Real-time monitoring for systematic investigation of catheter design and infusion protocol effect on CED performance

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INTRODUCTION

Convection Enhanced Delivery (CED) is a neurosurgical procedure for delivering agents related to the treatment of cancer and neurodegenerative diseases in the human brain which has been in development for approximately 20 years [1]. A disparate ensemble of infusion catheters, infusion flow rates, and techniques has been employed in an attempt to predict and control the ultimate infusion distribution while minimizing unwanted loss of infusate through a low pressure escape route along the exterior of the catheter, termed "backflow". MRI guidance and monitoring with application-specific catheters and infusion protocols have proven beneficial [2, 3]. However, the field would benefit from a generalizable understanding on how several variables within catheter design and infusion protocols influence the eventual drug distribution. We present an ongoing effort using real-time device manipulation and real-time MR monitoring to undertake a systematic study of the multiple variables utilized today to mitigate unwanted backflow.

MATERIALS AND METHODS

Our ongoing overall study investigates how backflow can be mitigated through catheter diameter, tip design, infusion initialization, maximum flow rates, and transition to maximum flow rates. Backflow alters the initial drug delivery point from the catheter tip, which produces a desired spherical drug distribution, to a variable length line, which produces a varied cylindrical drug distribution.

Infusions were targeted and delivered *in vivo* to gray matter regions in the thalamus of an adolescent pig. The swine model was selected as it is sufficiently similar to humans for our purposes without having the cost and complication of a non-human primate model. In each animal we perform up to four infusions, two in each hemisphere, including both control and test settings for the experimental variable in question.

Rapid device targeting and insertion is performed via prospective stereotaxy [4], accelerated with an in-house developed software plug-in that enables real-time device manipulation [5].We have conducted infusion experiments on 10 animals using quantitative high-resolution, 3D monitoring during the infusion (5 min acquisition/frame) to accurately record the final infusate distribution. Recently we have begun using rapid 2D single-plane monitoring during the infusion with the catheter tract in plane (13s acquisition) to reveal time-resolved characteristics associated with possible backflow. This localized monitoring has been performed on 6 animals to date.

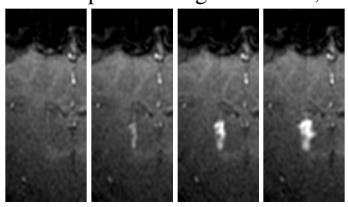

Figure 1: Temporal progression of significant backflow at t=0, 30, 150, 300 seconds, left to right, with constant flow rate. Catheter tip is located at the lower end of the hyperintense region and extends upward. Backflow height along the catheter tract is established early in the infusion, while additional infused volume spreads radially from the catheter.

Gradually ramping flow rate from a low to maximum flow rate is generally considered to mitigate backflow relative to starting the infusion immediately at the maximum flow rate. We report here specifically on a test of this hypothesis by ramping from 1 μL/min to 5 μL/min in 1 μL/min increments every 5 minutes versus a control at constant 5 μL/min. Each infusion consisted of 2mM gadodiamide suspension delivered via a stepped-tip, end-port, fused-silica catheter.

RESULTS AND DISCUSSION

Implementing prospective stereotaxy with real-time device manipulation allows us to perform trajectory alignment in approximately 1-2 minutes, and perform an entire infusion from initial target identification to retrospective 3D imaging of infusion results in approximately 1 hour. Our real-time MRI system enabled rapid performance of each experiment while providing either dynamic time-resolved 2D images of infusion progression or 3D volumetric images of final infusion morphology. The inclusion of rapid imaging for monitoring enables us to visualize time-dependent aspects of infusate propagation that are not visible with slower, volumetric imaging.

In comparison to constant flow (control), ramped infusions showed no less likelihood of backflow. Flow rate determined height of backflow along the catheter, independent of the ramping process (fig. 2). The use of 2D real-time imaging along the catheter indicates that backflow occurs at its full length within the first few seconds of an infusion (fig. 1). Previously it was believed to occur gradually. After the initial increase in backflow height, the remaining infused volume increases the radius of the infusion cloud, but not the height.

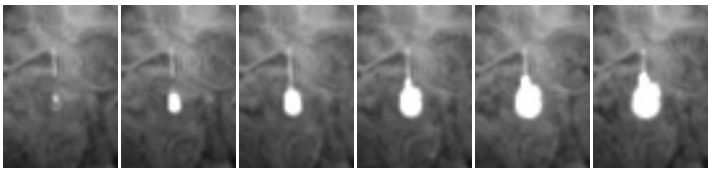

Figure 2: Temporal progression of ramped flow rate infusion, with flow rates pictured of 1, 2, 3, 4, 5 μL/min and end of infusion, from left to right. Infusion morphology begins as the desired, roughly spherical distribution at low flow rates then transitions to significant backflow at higher flow rates.

While adding MRI to *in vivo* investigation of the physics of infusion has brought new insight, controlled evaluation of CED procedures has been time consuming. By conducting our experiments in a porcine model, we can systematically obtain significant amounts of data without excessive personnel and time requirements. Many of these experiments were conducted with as few as 3 people present (2 MRI operators and one veterinary care specialist). With the addition of an in-room monitor to guide real-time trajectory alignment, the experiment would only require only one MRI operator.

CONCLUSION

The combination of ease and speed of operation of the trajectory guidance system, the availability of time-resolved imaging *in vivo* during the infusion, and low overhead requirements has enabled us to undertake a systematic investigation of many factors of infusion design that may influence the occurrence of backflow. This study has developed new insight into the nature of backflow, allowing better control of the ultimate drug distribution.

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