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MEASURING LINE PRESSURE IN CONVECTION-ENHANCED DELIVERY INFUSIONS

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Abstract

Convection-Enhanced Delivery (CED) is an investigative treatment for brain tumors. Reflux has been shown to be a key issue in the success of CED treatments. Minimal research has been conducted to determine the onset of reflux. Furthermore, the ability to identify reflux allows for corrective action to be taken before the consequences of reflux renders the treatment unsuccessful. Reflux could be quickly identified by changes in pressure measured in the catheter. In this study we examine the difficulties associated with measuring inline pressure. Results indicate the measured inline pressure will change depending on catheter length and orientation. Therefore, relative changes in pressure coupled with early treatment imaging could be utilized to determine the success of CED treatment.

Keywords: convection-enhanced delivery; microneedles; reflux; glioblastoma; pressure sensing

NOMENCLATURE

P_i	pressure at *i*
ρ	density
α_i	kinetic energy coefficient at *i*
$\overline{V}_i$	average velocity at *i*
g	acceleration due to gravity
h	catheter height
h_{lT}	total head loss
μ	kinematic viscosity
Q	volumetric flow rate
D_i	diameter at *i*

1. INTRODUCTION

Convection-Enhanced Delivery (CED) is an investigative drug delivery framework which utilizes a small diameter catheter placed directly into the brain to locally deliver therapeutics with pressure-driven flow [1]. One primary advantage of CED is its inherent ability to bypass the blood-brain barrier, giving it a marked advantage over systemically delivered therapeutics for the treatment of the highly aggressive brain tumor, glioblastoma. While CED treatment of glioblastoma was popular in pre-clinical environments, the only Phase III clinical trial (PRECISE) failed to demonstrate the benefit of CED over traditional therapies [2]. A retrospective study suggested that insufficient drug delivery may have been a key factor in the trial's failure [3]. Reflux of the infusate along the needle tract appears to be one cause of poor drug delivery volumes with CED [4]. Kruaze *et al.* proposed the first reflux arresting catheter which appears to ameliorate this concern through the addition of a step change at the tip of the catheter [5]. While preventing reflux with catheter geometry seems advantageous, there may be benefit in sensing if reflux is occurring, as this could allow for higher, patient specific flow rates of therapeutics just below the rate that would cause backflow to occur. Lewis *et al.* has shown that if reflux is identified early, its effects can be mitigated by reducing the flow rate of the infusate [6]. One method that could be used to sense the initiation of reflux is through the continuous monitoring of infusion line pressure. A drop in infusion line pressure may indicate the beginning of reflux. In the present study, we detail the challenges of accurately measuring infusion pressure in CED infusions.

2. MATERIALS AND METHODS

2.1 Experimental Setup

Two catheters were manufactured by adhering a glass capillary tube (ID 150 µm, OD 360 µm, LTSP150375, Polymicro Technologies, Phoenix, AZ) inside of a 22 G needle with a Luer lock connector. Total catheter lengths were 10 cm and 40 cm. The entry port of the catheters were connected to a t-couple with one arm of the t-couple attached to a pressure sensor (26PCBFA6G, Honeywell, Golden Valley, MN), P_1, and the other arm connected to a 3 m extension tube attached to another t-connector with one end of the connector connected to a second pressure sensor, P_2, and the other end of the connector attached to a 3 mL syringe. The syringe was driven by a syringe pump (Chemyx Fusion 100, Chemyx, Austin, TX), as shown in **Figure 1**. Infusions of deionized water were conducted at 0, 1, and 50

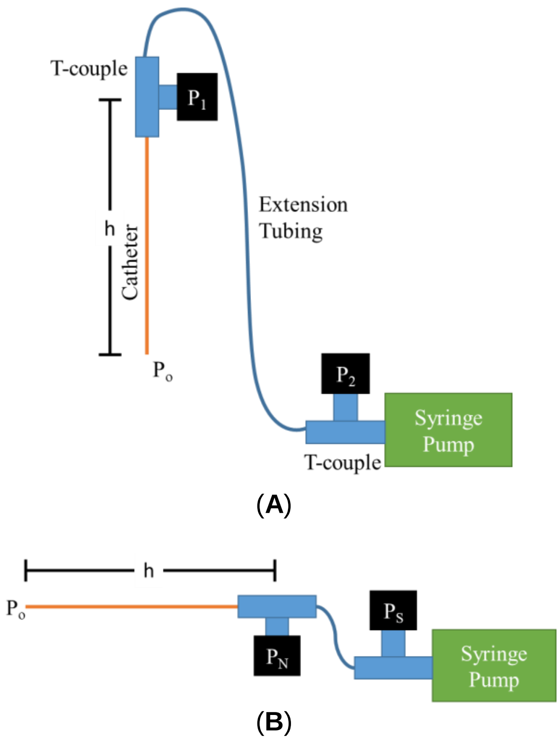

FIGURE 1: **A**) VERTICAL EXPERIMENTAL SCHEMATIC AND **B**) HORIZONTAL EXPERIMENTAL SETUP WITH P_1 AND P_2 REPRESENTING PRESSURE SENSORS 1 AND 2 RESPECTIVELY AND P_O REPRESENTING THE OUTLET PRESSURE OF AN INFUSION.

µL/min to compare the measured pressure of each catheter with the catheter oriented vertically (**Figure 1A**) and horizontally (**Figure 1B**). When the catheters were in the vertical position, the syringe pump as well as P_2 were oriented such that they were below the outlet of the catheter and when the catheters were horizontal, P_2 was oriented at the same approximate height as the outlet of the catheter. Infusions at each flow rate and catheter orientation were conducted for a 10 minute period, with catheter tip submerged in water (~ 1 mm) in order to prevent any pressure artifacts that may occur as water droplets fall off of the catheter. Pressure readings were measured at 1.613 kHz in LabView (National Instruments, Austin, TX) and the mean pressure of every 1000 samples was written to a file in order to reduce file size during experiments. The corresponding file was read into MATLAB (R2018a, MathWorks Inc., Natick, MA), then the time at which pressure stabilized was manually determined. Finally, pressure was averaged over the stable pressure span.

2.2 Theoretical Pressure in Catheter

Using the schematic shown in **Figure 1**, we can estimate the change in pressure from P_1 to P_o using the conservation of energy, the reduced form of which is shown in **Equation 1**.

$$\left(\frac{P_1}{\rho}+\alpha_1\frac{\bar{V}_1^2}{2}+gh\right)-\left(\frac{P_o}{\rho}+\alpha_2\frac{\bar{V}_2^2}{2}\right)=h_{lT} \qquad (1)$$

Where ρ is the density of water, α_i is the kinetic energy coefficient at i, $\bar{V}_i=\frac{Q}{A_i}$ is the average velocity of the fluid at i with volumetric flow rate Q and cross-sectional area A, g is the acceleration due to gravity, h is the distance from P_1 to the outlet, and h_{lT} is the total head loss in the catheter. The flow in the catheter at both 1 and 50 µL/min is laminar (Re = 9.5 and 475 respectively) therefore, $\alpha_1 = \alpha_2 = 2.0$. The total head loss is the sum of all head losses in the system, assuming the minor head losses are negligible, h_{lT} can be calculated as just the major head loss. The major head loss for laminar flow can be calculated using **Equation 2**.

$$h_{lT}=h_l=\frac{128\mu hQ}{\pi D_2^4} \qquad (2)$$

Where μ is the dynamic viscosity and D_2 is the diameter of the catheter. **Table 1** shows the parameter values used to estimate P_1.

TABLE 1: CATHETER MEASUREMENTS

Parameter	**Value**
Density of water at 25°C (ρ)	0.997 g/cm^3
Height of the catheter (h)	10 and 40 cm
Outlet pressure (P_o)	0 mmHg
Catheter internal diameter (D_2)	0.015 cm
T-connector internal diameter (D_1)	0.2 cm
Dynamic viscosity of water at 25°C (μ)	0.889 cP
Volumetric Flow Rate (Q)	0, 1, and 50 µL/min

3. RESULTS AND DISCUSSION

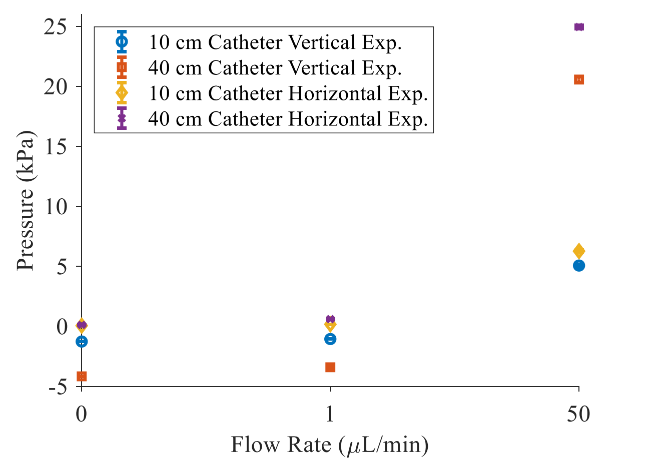

FIGURE 2: AVERAGE PRESSURE READINGS (P1) FOR THE 10 CM AND 40 CM CATHETERS POSITIONED BOTH VERTICALLY AND HORIZONTALLY, WITH INFUSION FLOW RATES OF 0, 1, AND 50 µL/MIN.

An average of 766 ± 107 pressure measurements were collected for each experimental group. As shown in **Figure 2**, pressure readings vary between the horizontal and vertical catheter arrangements as well as between catheter lengths. This is likely the result of the needle length acting as a water column, which serves to reduce the pressure measured in the catheter as gravitational force is playing a role in creating the flow of the water out of the catheter. Interestingly, this gravitational force results in a larger pressure than would ordinarily be required to create a 1µL/min flow rate for both the 10 cm and the 40 cm long catheters. In this case the syringe pump serves to slow the natural rate of infusion. However, at the 50 µL/min flow rate, the gravitational force is not enough and the pump serves to increase pressure to create the desired flow rate.

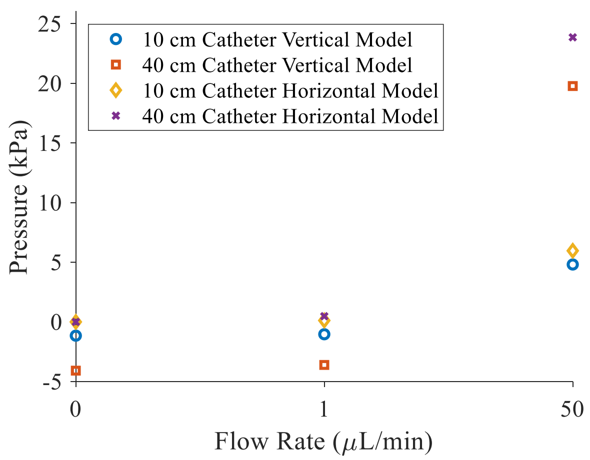

FIGURE 3: THEORETICAL PRESSURE READINGS FOR THE 10 CM AND 40 CM CATHETERS POSITIONED BOTH VERTICALLY AND HORIZONTALLY WITH INFUSION FLOW RATES OF 0, 1, AND 50 µL/MIN.

Figure 3 shows the theoretical pressure reading at P_1. The same trend is shown in the model as in the experiment. The difference between the theoretical values and the experimentally obtained values were near the expected repeatability of the pressure sensors with the exception of the horizontal and vertical 40 cm catheter infusing at 50 µL/min. In both cases, the theoretical value predicted a lower expected pressure value. This could be the result of neglecting minor head losses, the impact of which would be most prominent in the longer needle infusing at a high flow rate. Nonetheless, this simple model is reasonably accurate at predicting the expected pressure of low flow rate infusions which are most common in CED treatments.

Since catheter orientation is not always perfectly vertical and can vary depending on the optimal catheter trajectory for any given patient, it should be expected that measured inline catheter pressure will also vary from treatment to treatment. Due to this, it is unlikely that a single pressure measurement location can be used to determine if reflux is occurring during a CED infusion. Instead, either MR or CT imaging at the beginning stages of an infusion should be used to ensure the treatment is successful. Once baseline images prove reflux is not occurring, relative changes in pressure should be recorded in order to determine if adverse events begin at later stages of the infusion. This would allow for both the determination of the baseline, no reflux infusion line pressure and the ability to identify and react to reflux if it begins during the infusion.

4. CONCLUSION

The measurement of fluid line pressure during CED treatment may be useful in monitoring the presence of reflux. However, many variables such as catheter length and orientation will have an impact on the measured pressure and therefore, proper characterization and pressure correction should occur if it is to become a trusted metric for infusion success. If this can be achieved, true real time monitoring of CED infusions may be possible and the time delays associated with image-guided infusions may be avoided.

ACKNOWLEDGEMENTS

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