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Convective Leakage Makes Heparin Locking of Central Venous Catheters Ineffective within Seconds: Experimental Measurements in a Model Superior Vena Cava

Michael C. Barbour[1], Patrick M. McGah[1], Chin H. Ng[1], Alicia Clark[1], Kenneth W. Gow[2], and Alberto Aliseda[1]

[1]Department of Mechanical Engineering, University of Washington
[2]Seattle Children's Hospital and Department of Surgery, University of Washington

Central venous catheters (CVCs), placed in the Superior Vena Cava (SVC) for hemodialysis or chemotherapy, are routinely filled while not in use with heparin, an anticoagulant, to maintain patency and prevent thrombus formation at the catheter tip. The heparin- locking procedure, however, places the patient at risk for systemic bleeding, as heparin is known to leak from the catheter into the blood stream. We provide evidence from detailed in-vitro experiments that shows the driving mechanism behind heparin leakage to be convective-diffusive transport due to the pulsatile flow surrounding the catheter. This novel mechanism is supported by experimental planar laser induced fluorescence (PLIF) and particle image velocimetry (PIV) measurements of flow velocity and heparin transport from a CVC placed inside a model SVC inside a pulsatile flow loop. The results predict an initial, fast ($<$ 10s), convection-dominated phase that rapidly depletes the concentration of heparin in the near-tip region, the region of the catheter with side holes. This is followed by a slow, diffusion-limited phase inside the catheter lumen, where the concentration is still high, that is insufficient at replenishing the lost heparin concentra- tion in the near-tip region. The results presented here, which are consistent with previous in vivo estimates of 24-hour leakage rates, predict that the concentration of heparin in the near-tip region is essentially zero for the majority of the interdialytic phase, rendering the heparin locking procedure ineffective.

1 Introduction

Central venous catheters (CVCs) are commonly used to provide vascular access during hemodialysis in patients with end-stage renal disease. In recent years, the use of CVCs for hemodialysis has grown in the United States and they are used in approximately 25% of hemodialysis patients [1]. Despite their widespread use, CVCs used for hemodialysis have a high incidence rate of catheter-related infection and are associated with known elevated risk of mortality and morbidity [2]. When compared to arteriovenous fistulas,

catheters carry a 2-3 fold increase in a patient's risk of death and 5-10 fold increase in risk of infection [3]. In general, maintaining catheter patency is difficult, and as many as 15% of patients receiving a CVC report some form of complication [4].

One of the most common complications is thrombus formation at or near the catheter tip [5]. A thrombus will occlude the catheter lumen and restrict flow rates during dialysis, requiring an intervention and occasionally a full catheter exchange. In an attempt to prevent such complications, hospitals routinely administer an anticoagulant, often a heparin/saline solution, into the catheter lumens following dialysis - a procedure known as heparin locking. The recommended concentration for a heparin lock is 1,000 U/mL, but some centers will use concentrations as high as 10,000 U/mL [6]. The logic behind this practice is that in between dialysis sessions, the interdialytic period, the locking fluid remains inside the catheter lumens, preventing clot formation.

Although it has been the standard for many years, the benefits of heparin locking are controversial, and the process seems to have been adopted without sufficient supporting evidence [7]. A number of trials have found weak or conflicting evidence for the benefit of heparin in preventing catheter thrombus formation, in comparison to pure saline [8, 9, 10]. Heparin locking is also associated with added risks to the patient: during the interdialytic cycle heparin will leak out into the systemic blood circulation, placing both adult [11] and pediatric [12] patients at risk of systemic anticoagulation and bleeding incidences.

It has been reported that heparin leakage from central venous dialysis catheters occurs in two phases in vivo [13]. An early phase that occurs within the first 10 minutes following instillation and that is responsible for a 10-15% loss in initial lock volume. And a late phase, which constitutes the remainder of the interdialytic period, where another 10% of the initial heparin dose is passed to the patient's blood volume. A number of in vitro studies [14, 15] have reported early leakage rates of 15-20%, consistent with in vivo rates, and suggested that the early leakage is a result of the initial instillation process of the locking fluid into the catheter. Two in vitro studies have also investigated late-phase

leakage [16, 17] but their results reported losses as high as 70-80%, not consistent with the in vivo data.

All of the in vitro studies discussed thus far have measured the amount of locking fluid that leaks from a catheter placed in a static fluid. However, this is not representative of the hemodynamic environment that the catheter is exposed to in vivo. To date the influence of blood flow surrounding the catheter on heparin leakage has not been studied. Experimental data on convective mass transport, forced by the pulsatile flow of blood in the SVC or right atrium, of heparin from a CVC is missing. This paper closes this gap in the current understanding of locking solution leakage from central venous dialysis catheters. While all hemodilysis patient who receive a CVC are susceptible to heparin leakage, the options, in terms of size and design, are much more limited in pediatrics than in adults. As a result pediatric patients often end up with an over-sized catheter, placing them at greater risk of inadequate catheter locking or leakage. This study focuses on pediatric use of central venous dialysis catheters, and the experimental conditions are designed to mimic the hemodynamic environment inside a pediatric patient.

The manuscript is organized as follows. The experimental methods to measure velocity and transport of the locking fluid are described in Section 2. The results from the experiments are shown in Section 3. Section 4 puts the results in the context of current ideas and contradictions for the locking transport mechanisms. In combination with a computational study published recently by our group [18], we propose that heparin leakage is a result of instillation and, as a separate mechanism, convective-diffusive transport due to the pulsatile blood flow surrounding the catheter. The quantitative analysis, supported by our *in vitro* experiments and clinical observations in the literature, allows us to formulate a strong hypothesis for the mechanism of locking solution ineffectiveness in Section 5.

2 Materials and Methods

2.1 SVC Flow Conditions and Characterization of the Pulsatile Loop

The flow conditions inside the pulsatile flow loop are designed to mimic the hemodynamic environment of a pediatric (5-7 yrs. old) Superior Vena Cava (SVC). The working fluid is a 60:40 by weight water:glycerin mixture with a viscosity of 3.2 cP at a temperature of 25° C [19]. The density of the mixture, measured with a standard hydrometer, is 1,050 kg/m^3. The flow is driven by a pulsatile blood pump (Harvard Apparatus Inc., Holliston, MA) at 54 bpm (cardiac cycle of 1.11 s) with a stroke volume of 30 mL. The pump is set so that 35 % of the piston cycle is spent in expansion. The piston is contracting during the remaining 65 % of the cycle. These pump settings were chosen to match the pediatric SVC flow characteristics reported by Fung [20], Chavhan [21] and Ayabakan (figure 1) [22] The test section, shown in figure 1, consists of two straight acrylic 1/2" ID tubes connected by a T-joint where the catheter is introduced into the flow loop. The test section upstream of the t-joint is sufficiently long to ensure fully-developed, axisymmetric flow at the location of catheter introduction. To reduce the optical distortion caused by air-fluid index of refraction mismatch, the test section is placed inside an acrylic box filled with the same 60:40 water:glycerin mixture.

Characterization of the flow in the model SVC inside the pulsatile flow loop is performed by particle image velocimetry (PIV) starting at two vessel diameters upstream of the location where the catheter is introduced into the flow loop. A laser plane from a continuous wave Argon-Ion (Spectra-Physics, Santa Clara, CA) illuminates the centerline of the test section, along the streamwise direction. The flow is seeded with Lycopodium particles that act as flow tracers and scatter light as they flow along the laser plane. A high-speed camera (Phantom V12, Vision Research Inc., Wayne NJ.) is oriented perpen- dicular to the laser plane to collect the light scattered by the PIV seed particles, and

synchronized with the cardiac-simulating pump to control data acquisition in phase with the cardiac cycle.

PIV processing is done with GPIV software [23] to calculate velocity vectors from the cross correlation of sequential images of the particle scattered light within the region of interest [24, 25]. Velocity vectors along 20 radial slices are averaged together to calculate w(r, t), the streamwise velocity profile upstream of the catheter. This velocity profile is compared to the analytical Womersley solution [26] at 10 time points within the cardiac cycle in figure 3a. Good agreement can be observed between the measured velocity profile and analytical solution, with some deviation near the walls of the test section (top and bottom the plot), likely the result of the PIV images being slightly distorted by the curvature of the test section and the incomplete index of refraction matching.

The mean velocity, averaged across the vessel radial direction $\overline{w}(t) = \frac{1}{2\pi}\int_0^R w(r,t) r\, dr$, is shown in figure 3b. This waveform closely matches the SVC velocity profile reported by Fung [20] and Ayabakan [22]. The Re and W o numbers for this flow are 1050 and 8.5, respectively, and are representative of the conditions inside the SVC of 5-7 yr. old child [27].

Flow characterization is conducted upstream of the catheter as the flow downstream of the catheter is not entirely axisymmetric. The catheter is located inside the test section and the flow distal to the catheter contains small radial and azimuthal velocity components that are not captured with the 2-D PIV configuration. The PIV data gathered from the upstream location is axi-symmetric and allows for accurate flow rate calculations.

2.2 Measurements of Locking Solution Concentration and Transport Fluxes

We investigate the dynamics of heparin leakage from central venous dialysis catheters using planar laser induced fluorescence (PLIF). These measurements, together with the velocity profile measured by PIV, allow for the quantification of the amount of locking

solution that is lost from the catheter following instillation. Two separate experimental configurations are used in this study in order to investigate the influence of convective-diffusive flux on the leakage process. Locking fluid losses are measured from a catheter placed in both static fluid and the pulsatile flow loop, allowing for the calculation of losses caused by diffusion and convection respectively. Losses due to pure instillation are also measured from a catheter placed inside the pulsatile flow loop, but with the pump inactive, to separate the effect of instillation from convection.

PLIF has long been used to measure concentration and temperature fields in fluid flow [28]. In a PLIF measurement, a fluorescent species is seeded into the flow and excited by a laser plane, absorbing laser energy. The fluorescent dye then re-emits this energy as fluorescence, typically at a different wavelength than the incident light source. The re-emitted light intensity is proportional to the concentration of fluorescent species, within a calibration range, so the light captured by a sensitive camera-lens system can be correlated to the species concentration. In both the diffusion and convection experiments, the fluorescent dye Rhodamine B is used as a surrogate for heparin and instilled into the catheter lumens. The diffusivity of heparin in saline and RhB in water are both $\approx 10^{-10}\mathrm{m}^2/\mathrm{s}$ [29, 30]. PLIF measurements are used to measure the mass loss of locking fluid in both experimental configurations.

2.2.1 Diffusion Experiments

A Hemocath, 8 Fr, non-tunneled, single-body catheter, with a locking volume of 1.2 cc (0.6 cc per lumen), is filled and locked with a mixture of water and Rhodamine B at a concentration 500 ppm (by mass). This is a double-lumen catheter and each lumen is DD shaped. The catheter is placed into a square acrylic container, open at the top, filled with 130 g of water. A 532 nm pulsed Nd:Yag laser (Solo PIV 200XT, New Wave Research. Portland, OR.) is used to create a plane that illuminates the fluid horizontally through the test beaker wall 1 cm below the water surface. A CCD 4MPixel camera (Princeton

Instruments, Trenton, NJ) is placed above and aimed down at the test beaker, capturing light re-emitted by the dye on the plane illuminated by the laser plane. The laser pulses and camera acquisition are synchronized so that an image is captured every 15 minutes for a 24 hour period. A magnetic stirrer is placed at the bottom of the test beaker to ensure that any RhB that leaks from the catheter is fully mixed within the beaker. The rotational rate of the stirrer is kept low enough so that the catheter remains motionless and no momentum is imparted to the fluid within the near-tip region, the region of the catheter with side holes.

In order to infer RhB concentration from fluorescence intensity, or gray scale image, a calibration must be performed. At low enough dye concentration, the relationship between fluorescence intensity and concentration is linear:

$$C = \lambda F \qquad (1)$$

where C and F are the local RhB concentration and fluorescence respectively, and λ is a fluorescence constant that is dependent on the laser intensity, optical arrangement and fluorescent characteristics of RhB. Before experiments can be conducted it is necessary to determine the linear range for RhB in the specific experimental set-up. This linear calibration also determines the local fluorescence constant λ [31].

The calibration is done by placing various known concentrations of RhB dye and test fluid into the test beaker and measuring the light intensity emitted at each concentration. Eight different calibration mixtures are made with concentrations ranging from from 0 to 1 ppm. The linear calibration plot relating grayscale intensity vs RhB concentration is shown in figure 2. The linear correlation parameter R^2 is 0.99, demonstrating good linearity of the RhB fluorescence in the range of concentration used in the experiments. It should be noted that, although the concentration of RhB inside the catheter lumen (500 ppm) is well outside of the linear range, the experimental measurements of RhB concentration in the test section as a result of leaking from the catheter are found to be

in that linear range.

2.2.2 Time-resolved Concentration Measurements in Pulsatile Flow

An Ash-split, 10 Fr, non-tunneled catheter with a combined luminal volume of 1.8 cc is placed inside the pulsatile flow loop. This is a split-tip catheter where the venous and arterial lumens split and the lumen tips are separate. Time-resolved PLIF measurements are taken using a continuous wave, Argon-Ion laser (Spectra-Physics, Santa Clara, CA). A laser plane illuminates a cross-section of the SVC model 3 diameters downstream of the catheter. A high speed camera (Phantom V12, Vision Research Inc, Wayne, NJ.) is positioned at 45 deg with respect to the streamwise direction (normal to the illuminated cross section) to capture light re-emitted by the flowing dye as it crosses the laser plane in the entire flow cross-section (Figure 1). Due to the orientation of the camera an optical distortion must be corrected later with a spatial calibration (Section 7.1. RhB fluoresces at 590 nm so a 550 nm long-pass optical filter is placed in front of the camera lens to filter out light from the incident laser beam reflected or refracted by the flow loop test section materials.

The experiment is primed by turning on the pump and letting it run for 10 cycles to eliminate any effect from the start-up, transient, motion. After this, the synchronizer receives an impulse from the pump and triggers the camera system to begin recording. A volume of 0.9 cc of a RhB dye and water:glycerin mixture at a concentration of .1 ppm is instilled into each catheter lumen at a rate of 0.5 cc/sec. The camera records at a rate of 400 frames/sec for 10 flow cycles following instillation.

The PLIF measurements give a spatial distribution of locking mixture concentration along a slice of the test section. This concentration distribution is multiplied times the velocity measurements resulting from the PIV to obtain the locking solution mass flux across that plane perpendicular to the flow direction. This gives the instantaneous mass flux coming from the catheter, with a small time delay given by the 3D downstream

offset between the catheter tip and the cross section where the concentration is measured. This offset improves the quality of the measurements, by allowing the concentration level to come down into the linear range from the high initial concentration in the catheter, with a minimum delay that is easy to relate to the transit time between catheter tip and measurement station.

2.2.3 Concentration Balance

Along with the time-resolved PLIF measurements of RhB mass flux downstream of the catheter, the concentration of RhB inside the catheter lumen is measured before and after the experiment, providing an additional measurement of cumulative RhB mass flux. Following each experiment the pump is turned off and the catheter lumen volume (0.9 cc, the same that was instilled), is carefully removed from the catheter, poured into a transparent container and its RhB concentration measured via PLIF. The difference between the initial and final concentration, times the catheter volume is the cumulative mass flux, from instillation and convection, measured from mass balance.

To evaluate the longer term convective flux, beyond the first 10 cardiac cycles, cumulative RhB flux measurements were conducted after 60 cycles of convective flux (flow loop pump turned on). Limitations on the high speed camera precludes the time-resolved PLIF measurements for longer than 10 cardiac cycles. Thus, the mass of RhB inside the catheter lumen is measured after the 60 cycles of convective flow, by collecting the lumen volume and performing PLIF on that volume. To separate the effect of instillation from convection in this study, control experiments are also conducted with the pump off. The locking mixture is instilled into the catheter lumen and, after 10 seconds in which the inertia from the instillation induces flow out of the catheter and into the model SVC, the lumen volume is removed, poured out and measured with PLIF. The difference be- tween the initial and final RhB mass (measured concentration times the catheter volume) represents the instillation flux.

The time-resolved PLIF measurement configuration requires a separate RhB concentration-to-fluorescence calibration table, as the concentration range differs from the static diffusion experiment according to the different time scales (hours vs seconds/minutes). The same procedure described in Section 2.2.1 is followed for this configuration with the difference that the RhB range in this case is from 0 to 0.2 ppm. Lower concentration is used to improve the accuracy of the time-resolved measurements, in which small differences over a few seconds need to be measure, making the attenuation of the incident laser plane by RhB negligible [32]. Fifty 12-bit images are taken of each calibration mixture and averaged so that small fluctuations in the laser intensity do not influence the scaling. For each pixel in the region of interest (ROI), a linear calibration curve between pixel gray scale and RhB concentration is calculated.

3 Results

3.1 Diffusion Experiments

The RhB mass diffused from the catheter is plotted versus time in figure 4 (from four separate experiments). Diffusion losses are measured to be very small over a 24 hour period. The total mass of RhB measured in the entire beaker is normalized with the initial mass of RhB locked into the catheter lumen, showing that diffusion contributes $1-2\%$ of the locking solution to the flux that leaks out from the catheter in the interdialytic period. There is an initial spike in RhB concentration observed in some of the tests in figure 4 as a result of initial leakage from the catheter as it is slowly dipped into the test beaker.

For comparison, diffusion rates predicted by diffusion theory from a point source is expressed via the solid bold curve in figure 4. The theoretical curve for Fickian diffusion from a one-dimensional object predicts that the concentration of RhB will increase at a rate proportional to the square root of time. Expressed in terms of initial RhB mass

inside the catheter lumen, the expression for cumulative percent leakage of RhB is:

$$C_{RhB} = b1\sqrt{t} \qquad (2)$$

$$b1 = 2\frac{A_C}{V}\sqrt{\frac{D_{RhB}}{\pi}}$$

where A_c and V are the cross sectional area and internal volume of the catheter lumen respectively, D_{RhB} is the diffusivity of RhB, and C_{RhB} is the cumulative percent leakage. Using the diffusivity of RhB in water ($D_{RhB} = 4.2 \times 10^{-10} m^2/s$) [29], the locking volume ($V = .68mL$) and cross-sectional area ($A_c = 1.9 \times 10^4 m^2$) of the Hemocath CVC, the value for b1 at room temperature is computed to be $.388 hr^{-1/2}$. The experimental value of b1 was found through curve fitting the four experimental datasets shown in figure 4 to the function defined in equation 2. The mean value of b1 from the four independent experiments was $.394 hr^{-1/2}$, in good agreement with the theoretical prediction.

3.2 Pulsatile Flow

Data from a time-resolved PLIF experiment is shown in figure 5 (top). The RhB concentration in the measurement plane, $C_{RhB}(r, \theta, t)$, is integrated over the cross sectional area of the model SVC and plotted versus time, expressed in cardiac cycles. The concentration of RhB measured downstream of the catheter tip rapidly rises and then decays in an almost exponential manner following the onset of convection. The peak in RhB concentration and convective mass flux only lasts a few seconds (cardiac cycles), after which a negligible flux of locking solution is detected.

The instantaneous mass flux, shown in figure 5 (bottom), is calculated in combination with the PIV velocity measurements, following:

$$\dot{m} = \int_{A_T} \rho C_{RhB}(r, \theta, t) w(r, \theta, t) \cdot n dA \qquad (3)$$

where $w(r, \theta, t)\cdot n$ is the Womersley velocity field, measured by PIV, and A_T is the cross sectional area of the model SVC. The full streamwise velocity field at the measurement plane is not available and the Womersely solution, calculated from PIV measurements along a radial line in the measurement plane, is used by assuming the velocity is axi- symmetric. The cumulative mass flux of RhB that leaks out of the catheter is then found by integrating equation 3 over time. The average mass flux of locking solution convected out of the catheter over 10 cardiac cycles, as a percentage of the initial mass inside the catheter lumen, was measured to be 34.2 % (from 10 independent experiments, StDev = 4.2%). The mass flux of RhB that leaks out of the catheter is broken down into cardiac cycles according to:

$$m_{cyc} = \int_{nT}^{(n+1)T} \dot{m}(t)dt \quad (4)$$

where T is the cardiac period (in seconds) and n ranges from 0 to 9. The result, normalized by the initial mass of locking solution in the lumen, is shown in figure 6. Each data point represents the mean from 10 independent experiments with 95 % confidence interval shown as brackets. It is clear from these results that the majority of leakage occurs very rapidly and that the losses are small after only a few seconds of convection.

The results from the cumulative mass flux, measured from concentration balance, are shown in table 1. Three rows show measurements of locking solution mass leaked out as a percentage of initial mass inside the catheter lumen, before and after instillation (no convection - pump off), instillation and convection for 10 cardiac cycles and instillation and convection fro 60 cardiac cycles. The mean RhB leakage from instillation alone is 28.16 % of the initial RhB mass in the catheter lumen. When the catheter is subjected to pulsatile flow conditions for 10 cycles and 60 cycles, the convective losses increase to 42.96% and 43.9% respectively.

The mass loss calculated from the time-resolved PLIF measurements (combined with the velocity from PIV measurements using equations 3 and 4) is 34.6%, slightly different from the cumulative RhB mass flux measured from mass balance under the same conditions, following 10 seconds of convection, (42.96%). This discrepancy is assumed to be a result of the axisymmetric velocity assumption, implied in equation 3. This is further discussed in the limitations section.

The three measurements of cumulative mass fluxes obtained from mass balance in the catheter lumen (instillation, convection for 10 cardiac cycles and convection for 60 cardiac cycles) are compared using an independent t-test and a Wilcoxan Rank-Sum test, in table 2. When comparing the mass fluxes due to convection, 10 cardiac cycles vs 60 cardiac cycles), the p-values for the independent t-test and Wilcoxan Rank-Sum test are

.723 and .596, respectively. Thus, the measurements are found to be equivalent (they could be measuring the same quantity). This is consistent with the data from the time-resolved mass flux that shows only the first few cardiac cycles contribute to the cumulative mass flux. When instillation-only fluxes are compared to convective flux experiments (for

10 cardiac cycles), however, the p-values from both tests are $< .01$, rejecting the null hypothesis and showing statistically significant differences: the leakage due to catheter instillation are distinct from those due to instillation and convection.

4 Discussion

The results presented here, in conjunction with our numerical work published previously[18], suggest a clear two-stage mechanism for heparin leakage from CVCs. The early stage leak- age, which lasts less than 10 seconds, is caused by instillation imparting momentum to the lock fluid and to a convective flux from the surrounding pulsatile flow.

The late stage leakage, which constitutes the remainder of the interdialytic phase, is limited by the slow diffusive flux of heparin from inside the catheter lumen where the concentration is still high.

Leakage in the early phase occurs very rapidly and contributes to significant losses of up to 40% of the initial catheter locking solution. Previous studies[13] have suggested that early phase leakage lasts for 10 minutes post-instillation, but the instantaneous PLIF results presented here show that the majority of lock fluid losses occur within the first 10 cardiac cycles. The comparison of PLIF mass balance measurements of RhB leakage from a catheter subjected to pulsatile conditions for 10 vs 60 seconds show that there is no statistical difference between the two. In other words, the losses that occur after 10 seconds are statistically insignificant when compared to the losses that occur during the first 10 seconds. This new early phase time-scale of 10 seconds is in agreement with our recent numerical study [18] which estimates the time necessary to deplete the near-tip region of an addeddouble-lumen, single-body catheter to be $<$ 10 seconds.

The comparison of mass losses from experiments with and without pulsatile conditions after instillation demonstrate that the early phase leakage is a result of two separate mechanisms: instillation and convection. Previous in vitro studies [15] have reported instillation losses in the range of 20-30% but the influence of pulsatile flow conditions on locking solution leakage had yet to be quantitatively studied. The instillation loss rates in our study are consistent with this previous study. Further, after subtracting this instillation loss, we find that convection due to the pulsatile flow environment around the tip of the catheter inserted into the SVC or right atrium, induces a fast flux where an additional 10-15% of locking fluid is leaked from the near-tip region. We hypothesize that these additional losses are due to a convective flux of locking solution forced by the hemodynamic flow around and into the near-tip region. The time-dependent pressure gradient induced by the inertia of the pulsatile blood flow creates a force that drives locking solution out of the catheter through the most distal side holes of the catheter. This lost locking fluid is replaced by blood flowing into the catheter from other upstream side

holes. Therefore the replenishment of heparin concentration at the tip is only through diffusion from the remainder of the catheter luminal volume, which is slow. Our previous numerical study, of the same catheter design and under the same pulsatile flow conditions, also showed a 10 % loss of heparin due to convective fluxes out of the catheter tip side holes. CFD of the near-tip region showed flow, modeled as blood, entering the catheter through the side holes and transporting heparin out of the catheter and into the systemic circulation [18]. The near-tip region constitutes approximately 10% of the catheter locking volume. Since convective fluxes only act on fluid contained in this near-tip region, early-phase convective losses are limited to approximately 10% for the catheter used in this study. This result implies that, unlike instillation losses that push locking solution out of the tip but replaces it with more locking solution with approximately concentration, convective fluxes deplete the near-tip region of nearly all heparin replacing the locking solution with blood from the SVC.

Instillation losses are a result of the inertia due to the flow velocity that develops inside the catheter lumen as it is filled, leading to transport of locking solution out into the systemic circulation. The losses due to instillation likely depend on the rate at which instillation occurs and slower instillation will result in less initial leakage. Several studies [14, 17] have also investigated the effect of instillation volume on loss rates, and it has been suggested that larger instilled volumes (of non-heparin solution) should be used as they are more likely to result in a full near-tip region. In contradiction to this hypothesis, our results suggest that, regardless of the losses that occur during instillation, convection will still act to deplete the heparin concentration of the near-tip region. Heparin not located in the near-tip region is shielded from the bulk hemodynamic motion, and, following the early-leakage phase, no convective mass flux of locking solution occurs upstream of the side holes in the catheter lumen. In the late stage, convective forces will continue to cycle fluid (blood) external to the catheter into and out-of the near-tip region of the lumens. In vivo this blood will mix with the locking solution from the upstream regions of the catheter where concentrations remain high only through diffusive flux, as the Reynolds number of the flow

inside the catheter is extremely small ($Re < 1$) and no recirculation or vortices can be forced by the pulsatility in this close-ended region of the catheter. The experimental diffusion results presented here, consistent with one- dimensional Fickian diffusion theory, show only a 2% loss of the initial locking solution mass over a 24 hour period. While heparin was not used in this experiment, the diffusivity of RhB in water ($D_{RhB} \approx 10^{-}10m^2/s$) is very close to that of heparin in blood, making these results directly relevant to in vivo conditions. Our recent numerical study also calculated diffusion rates for heparin in blood consistent with leakage rates of $\approx 3\%$ over a 48 hour period.

The discrepancy of leakages during the late and early phase is a result of the two distinct flow regimes that exist inside the catheter lumen. Inside the near-tip region, the flow is similar to the surrounding vascular flow - high Re, shear, and the presence of vortical structures (convection dominated). Upstream of the side holes, the flow is characterized by a $Re > 1$, no shear or voritcal structures (diffusion dominated). This results in the near-tip region being rapidly depleted of heparin, while the upstream portion acts as a reservoir of heparin - slowly allowing new heparin to diffuse in the catheter tip where it is rapidly Inside the near-tip region

It has been proposed that a buoyancy force, caused by a density difference between the locking solution and the surrounding blood, drives leakage from the catheter [16]. Blood ($1050kg/m^3$) is a heavier fluid than the heparin/saline mixture ($1010kg/m^3$) and buoyancy-driven motion would occur if blood were placed above the heparin/saline mix-ture. If the patient is in an upright position , however, the lighter locking solution typically rests above the surrounding, heavier blood, a state that would not result in buoyancy- driven instability and mixing. Two in vitro late-phase studies report high losses when the locking solution is more dense than the surrounding fluid, an unrealistic representation of in vivo conditions for large parts of the patients day [16, 17]. One of these studies [16], however, reports that when a lighter fluid is instilled into the catheter and the density gra- dient matches in vivo conditions, fluid motion inside the catheter lumen is suppressed and late-

stage losses are negligible. As discussed earlier, heparin/saline locking solution is less dense than blood and, in a patient's upright position, buoyancy forces will suppress, not induce, instability and mixing of the locking solution. This is not to say that bouyancy forces do not cause heparin leakage as there are instances when the catheter becomes inverted and density gradient would cause flow instabilities and leakage. The experiments reported on here, however, use a locking fluid with the same density as the surrounding fluid. The results suggest that regardless of the locking fluid density or patient orientation, convective and diffusive transport will act to remove the locking solution from the catheter lumen.

A previous in vivo study estimated late phase leakage rates to be as high as 10-15% of the initial locking solution mass [13]. The discrepancy with our findings is likely due to anatomical motion not captured in this in vitro study. A catheter may be caused to shift or move due to patients normal daily routine, enhancing locking solution mass transfer. Buoyancy driven motion that arises when the patient is lying down may also contribute to additional losses not captured in our experiment.

The use of heparin in catheter locking is based on the assumption that the concentration in the near-tip region is approximately equal to that of the instilled locking solution during the interdialyitic period, thus preventing thrombosis. The results presented here, however, suggest that convective fluxes act to rapidly deplete the concentration of locking solution from the near-tip region, replacing it with a very low concentration of locking solution in blood. Diffusive fluxes can only bring more locking fluid into the near-tip region, while convection will keep flushing the diffused heparin away from the catheter. Thus, the concentration of heparin that remains in the near-tip region over long time periods will be negligible, in comparison to the instilled concentration. It was estimated that, following the early-phase leakage, the ratio of near-tip region concentration to instilled concentration can be as low as 1:1,000[18]. This estimate does not suggest that an increase in initial concentration would result in higher tip concentration for the duration of the interdialytic period. As discussed earlier, regardless of locking fluid concentration,

convective fluxes will still deplete the catheter tip volume of locking fluid, and higher initial locking fluid concentration would only result in higher systemic heparinization.

This study was motivated by the use of heparin/saline solutions as catheter locking fluid due the adverse systemic risks that are placed on patients. While care can be taken to reduce locking solution losses during instillation, the results presented here suggest that convective fluxes will always deplete the near-tip region of locking fluid, rendering the heparin locking procedure ineffective.

4.1 Limitations

We are aware of a number of limitations in this study. The velocity field that is used in equation 3 to calculate the mass flux of RhB is the axisymmetric Womersley solution. However, the catheter is free-floating in the test section and causes small azimuthal and radial velocity components to develop downstream of the catheter. These non-streamwise velocity components act to make the velocity profile asymmetric.

While the use of pulsatile flow conditions creates a hemodynamic environment that is closer to in vivo conditions than previous in vitro studies [15, 17], many idealizations are still present in this study. The test section into which the catheter is placed is straight and hence, asymmetries created in the velocity field by vessel curvature are not captured in our experiment. Also the catheter motion is only caused by the pulsating flow, and so the daily motion of a patient is not accounted for. Patient to patient variability in vessel diameter, geometry and catheter placement are also not considered.

Furthermore, in the pulsatile and diffusive experiemnts a single, although different, catheter type was used in each experiment. A more thorough study would be needed to investigate convective and diffusive mass transfer rates from catheters of different geometries and placement of side holes. Of particular interest would to study catheters designed without side holes as they may be less susceptible to convective fluxes. This information would aid physicians in catheter selection with the goal of minimizing risks to the patient,

as well as determine whether or not new catheter designs have minimized the leakage process.

The results and conclusions presented here are drawn from experimental conditions designed to match flow in a pediatric SVC. We acknowledge that a catheter placed in a different location, such as the atrium or brachiacephalic vein, would be subject to different flow conditions resulting in different loss rates. However, due to the disparate time scales of convection and diffusion, the orders of magnitude of locking fluid losses would not change.

5 Conclusion

The influence of pulsatile flow on locking solution losses from central venous dialysis catheters is investigated using a pulsatile flow loop and PLIF measurement techniques. Previous in vitro studies have used static flow environments to study locking fluid leakage rates but none consider the dynamic environment that the catheters experience in vivo. We find that the heparin leakage process occurs in two separate phases. During the early phase, which lasts < 10 s, significant locking fluid losses occur and the near-tip region is rapidly depleted of heparin. In agreement with previous studies, instillation is responsible for significant leakage during this phase - about 25-30% of the total lock. However, we find that an additional mechanism, convective transport, further depletes the catheter by $\approx 10\%$ of the initial locking solution mass, a percentage corresponding to the lumen volume between the most upstream side hole and the tip. Convective transport of locking fluid by the surrounding flow occurs regardless of instillation losses and buoyancy forces. During the second phase of the leakage process, heparin from inside the catheter lumen slowly diffuses into the near-tip region, but is immediately transported away from the catheter by the blood-driven convective fluxes. Due to the low diffusivity of heparin, the losses in the late phase are small and amount to $\approx 2\%$ mass loss over a 24 hr. period.

Based on the volume of the near-tip region and mass losses due to convection, our results suggest that convective fluxes will deplete the entire near-tip region of heparin. Diffusive fluxes are too slow to transport a significant amount of heparin into the catheter tip to replenish its concentration in this region, and any heparin that does make it into the near-tip region will be transported into the SVC by convective flux. Hence, the concentration of heparin at the catheter tip for the majority of the interdialytic cycle is orders of magnitude lower than the instilled concentration. This leads us to believe that the heparin locking procedure is likely ineffective at preventing thrombosis at the tip of a CVC. We propose that research efforts should be focused on designing new CVCs that either inherently reduce the likelihood of thrombus formation or are conducive to holding the concentration of locking solution high in areas susceptible to thrombosis. The hemodynamic environment that CVCs are subjected to is crucial to understanding the leakage process and must be considered in the design of new catheters.

6 Acknowledgements/Conflict of Interest Statement

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7 Appendix

7.1 Image Calibration

In the instantaneous PLIF configuration the camera is positioned at an off-axis angle, making the recorded images distorted. A calibration, however, allows for the following mapping,

$$x_i = f(X_i) \qquad (5)$$

where every point in the image plane, denoted by subscript i and defined by coordinates X_i is uniquely mapped onto a point in the object plane, x_i by the mapping function f.

Here a second order mapping function, proposed by Westerwall and van Oord [33], is employed,

$$x = a_1X^2 + a_2Y^2 + a_3XY + a_4X + a_5Y + a_6$$

$$y = b_1X^2 + b_2Y^2 + b_3XY + b_4X + b_5Y + b_6$$

The coefficients a_j and b_j of the mapping function f, with $j = 1 - 6$, can be found using a least squared solution to the linear equations,

$$\mathbf{A}a_j = x_i \;\&\; \mathbf{B}b_j = y_i$$

where

$$A = B = \begin{bmatrix} X_1^2 & Y_1^2 & X_1Y_1 & X_1 & Y_1 & 1 \\ X_2^2 & Y_2^2 & X_2Y_2 & X_2 & Y_2 & 1 \\ \vdots & \vdots & \vdots & \vdots & \vdots & \vdots \\ X_n^2 & Y_n^2 & X_nY_n & X_n & Y_n & 1 \end{bmatrix}$$

The calibration process involves placing a target image, with ticks or marks placed at known locations, into the test section at the location of the laser plane. The physical locations of the marks on the target image define the points X_i and the corresponding

locations in the image define x_i. The image locations, x_i are originally defined in units of pixels but are converted SI units by imaging a scale through the use of ruler. With the locations, X_i and x_i known, equations can be solved and the mapping function is known.

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Figure Legends:

Figure 1: Pulsatile flow loop diagram with instantaneous PLIF camera configuration. The catheter is introduced through the side of the test section so that it rests inside the model vessel, nearly at the centerline, parallel to the direction of the flow.

Figure 2: RhB concentration (ppm) as a function of greyscale intensity

Figure 3: 3a) Stream-wise velocity calculated from PIV data (red) and Womersley solution (blue) across a radial slice of the test section. Each plot of taken from a different temporal slice. 3b) Mean stream-wise velocity vs non-dimensional time

Figure 4: Percentage of Rhod. B conentration that has leaked from a Hemocath 8 Fr, single-body dialysis catheter vs. time. The catheter is placed in static fluid, indicating leakage due to diffusion.

Figure 5: Concentration and Mass Flux of RhB three diameters downstream of a 10 Fr. Ash-split catheter tip a function of time. Catheter is places inside a pulsatile flow loop.

Figure 6: Percentage of initial RhB mass lost during each cardiac cycle. Period, T, equals 1.11 s.

Figure 1.

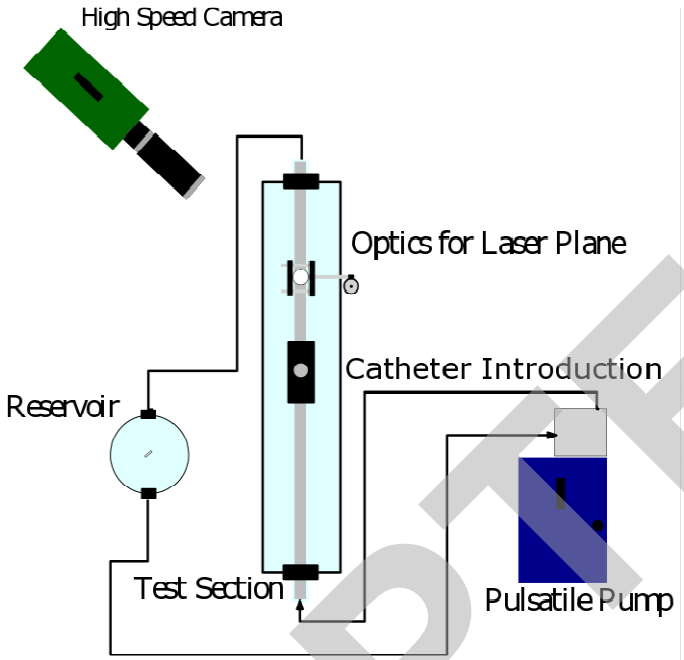


Figure 2.

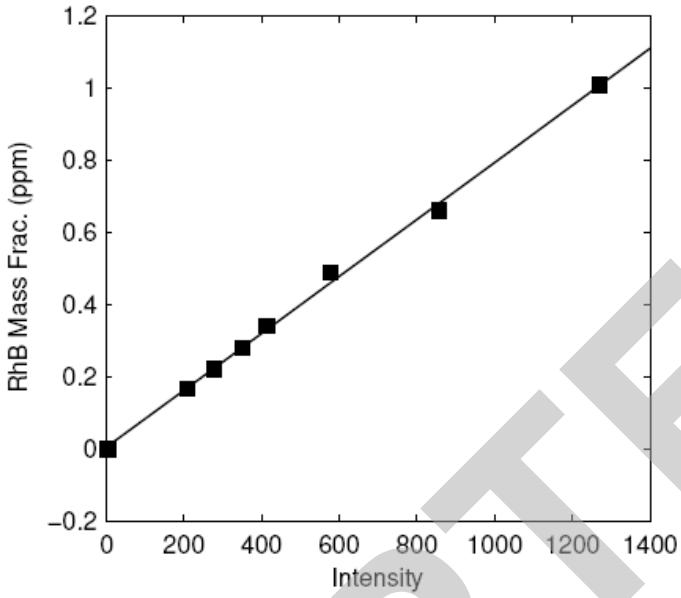
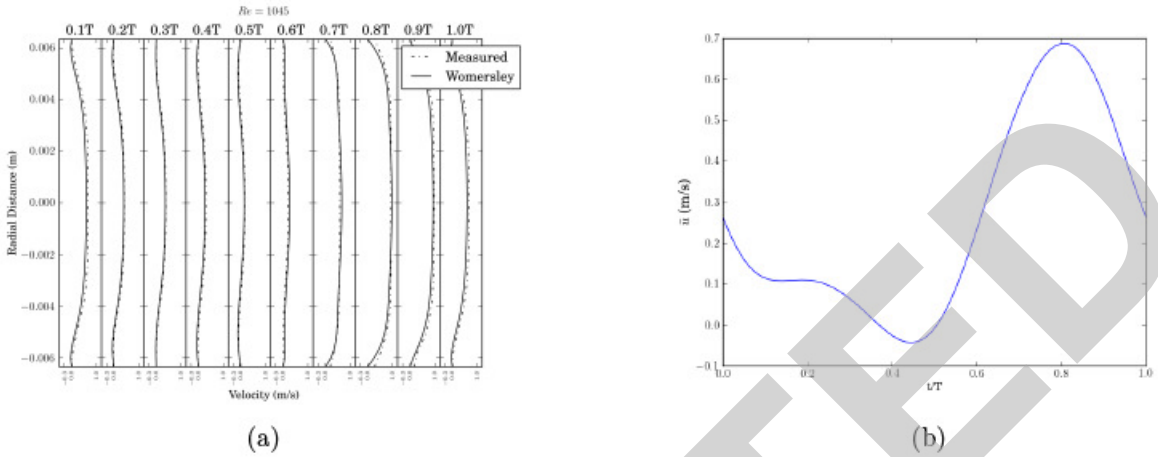


Figure 3.



(a) (b)

Figure 4.

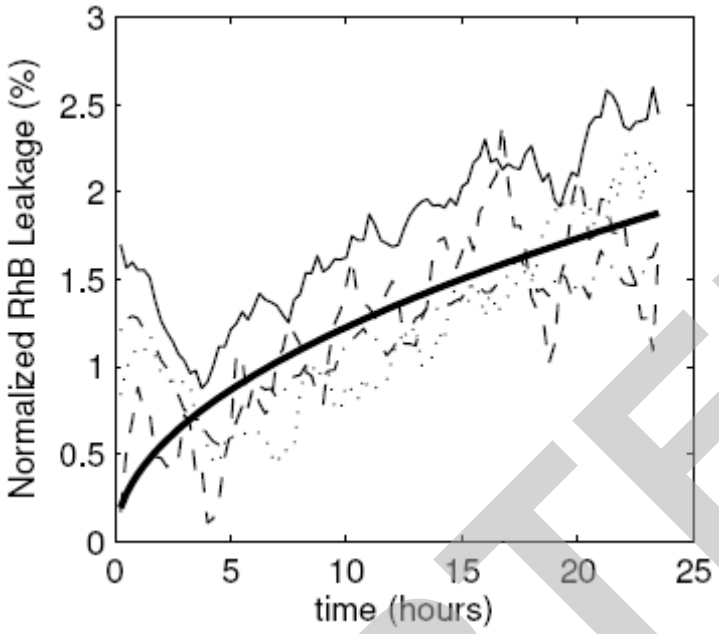


Figure 5.

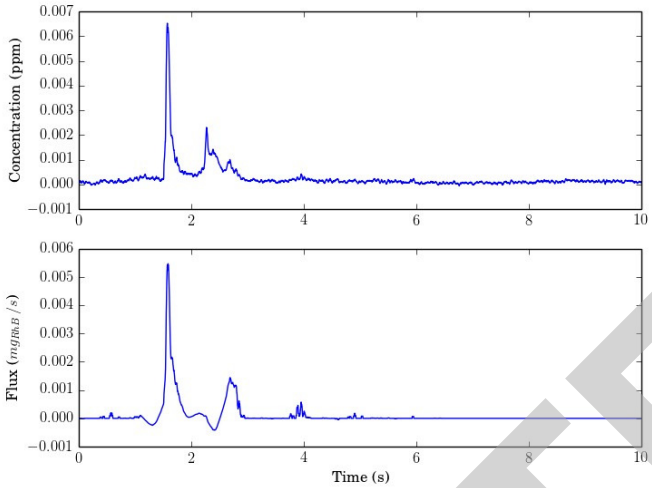


Figure 6.

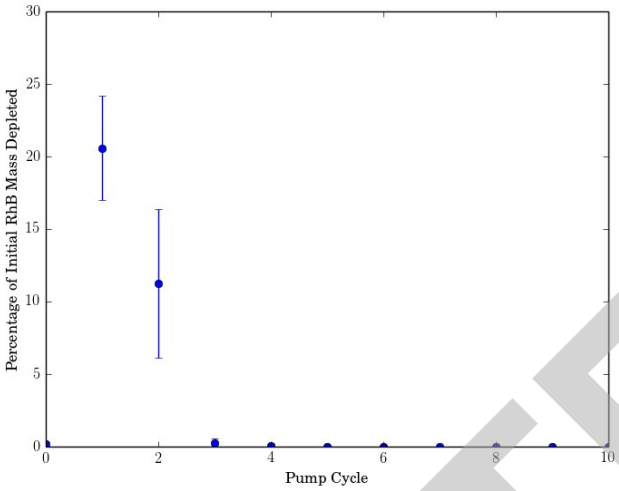


Table 1: Percentage of initial CVC RhB mass lost

	Mean	Std.	N
Instillation Only	28.16	3.5	10
Pump on 10 sec.	42.96	6.63	10
Pump on 60 sec.	43.9	4.1	10

Table 2: Statistical Tests: p-value

	T-Test	Wilcoxon Rank-Sum
Pure Instillation vs. Pump on: 10 sec.	< 0.01	< 0.01
Pump on: 10 sec. vs 60 sec.	.723	.596