Measuring Coronary Artery Flow Rates using Intravascular Optical Coherence
Tomography to Improve the Assessment of Percutaneous Coronary Intervention

by

Ha Yun Anna Yoon

Submitted to the
Department of Mechanical Engineering
in Partial Fulfillment of the Requirements for the Degree of

Bachelor of Science in Mechanical Engineering

at the

Massachusetts Institute of Technology

June 2019

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ABSTRACT

In this project, a blood flow quantification technique was developed based on a novel backscattering indicator-dilution approach for intravascular optical coherence tomography (IV-OCT). It achieved the goal of obtaining the flow velocity in a coronary artery of interest by analyzing the backscattering signal from blood after passage of a bolus of Ringer's lactate or another transparent injectate, in parallel to thermodilution coronary flow reserve (CFR). In contrast to thermodilution CFR, the structural OCT image can be used to determine the bolus volume and transit time, as well as used to account for motion and volume change between the two flow readings. More importantly, this technique allows the absolute blood velocities to be determined, providing information that has been challenging to obtain in the past.

The experiments conducted using porcine blood in a phantom setup and saline bolus injectate allowed the author to develop an analysis technique to determine transit time, confirming a relation between transit time and flow rate and a relation between the derivative of the transit time and flow rate. Flushing time (τ), defined as the time when the normalized flushed area reaches 50%, is inversely proportional to flow rate. Therefore, experimental results validated the feasibility of using OCT to determine transit time of the blood circulation in coronary arteries.

Future implication of this experiment is the ability to get more accurate measurement of the blood flow rate at any location regardless of the blood vessel geometry. Findings of this and future experiments can be used to implement intravenous OCT flowmetry for clinical use in diagnosing cardiovascular diseases.

Thesis Supervisor: Prof. Brett Bouma
Tile: Professor of Dermatology and Health Science and Technology

ACKNOWLEDGEMENTS

First, I would like to thank my advisors Dr. Nestor Uribe-Patarroyo and Prof. Brett Bouma for their help and guidance on this research project and writing of this thesis.

Besides my advisors, I would like to thank the students and faculty of the Department of Mechanical Engineering at MIT for teaching me and challenging me intellectually for the past 4 years at MIT.

Finally, I would like to thank my family and friends for their unconditional love and support. Special thanks to my Dad, for inspiring me to study Mechanical Engineering and to pursue academia as my future career path.

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1. Introduction

1.1 Motivation

Validating the feasibility of using an optical version of the thermal indicator-dilution technique for measuring blood flow will improve percutaneous coronary intervention (PCI) assessments. Thermal indicator dilution measures blood velocity intravenously by calculating the transit time—as shown by temperature gradients—and the concentration of the indicator injected suddenly in the blood flow of a coronary artery [1]. This project implements a proof-of-concept technique using an intravascular OCT (IV-OCT) catheter system to obtain functional information in the form of measurements of coronary artery absolute flow rate across a stenosis. The implications of this experiment are: first, to add functional imaging to the purely structural imaging provided by OCT; and second, to have the ability to obtain more accurate measurements of blood flow rates at any location regardless of the blood vessel geometry, a common flaw of the traditional thermal indicator dilution techniques [2].

A proof-of-concept experiment was implemented using our initial technique based on a backscattering indicator-dilution approach, which relied on analyzing the backscattering signal from blood after passage of a bolus of Ringer's lactate, in parallel to thermodilution CFR [3]. Once the constraints for this OCT technique were determined, the technique was validated in vitro with blood to determine if the differences in backscattering properties between the phantom fluid and the blood required any modifications to the analysis.

1.2 Thermal Indicator Dilution Theory

Thermal indicator dilution measures blood velocity intravenously by calculating the transit time—as shown by temperature gradients—based on the concentration of the suddenly injected indicator in a flow system [4]. For each indicator amount, the concentration is plotted

against time. The mean transit time ($\bar{t}$) of the fluid is calculated from the concentration-time curve based on:

$$\bar{t} = \frac{V}{Q} \tag{1}$$

where V is the unknown vascular volume between injection and imaging site, and Q is the blood flow rate. This information can be used to measure cardiac output as well as blood and volume flow. This information can be misleading if flow changes at the rate close to that of transport functions [4]. The assumptions of this theory are that there is a single inflow and outflow, resulting in no recirculation, flow and volume is constant during the period of measurement, and that the frequency at which each transit time occurs remain constant [5]. A common flaw of the traditional thermal indicator dilution techniques is the inaccurate measurements of blood flow rate at certain locations depending on the blood vessel geometry [6]. There are other shortcomings of this theory. In a real vascular system, there is no single inflow or outflow, resulting in recirculation. In this project, recirculation is addressed by imaging the flow of the setup that includes the recirculation as it would happen in a normal human subject.

1.3 Optical Coherence Tomography (OCT)

Optical Coherence Tomography (OCT) is a medical non-invasive imaging technique that uses light and produces cross-sectional images of biological tissues based on the scattering of the light. As an optical analog of ultrasound, since light travels faster than sound, OCT system has spatial resolution of μm and detect reflected signals of $\sim 10^{-10}$ of the incident optical power [1]. The OCT system uses interferometry to produce 2D images of optical scattering from internal tissue microstructures by measuring the echo time delay and magnitude of backscattered light from a sample [7]. Optical scattering and reflections are based on the refractive indices of the

materials being measured. An optical signal transmitted or reflected from a biological tissue

gives spatial information about tissue microstructure. In this case, multiple longitudinal scans at

a series of lateral locations will result in a 2D map of the sample.

Currently, OCT is used for retina imaging as well as for cardiovascular disease diagnosis

by analyzing the structural appearance of stenosis in coronary arteries. The current OCT

technology only shows image but no functional value for flow rate. To get the flow rate value,

the physician has to use an indirect or relative flow catheter to get flow rate. However, there is no

absolute flow catheter in the field yet.

1.4 Coronary Flow Rate

As shown in Figure 1-1, human coronary arteries split during circulation mainly to left

anterior descending artery (LAD), left circumflex, and right coronary artery (RCA).
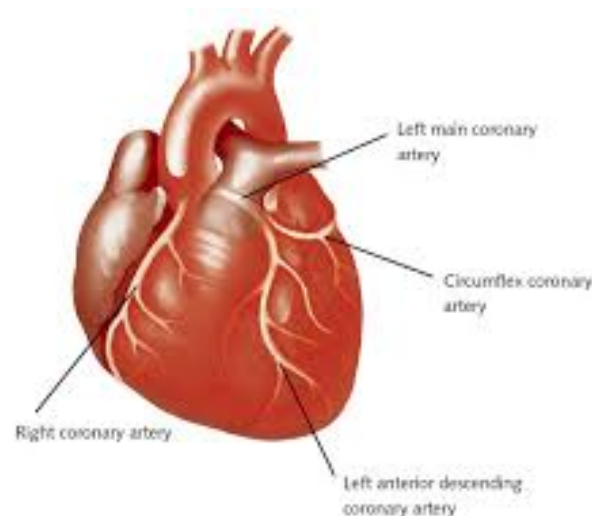
Figure 1-1: Diagram of Human Heart. The left main coronary artery splits into the circumflex coronary artery and the left anterior descending coronary artery (LAD). The right coronary artery (RCA) and the two left coronary arteries receive the majority of the circulation volume.

The total coronary flow rate ranges from 50 to 300mL/min [8]. In healthy humans, the

LAD has systolic peak and mean velocity of 0.94 and 0.30 mL/s. Its diastolic peak and mean

velocity is 2.42 and 0.43 mL/s. The RCA systolic peak and mean values are 1.96 and 0.74 mL/s, and its diastolic peak and mean values are 1.80 and 0.83 mL/s [8].

1.5 Stenosis and Percutaneous Coronary Intervention (PCI)

A stenosis is an abnormal narrowing of the blood passage in the human body. Stenosis is labelled severe if fractional flow rate (FFR) ≤ 0.8. The mean blood flow rate in severe coronary stenosis was 2.54 mL/s as compared to 4.81mL/s in stenosis with FFR > 0.8 [9]. Most common cardiovascular disease caused by coronary stenosis is coronary artery disease [10]. In many countries, physicians perform percutaneous coronary intervention (PCI) to improve outcome and reduce mortality of the patients with this disease.

PCI is a nonsurgical procedure that improves blood flow to the heart. PCI is used to open the narrowed or blocked coronary arteries due to atherosclerotic plaque buildup. It relieves symptoms of coronary heart diseases and mitigates heart damage after a heart attack. Also known as coronary angioplasty, PCI requires catheter and an iodine-based injectate dye into coronary artery [11].

2. Experimental Design

The aim of the project was to design, build, and validate an in vitro system for cardio flow OCT testing.

2.1 Overall Design of the In Vitro System

The system design requirements contain a reservoir and a peristaltic pump that drives and supplies the circulation. Also, the pulse dampener removes bubbles from the circulation flow to create a constant flow throughout the system. The guide catheter, containing the bolus syringe injection and the OCT catheter that originates from the rotary junction, enters the circulation and

ends 3 to 6cm before the imaging spot. The OCT system image as is performed inside a tube simulating the coronary artery where the bolus mixes with the circulation.

The injected bolus exits and mixes with the circulation at the end of the guide catheter. At the point of imaging shown in red in Figure 2-1, the bolus initially displaces the circulation and mixes fully with the circulation flow as the circulation returns.

Figure 2-1: Diagram of Bolus Injection Entering the Circulation. The bolus injected travels through the guide catheter and exits at the end of it to enter the circulation. The bolus travels through, initially displacing the entire circulation and mixes fully with the circulation flow as the circulation returns.

2.2 System Validation Testing

To validate the feasibility of using the OCT system to measure absolute coronary blood flow, three sets of tests were performed on in vitro setup.

2.2.1 Galvo OCT Test with Intralipid Circulation and Water Bolus

The proof-of-concept experiment involves two main fluids—Intralipid and water. Intralipid (n= 1.365) is a lipid emulsion with pH range of 6 to 8.9, which is used as a tissue phantom for optical measurements. Because Intralipid has spherical lipids (consisting of 20% soybean oil, 1.2% egg yolk phospholipids, and 2.25% glycerin) suspended in water, the light is reflected strongly [12]. Since Intralipid is a highly scattering substance, Intralipid is diluted to 0.4% for this experiment. Based on high contrast of refractive index between water (n= 1.333) and lipid, the backscattering of the light can be sensed. On the OCT system, water gives strong surface

reflectance but negligible subsurface signals, while Intralipid gives high intensity subsurface

signal. Therefore, Intralipid was circulated with water injections for this experiment to better

mimic what will happen *in vivo*.

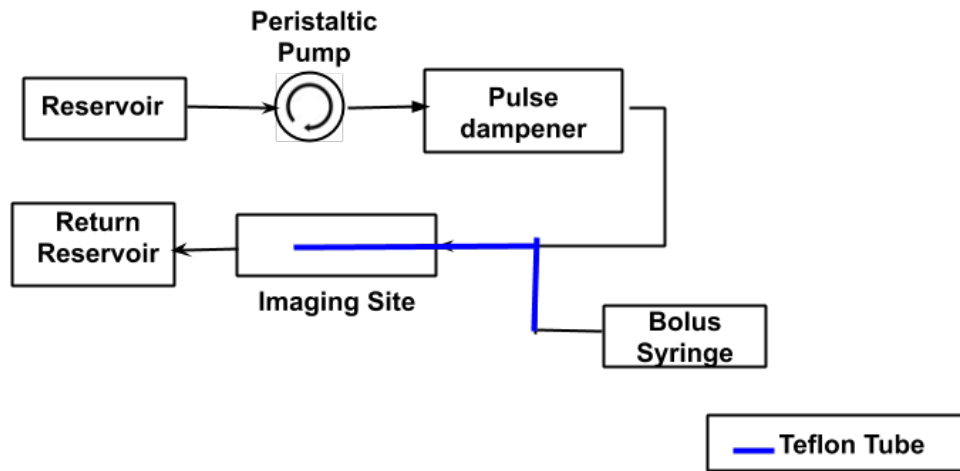A schematic of the overall *in vitro* system is shown in Figure 2-2.

Figure 2-2: Schematic of Open Flow Circulation. The peristaltic pump drives the fluid circulation from the reservoir, sending it to the pulse dampener to remove air bubbles and keep the flow rate constant. The resulting circulation merges with the Teflon tube simulating a guide catheter, carrying the bolus injection, and continues to the imaging site. After the bolus and the flow rate is imaged, it continues to flow to the return reservoir.

In this first proof-of-concept test, an in-house OCT system was used (wavelength-swept laser

centered at 1300nm, 105nm bandwidth, 54kHZ repetition rate) with galvo mirrors to scan at 5cm

from the Teflon tube at 50fps. The inner Teflon tube with 1.0mm diameter represents a guide

catheter. The Teflon tube is placed so that the tip was 5cm from the point of measurement to

ensure that the fluid entering via injection is fully mixed with the flow system before the OCT

measurement [2]. From the previous experiments by Pijils (2016) and van't Veer et al. (2016),

holes were drilled on the side of the Teflon tube to mix fluids completely between injection site

and the sensor position [14]. In this experiment, the Teflon tube is epoxied on the end, 8mm from

the holes, and drilled four holes with diameter of 250 μm at 0°, 90°, 180°, 270° around the tube.

Transparent injectate is flushed via the Teflon tube. Intralipid at 0.4% flows (blood phantom) in an open circuit. The experiment was conducted on a constructed flow phantom. It was used to perform repeatable flow dynamics experiment with OCT measurements. The imaging of the Intralipid circulation with water flush were conducted at four different flow rates—17, 30, 43, 57 mL/min—to simulate the target flow of 100 to 400 mm/s. The blood vessel was simulated by tubing with diameter of 3.2mm because lumen diameter of normal human left circumflex artery is 3.4 ± 0.5mm [13].

Manually, a 1.5mL bolus of transparent injectate was delivered, fully displacing the intralipid circulation as it is regularly seen during traditional OCT imaging [15]. The time it takes for the injectate to fully disappear from the cross-sectional image (and therefore the time it takes for blood to fill the vessel lumen) is proportional to the flow velocity. Once the flow velocity is determined, the cross-sectional lumen area from the OCT image is used to determine the absolute blood flow rate, or in this case, the absolute intralipid circulation flow rate.

2.2.2 Optimized Experimental Conditions

Successful results obtained in the OCT galvo system is transferred into an intravascular OCT (IV-OCT) catheter-based system. Series of in vitro experiments are conducted to study the constraints.

The new setup includes 3 outlets vessel imitating the heart. The intralipid flow is replaced with porcine blood circulation and saline injectate to simulate optical backscattering of the actual OCT system if it is to be conducted in a human. A power injector pump is used to inject bolus for better repeatability. Bolus injection volume is set to 5.0mL to ensure clearing of the entire lumen area of interest. To prevent the bolus injectate from getting washed out at fast flow rates, the injection occurs in 0.4s, giving the injection flow rate of 12.5mL/s. The imaging site is 7cm

from the end of the guide catheter to ensure the bolus mixes fully with the circulation when it reaches the site of imaging. The finalized experimental conditions used in the setup reduce variability in fluid injection rate, and confirm that the system gives promising data trend results when the porcine blood is used for circulation. Since Intralipid and human blood have different scattering properties, it is critical to use animal blood before determining the clinical implementation potential since the measured flow data would be similar to human blood. During the experiments, the bolus fluid was chosen as 0.9% saline.

2.2.3 IV-OCT Test with Porcine Blood and 0.9% Saline Bolus

The use of human blood for testing purposes is associated with the risk of infection, restricted availability, and high cost. Porcine blood is more practical solution due to sufficient availability in terms of quantities. Porcine blood is used to simulate intravascular OCT system within the coronary artery because it is similar to human blood, especially in RBC aggregation tendency [16]. Thus, test results with porcine blood sample is a safe estimation for human blood. Salinity of blood is 0.9%, so 0.9% saline bolus were injected to facilitate bolus mixing in the circulation without changing the optical properties of blood.

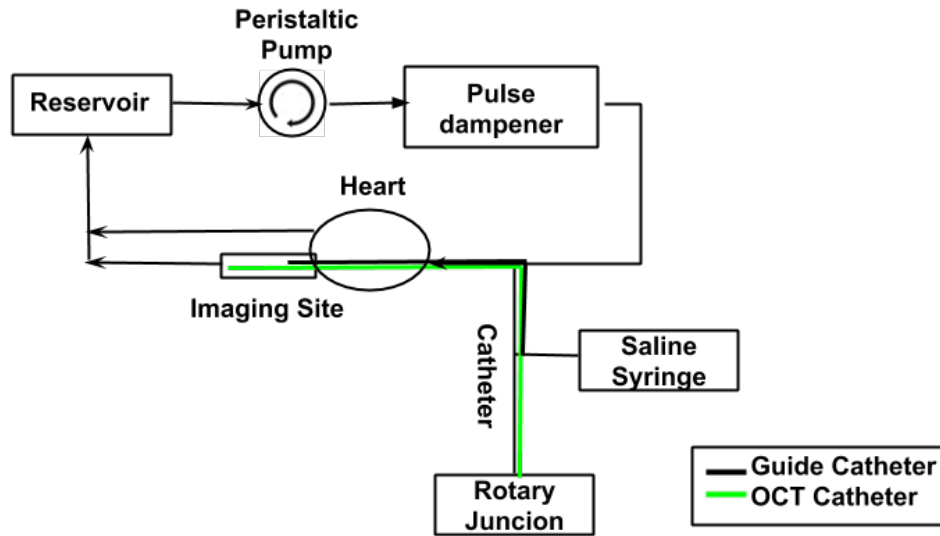A schematic of the overall *in vitro* system is shown in Figure 2-3.

Figure 2-3: Schematic of Experimental Closed Flow Circulation. The peristaltic pump drives the fluid circulation from the reservoir, sending it to the pulse dampener to remove air bubbles and keep the flow rate constant. The resulting circulation merges with the guide catheter, containing the OCT catheter and the bolus injection, entering a vessel simulating the heart and continuing to one of the outlets which is the imaging site. After the bolus and the flow rate is imaged, both of the outlets form the heart continue to flow to the reservoir, where it creates a closed loop and recirculates.

In this OCT test with porcine blood, an IV-OCT system (wavelength-swept laser centered at 1300nm, 105nm bandwidth, 54kHZ repetition rate) with a standard guide catheter and an IV-OCT catheter is used to image at 3cm from the guide catheter at 50fps. Transparent injectate is flushed via the guide catheter. Porcine Blood flows in a closed circuit. The imaging of the porcine blood circulation with 0.9% saline flush were conducted at various, different flow rates—15, 25, 35, 45, 55, 65, 75, 85, 95, 105, 115, 125, 135, 145, and 155 mL/min—to simulate the target flow of 0.30 to 2.42 mL/s in the normal human coronary artery. The blood vessel was simulated by tubing with diameter of 3.2mm because lumen diameter of normal human left circumflex artery is 3.4 ± 0.5mm [13].

Using a power injector pump to make the injections repeatable, a 5.0mL bolus of 0.9% injectate was delivered in 0.4s at the rate of 12.5mL/s, fully displacing the blood as it is regularly seen during traditional OCT imaging [15]. The time it takes for the injectate to fully disappear

from the cross-sectional image (and therefore the time it takes for blood to fill the vessel lumen) is proportional to the flow velocity. Once the flow velocity is determined, the cross-sectional lumen area from the OCT image is used to determine the absolute blood flow rate.

3. Results

3.1 Image Processing

While analyzing the data, it was noticed that the data acquired from flow rates faster than 60mL/min deviates from other slow flow rates. Therefore, such flow rates greater than 60mL/min are reserved for the future experiments to figure out what is causing it to deviate from other slower flow rates. The OCT image data was analyzed with MATLAB to track geometry. The Bscan in polar coordinates is converted into a 512x512 pixel image in Cartesian coordinate and defines the n by n pixel lumen region of interest as shown in Figure 3-1. The vessel lumen is segmented in all frames, starting from the frame of minimum average intensity.
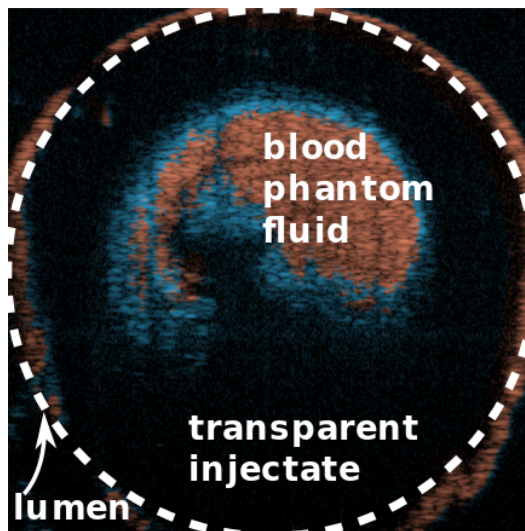

Figure 3-1: Diagram of Example OCT Frame Analysis. The lumen region is segmented to gather data of interest. The image intensity is encoded in the image luminance, and the hue shows pixels deemed to have enough backscattering signal (red) and those that do not yet (blue).

Pixels with moderate intensity (>15dB over noise floor) for greater than 5 frames are considered flushed. In this experiment, the term "flushed" is defined as when the contrast is

flushed, not when the circulating fluid—or blood—is flushed. The fraction of flushed pixels for each frame, as shown in Figure 3-2, is calculated.
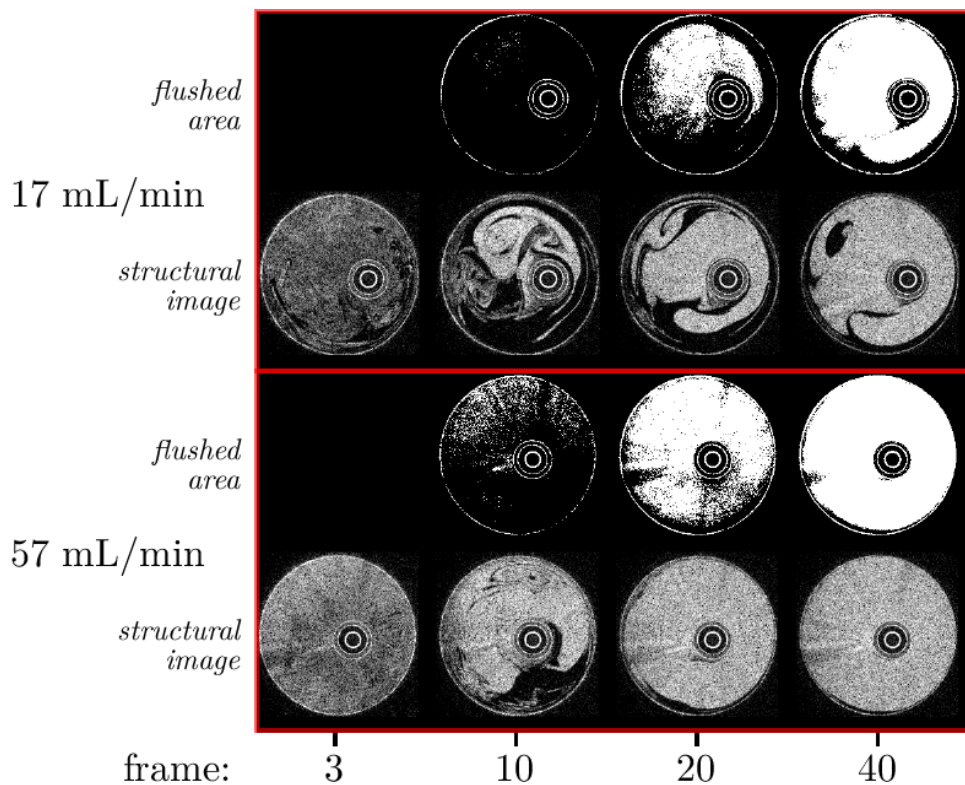

Figure 3-2 Structural Image Conversion to Flushed Area of the Lumen. The processed image gives data used to calculate the fraction of flushed pixels for each frame of the OCT cross-sectional image scans.

The threshold intensity is set based on the acquired data to filter out the noise. For every pixel with an image intensity greater than that threshold—specific value is mentioned in each corresponding section—is assigned value of 1, which denotes the data point of interest. The designated data points in each frame are filtered and integrated to get the total dilution area of the fluid flow per frame. The flushed area plot is also normalized to remove the effect of differing maximum flow area for different flow rates. The integrated flow area graphs and the normalized integrated flow graphs are plotted against the Bscan frames to show the transit time trend with increasing volumetric flow rate. The differentiated flow area curves are also plotted with respect to the frames to show the transit velocity trend with increasing volumetric flow rate. In fact, the

time (in terms of frames) at which the backscattering dilution curve recovers 50% of the backscattering signal are plotted, which shows the inverse proportionality of transition time with flow rate.

3.2 Intralipid Circulation and Water Bolus

The four flow rates data—17, 30, 43, and 57 mL/min—are grouped and analyzed together. In this experiment with intralipid circulation and water bolus, the threshold intensity for the data of interest is set to 80 dB. The data points of interest in each frame is filtered and integrated to get the total dilution area of the fluid flow per frame. As shown in Figure 3-3, the frame mean intensity per frame provides indication of adequate flushing, but it is too noisy to accurately determine the flow rate.
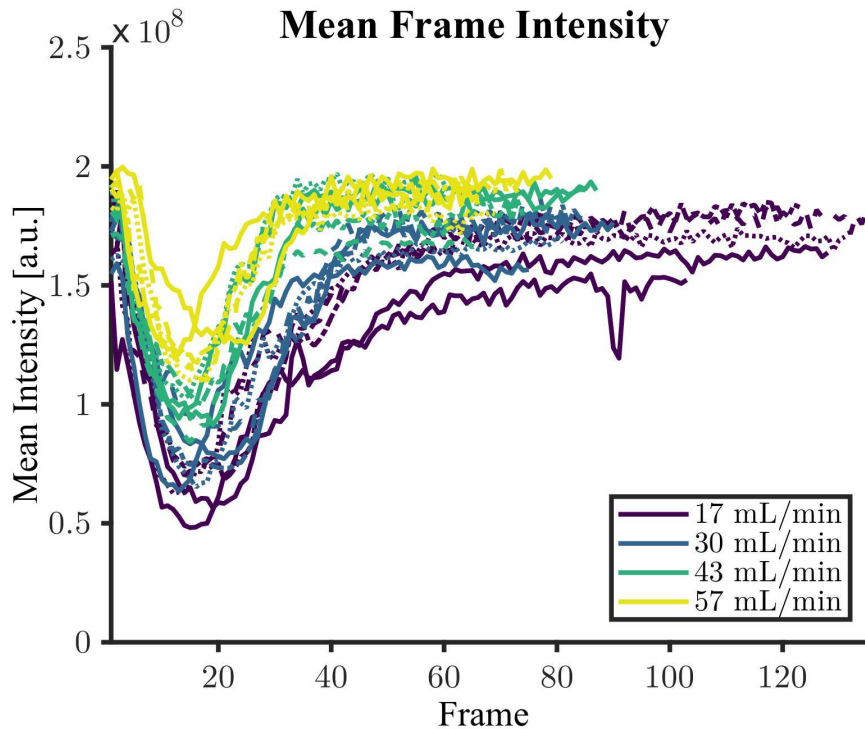

Figure 3-3: Plot of Mean Frame Intensity Per Frame in the 4 Different Flow Rates. The mean intensity of each frame indicates adequate flushing in each of the four flow rates. However, it is too noisy to utilize to accurately determine the transit time. It is clear that the duration between the minimum mean intensity point and full recovery is inversely proportional to the flow rates.

Figure 3-4 shows the cumulative summation of pixels with signal (red pixels in Figure 3-1) as a fraction of total pixels inside lumen as a function of time as the bolus passes through the given OCT cross section.
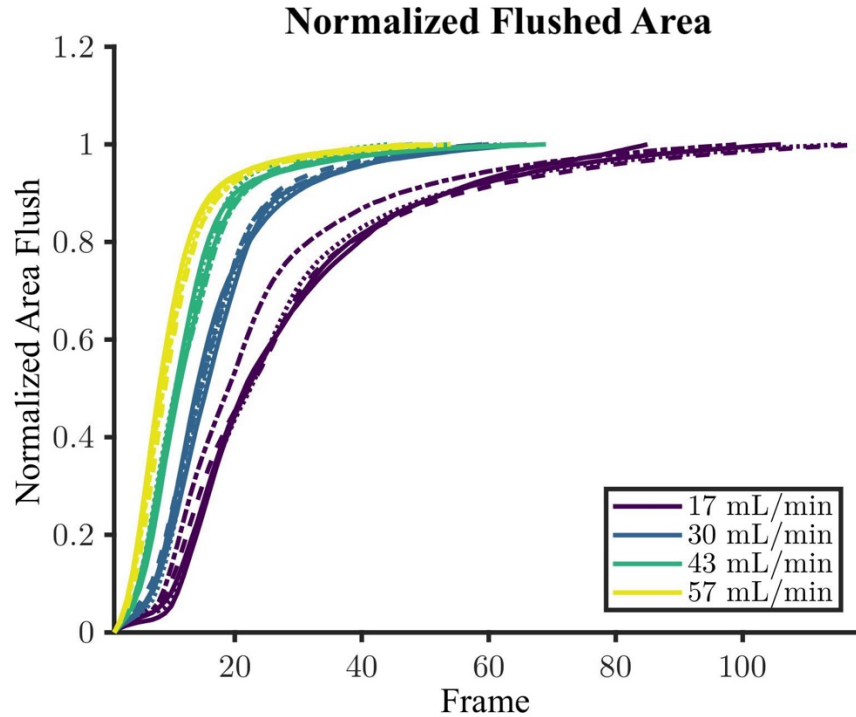

Figure 3-4: Plot of Normalized Flushed Area in 4 Flow Rates. The plot shows the fraction of total pixels inside lumen area as a function of time (or in this case, frames) as the bolus passes through the given OCT cross section. As shown, the transition time is inversely proportional to the flow rates.

The normalized integrated flow graphs—because the maximum flow areas differ for different flow rates—are plotted with respect to the frames to show the transit time trend with increasing volumetric flow rate. The normalized flushed area is more robust than the mean intensity plot and exhibits clearly the differentiated behavior for different flow rates.

The derivatives of the normalized flow area curves are plotted with respect to the frames to show the flushing time trend with increasing volumetric flow rate. The flushing time (τ), or the mean transit time, is defined as the time when the normalized flushed area reaches 0.5. The normalized flushed area of 0.5 indicates that the backscattering dilution curve recovers 50% of the

backscattering signal at that frame or time. As shown in Figure 3-5, the inverse flushing time (τ^{-1}) exhibits a linear relationship with flow rate.
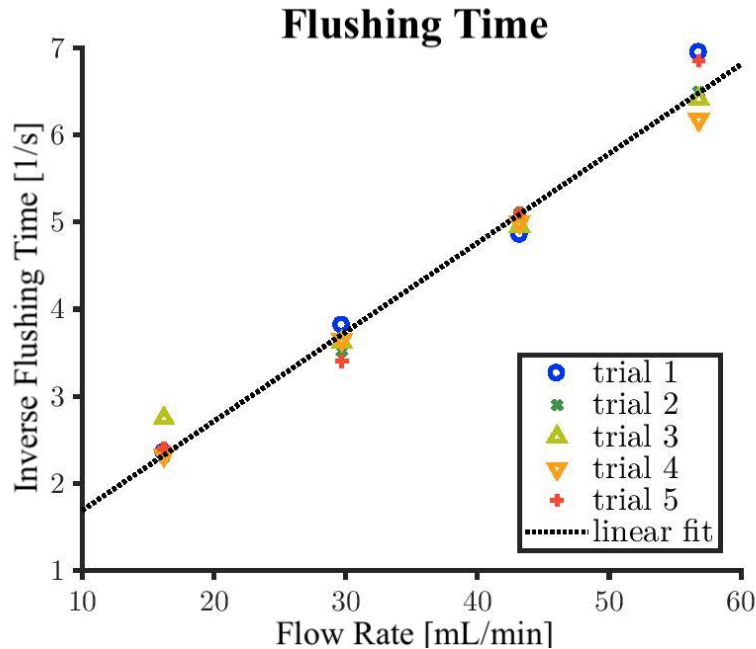

Figure 3-5: Plot of Inverse Flushing Time against Different Flow Rates. The inverse flushing time is linearly proportional to the flow rates.

This proof-of-concept experiment data has a simple geometry of a circular lumen. Therefore, it is analyzed with a circular mask to prove that this approach can work in principle. The main results are: the development of an analysis technique to determine transit time, confirming a relation between transit time and flow rate and a relation between the derivative of the transit time and flow rate. Preliminary validation *in vitro* in a OCT galvo benchtop system using a phantom fluid reveal that this analysis provides a backscattering indicator-dilution curve with a slope that is dependent on flow rate.

3.3 Porcine Blood Circulation and 0.9% Saline Bolus

Unlike the initial experiment above, the analysis is more involved with the use of an IV-OCT system due to different geometry and the motion artifacts associated with endoscopic imaging. Due to the different optical property of blood, the data can no longer be analyzed with a circular mask. Instead, the lumen only appears circular when the entire area is completely flushed; otherwise, it appears elliptical in image. Thus, the data for porcine blood circulation imaging is analyzed with an elliptical mask.

Based on the faster flow rate deviating from the trend, the flow rates were grouped in three distinct groups: slow rates (15, 25, 35, 45, and 55mL/min), medium rates (65, 75, and 85mL/min), and fast rates (95, 105, 115, 125, and 135mL/min). For 145 and 155mL/min flow rate data, the circulation is too fast that the noise is too significant for any accurate analysis.

The slow rates clear the entire lumen as seen in the previous Intralipid test. However, for the medium and fast rates, the images never show the clearing of the entire lumen area. Instead, the middle rates do not clear enough for some of the scans that it is difficult to tell the lumen edges. For the fast rates, two flushing are seen even though the bolus was injected only once. Although the fast rates do not clear the entire lumen either, more of the lumen area is cleared compared to the middle rates.

In this experiment with porcine blood circulation and saline bolus injectate, the threshold intensity for the data of interest is set to 85 dB. The data points of interest in each frame is filtered and integrated to get the total dilution area of the fluid flow per frame. The low rates normalized flushed area plot is shown in Figure 3-6.
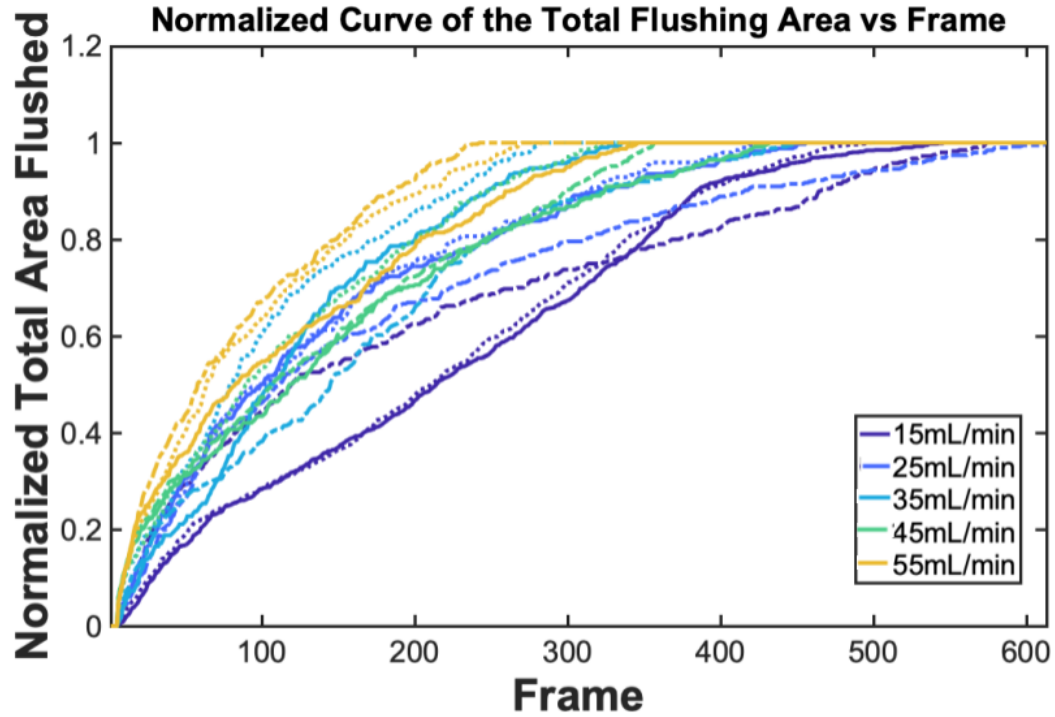
Figure 3-6: Plot of Normalized Flushed Area in 5 Slow Flow Rates. The plot shows the fraction of total pixels inside lumen area as a function of time (or in this case, frames) as the saline bolus passes through the given OCT cross section. As shown, the transition time is inversely proportional to the flow rates in the slow regime.

The medium rates are grouped from 65 to 85mL/min because within these rates, the lumen does not flush entirely. There are also not enough—very limited—area of clearing within the lumen after the bolus is injected. As shown in Figure 3-7, the normalized flushed area still exhibits the same trend as shown in the slow flow rate regime and in the previous intralipid circulation experiment. The limited clearing area may explain the deviation of one set of the 65mL/min scans from rest of the trend.
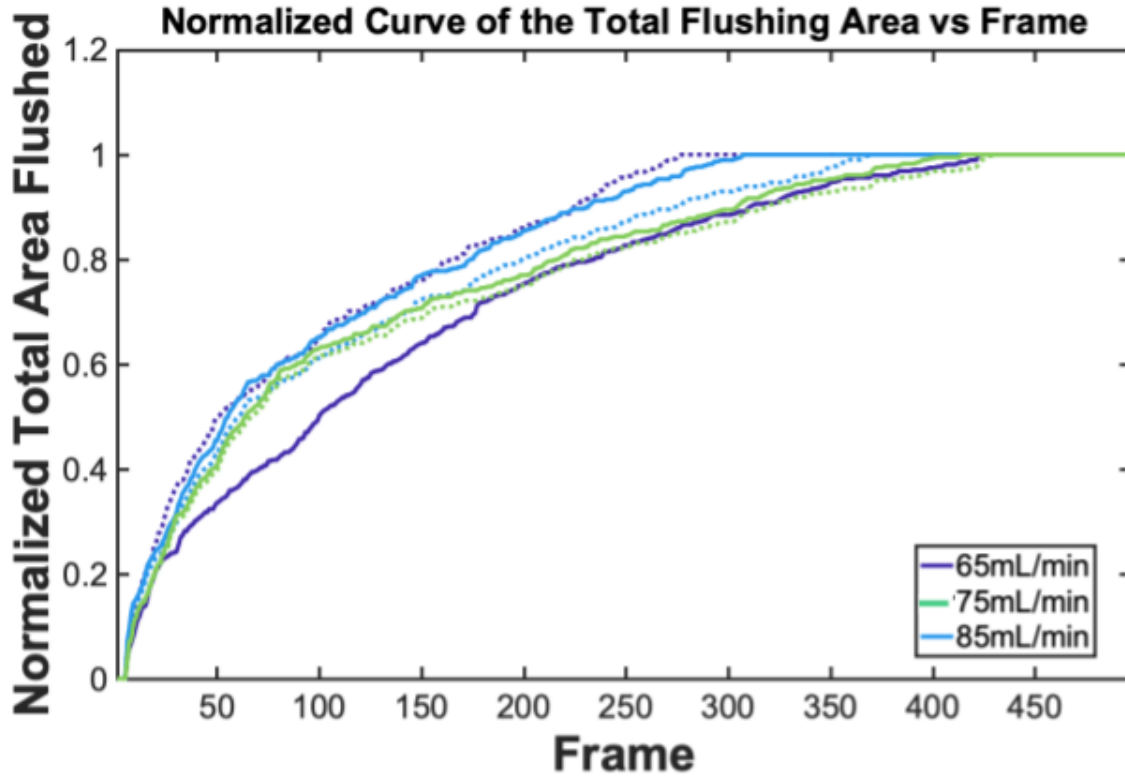
Figure 3-7: Plot of Normalized Flushed Area in 3 Medium Flow Rates. The plot shows the fraction of total pixels inside lumen area as a function of time (or in this case, frames) as the saline bolus passes through the given OCT cross section. As shown, the transition time is inversely proportional to the flow rates in the slow regime. There is one of the trials for 65mL/min that deviates from the rest of the trend. It might have been caused by the lack of enough clearing for the lumen for proper normalized flushed area trend.

The fast rates are grouped from 95 to 135mL/min because within these rates, the lumen does not flush entirely. However, unlike the medium rates (65-85mL/min), there are greater clearing areas within the lumen than the medium rates after the bolus is injected. As shown in Figure 3-8, the normalized flushed area still exhibits the same trend as shown in the slow flow rate regime and in the previous intralipid circulation experiment.
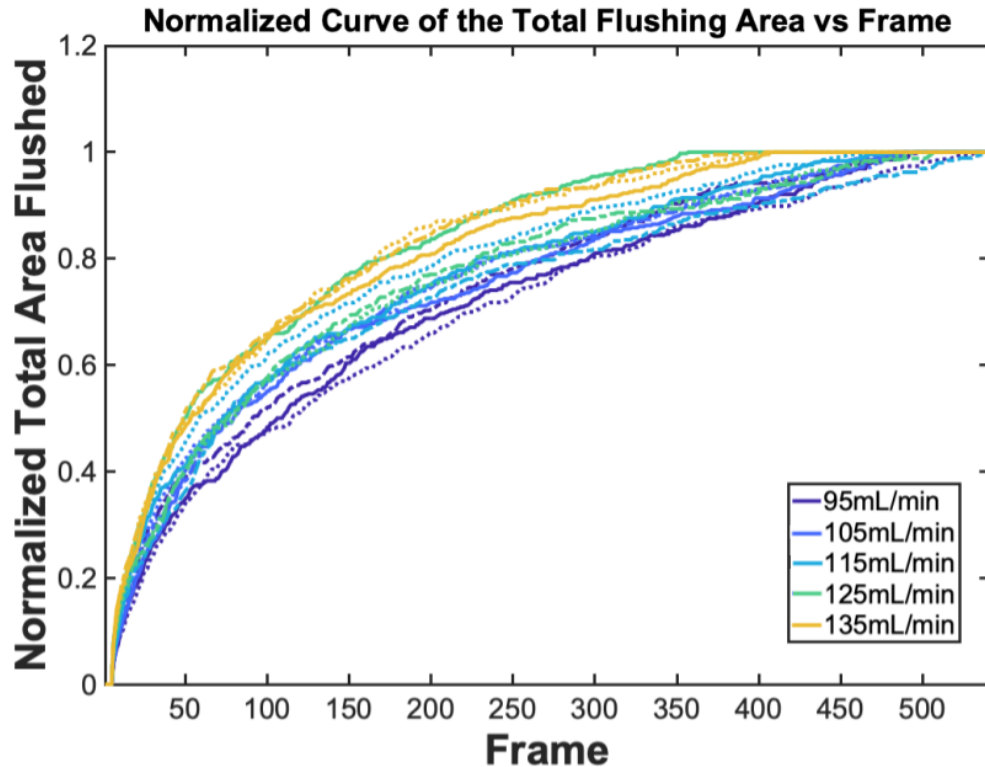
Figure 3-8: Plot of Normalized Flushed Area in 5 Fast Flow Rates. The plot shows the fraction of total pixels inside lumen area as a function of time (or in this case, frames) as the saline bolus passes through the given OCT cross section. As shown, the transition time is inversely proportional to the flow rates in the fast regime.

As seen in the plots, the minimum flow rate that this technique is still valid for is 15mL/min. This minimum flow rate value is less than the extremes of the coronary flow rates, which the minimum normal flow is 18mL/min. For the middle and fast rates not clearing the entire lumen as it should, it can be solved by injecting continuous flow of saline injectate until the lumen clears entirely. In this experiment, the bolus was injected in continuous flow until it reached the set bolus volume (5mL). However, to prevent issues with the lack of lumen area clearing, the injectate should be injected until the clear lumen imaging is obtained as would in an IV-OCT imaging in a human subject.

For this experiment, the derivatives of the normalized flow area curves are also plotted with respect to the frames to show the flushing time trend with increasing volumetric flow rate. The

flushing time (τ), or the mean transit time, is defined as the time when the normalized flushed area reaches 0.5. The normalized flushed area of 0.5 indicates that the backscattering dilution curve recovers 50% of the backscattering signal at that frame or time. As shown in Figure 3-9, the inverse flushing time (τ^{-1}) exhibits a linear relationship with flow rate for the slow flow rate grouping.

Figure 3-9: Plot of Inverse Flushing Time against Different Flow Rates in the Slow Regime. The inverse flushing time is linearly proportional to the flow rates.

The medium rates are grouped from 65 to 85mL/min because in these flow rates, the lumen does not flush entirely due to the fast circulation rate. As shown in Figure 3-10, the trend of inversely proportional flushing time to the different flow rates.
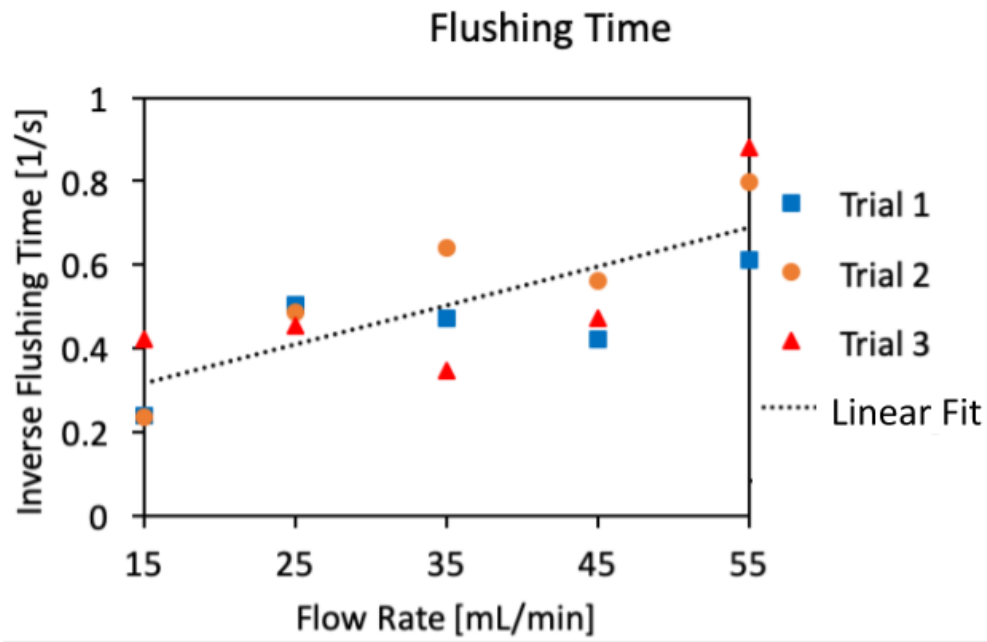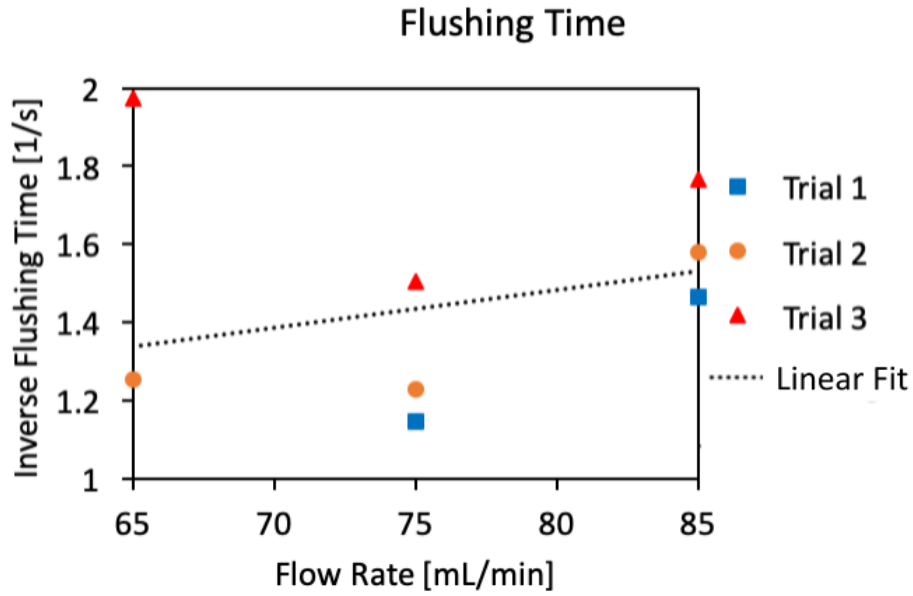
Figure 3-10: Plot of Inverse Flushing Time against Different Flow Rates in the Middle Range. The inverse flushing time is linearly proportional to the flow rates. However, it is not as clear or strong of a correlation between the inverse flushing time and the flow rates. This phenomenon may be due to the entire lumen not completely flushing.

As seen above, the middle range of flow rates [65, 75, and 85mL/min] do not have as strong correlation for the inverse flushing time vs flow rates as the other two flow rate groupings. This is likely due to the fact that the lumen does not clear entirely. Thus, there is not complete clearing in these data to get the true minimum intensity cross-sectional OCT scan.

The fast flow rate grouping exhibits the same inverse flushing time trend as the slow flow range and the proof-of-concept data. As shown in Figure 3-11, the flushing time is inversely proportional to the flow rate.
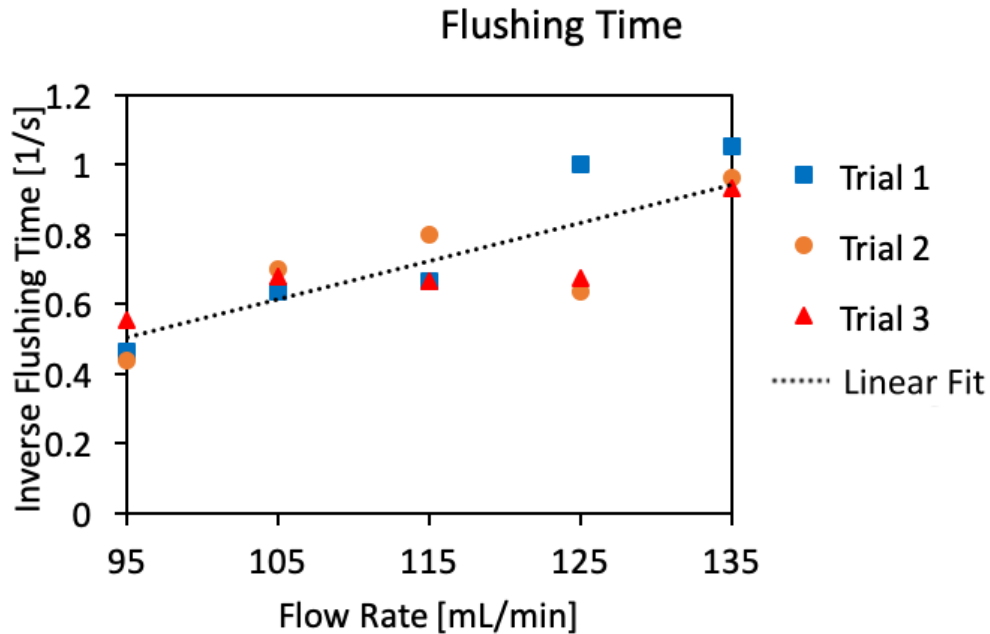
Figure 3-11: Plot of Inverse Flushing Time against Different Flow Rates in the Fast Range. The inverse flushing time is linearly proportional to the flow rates within [95, 105, 115, 125, and 135mL/min].

Currently, the inverse flushing time (τ^{-1}) for fast rates and slow rates overlap. For example, τ^{-1} of 35mL/min and 95mL/min are both approximately 0.5. If the trend from the slow and middle rate groups is extrapolated, 95mL/min should have the τ^{-1} of approximately 1.5. This issue is also due to the fact that the scans for the fast rates show two flushes even though the bolus was injected only once. Also, the fast rates do not clear the entire lumen, affecting the normalized flushed area calculation. This issue can be solved by injecting the bolus injectate until the lumen clears entirely as mentioned previously. In this experiment, the bolus was injected in continuous flow until it reached the set bolus volume (5mL). However, the injectate should be injected until the clear lumen imaging is obtained as would in an IV-OCT imaging in a human subject.

This IV-OCT system experiment data has an elliptical lumen in the cross-sectional images due to the blood optical properties. When it is analyzed with an elliptical mask to prove that this approach can work in principle, it verified and validated the results obtained from the original OCT

benchtop system for the proof-of-concept experiment previously. It confirms the development of an analysis technique to determine transit time, confirming a relation between transit time and flow rate and a relation between the derivative of the transit time and flow rate even in porcine blood. Once the issues mentioned previously are solved, the data gathered from these experiments suggest that this analysis technique can be applied to human clinical application.

4. Discussion

In the first sets of experiments conducted, Intralipid is used to validate the feasibility of using OCT system for transit time determination. Intralipid and blood have different scattering properties. Therefore, when animal blood replaced Intralipid, the second set of experiments validated the feasibility of the technique in blood optical properties. Since Intralipid and blood have different scattering coefficients, it is critical to apply the experiment to animal blood before determining the clinical implementation potential. With validation in both cases, it can be said the technique should be applicable to human clinical uses.

In this project, a blood flow quantification technique was developed based on backscattering indicator-dilution approach for intravascular optical coherence tomography (IV-OCT) system. It achieved the goal of obtaining the flow velocity in a coronary artery of interest by analyzing the backscattering signal from blood after passage of a bolus of Ringer's lactate or another transparent injectate, in parallel to coronary flow reserve (CFR). In contrast to thermodilution CFR, the structural OCT image can be used to determine the bolus volume and transit time, thus enabling the determination of absolute coronary flow rates with standard OCT systems. The OCT image can also be used to account for motion and volume change between the two CFR flow readings, potentially improving CFR accuracy. For example, access to the structural image could account for vessel diameter and catheter location changes.

A very simple analysis and a straightforward flushing technique as mentioned above, compatible with standard OCT imaging, is capable of measuring absolute flow rates *in vitro*. The 0.8mm diameter catheter used corresponds to an area stenosis of <10% in a 3.2mm diameter segment. Thus, it is unlikely to decrease the measured blood flow.

However, there are limitations to the current techniques. The pump for bolus injection currently is not within specs to flush the entire lumen at higher flow rates. However, in typical cardiovascular catheter lab, the entire lumen would be flushed with an injectate as it is imaged. As mentioned previously, the technique should not inject a set volume of bolus. Instead, the injectate should be injected into the guide catheter until the entire lumen clears. Also, from the analysis of the data gathered, it has been noticed that the current technique does depend on the catheter lumen location. Thus, further rigorous validations should be completed to determine whether technique can ever be immune to the catheter lumen location.

 Further validation should be completed to study the technique and its impact on different vessel diameters imaging. Other factors, such as the downstream length, should be tested to confirm the capability to measure flow speed and absolute flow rates. Injectate is currently fully infused into the vessel of interest, immunity to losses need to be confirmed. An alternative catheter design with a built-in flushing channel could guarantee complete deposition of injectate.

Once the technique is validated for the above factors, *in vivo* experiment should be conducted to validate the technique within animal and/or human testing.

The experiment can be furthered by imaging the differences in flow measurements when a stenosis is created versus without a stenosis. This data would confirm the clinical value of potentially having quantitative measurements of flow via OCT imaging. Also, more rigorous validations should be completed to taken into account different vessel diameters.

Future implication of this experiment is the ability to get more accurate measurement of the blood flow rate at any location regardless of the blood vessel geometry. Findings of this and future experiments can be used to implement intravenous OCT system for clinical use in diagnosing cardiovascular diseases.

5. Conclusion

In this project, *in* vitro system for cardiovascular coronary flow testing was designed and fabricated. Two sets of experiments were conducted first, to validate the feasibility of using optical analog of Thermodilution-Indicator Theory, and second, use IV-OCT system to determine the flow rate in blood optical properties. The project has shown that a simple technique could provide standard cardio OCT systems with flowmetry capabilities. Flowmetry can be used to measure CFR or absolute blood flow without any hardware change, and with potentially higher accuracy than thermo-CFR. Combined with OCT catheters equipped with pressure transducers, this technique could provide accurate stenosis and microcirculation disease assessment in a single instrument. Further tests should be conducted to study the effect of other factors such as different vessel diameters. The technique should also be validated via *in vivo* experiment to confirm the future implication of implementing this technique for clinical use in diagnosing cardiovascular diseases.

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