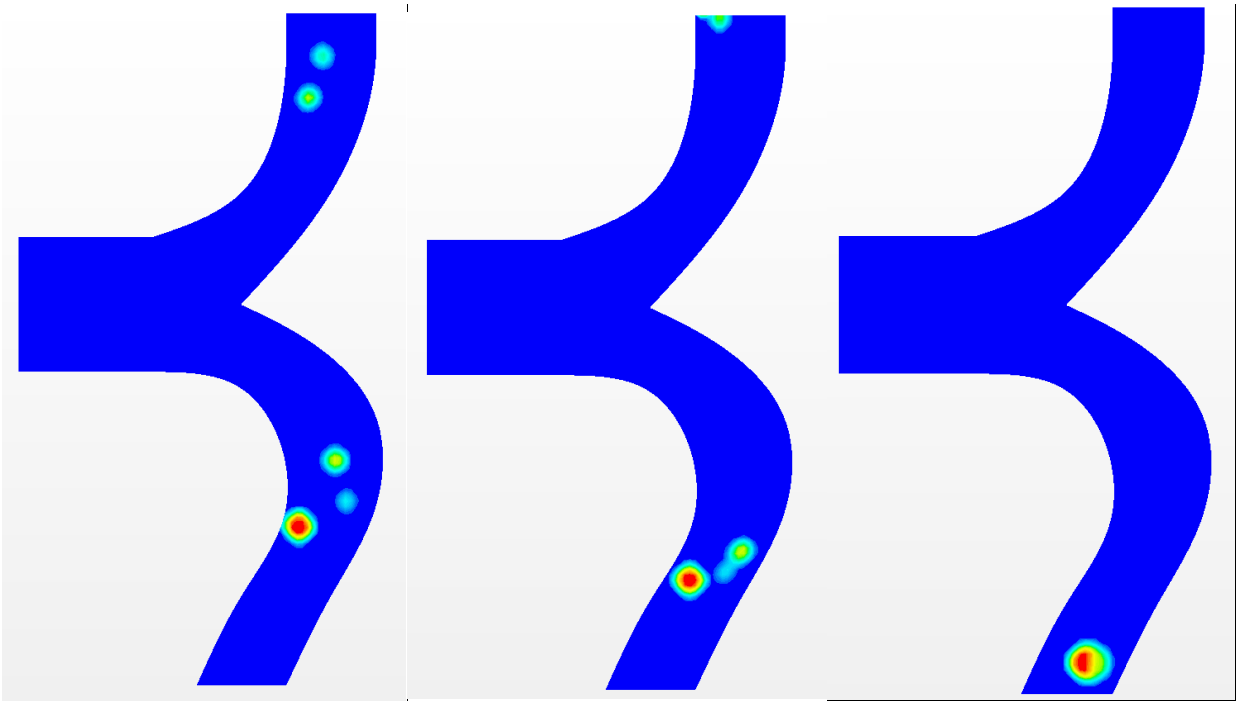

Figure 9: Branching Geometry Thrombus Interaction (Part 2)

The results from this simulation are noteworthy. As seen above, four thrombi of varying sizes enter each branch. Concerning the pressure field as shown in figure 9, the larger thrombi are effected more by pressure than the smaller thrombi. Figure 6 shows the thrombi in line in the top branch, while the bottom branch has smaller thrombi overshooting the path of larger thrombi, creating a collection of thrombi near the end of the branch. Figure 8 shows this collection colliding and forming one large thrombus. This result suggests that the geometry of blood vessels that create pressure variation along the cross-section can cause thrombus interaction and larger thrombus formation. The irregularity of the cross-section geometry of the bottom branch is what causes this pressure variation.

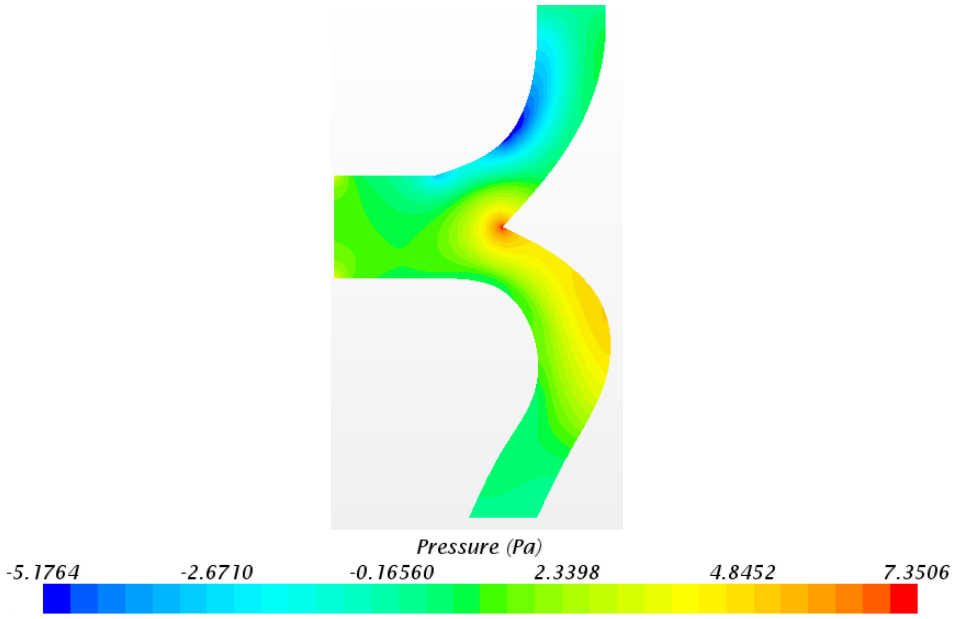

Figure 10: Pressure Field of Branching Aorta

CHAPTER SIX: CONCLUSION

With the application of predicting myocardial infarction or stroke, the findings of this study are of great significance. The Volume of Fluid method utilized by the Star CCM+ model provided a unique method to characterize thrombus interaction to vessel walls and other thrombi. Physical properties of thrombi, including density and viscosity, collected by this study allow for accurate simulation of thrombus interaction in patient specific vessel geometry applications. Quantified hemodynamic factors for thrombosis also give way to accurate simulation of sites for thrombosis in blood flow fields. Understanding the experimental relationships of thrombosis and quantifying these relationships contribute to a proper method of thrombus analysis and subsequent treatment, reducing possible risk of serious health problems in patients.

APPENDIX

Appendix A: Non-Offset Thrombus to Thrombus Interaction

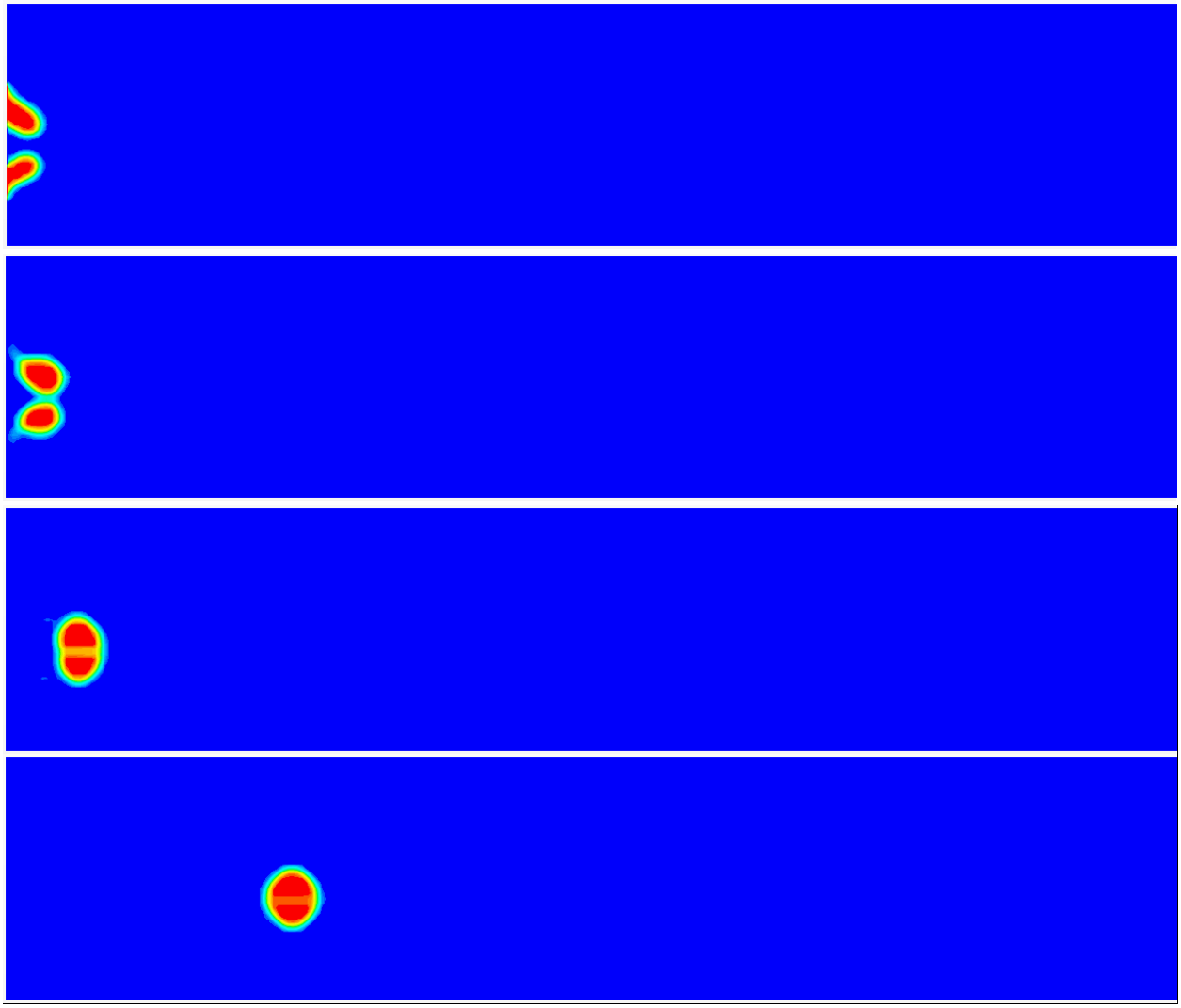

Figure 11: Non-Offset Thrombus to Thrombus Interaction

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