Backflow variability shows importance of MR monitoring of CED infusions

Ethan K. Brodsky[1,2], Benjamin Grabow[1], Martin L. Brady[3], Raghu Raghavan[3], Chris D. Ross[4], and Walter F. Block[1,2]

[1]Medical Physics, University of Wisconsin, Madison, WI, United States, [2]Biomedical Engineering, University of Wisconsin, Madison, WI, United States, [3]Therataxis, LLC, Baltimore, MD, United States, [4]Engineering Resources Group, Inc., Pembroke Pines, FL, United States
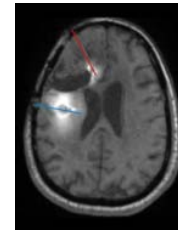
TARGET AUDIENCE

This work will appeal to those interested in MR-guided interventional procedures, particularly in the neurological field.

PURPOSE

Convection-enhanced delivery (CED) is a neurosurgical procedure for delivering large molecular and viral vectors related to the treatment of cancer and neurodegenerative diseases in the brain which has been in development for approximately 20 years [1]. Typically these procedures are guided stereotactically using pre-operative MR. However, the resulting drug distribution can be highly variable due to uncertainties of delivering agents under pressure into the highly heterogenous brain, as illustrated in Fig. 1 where two identical infusion protocols generated quite different distributions [1]. We have completed a comprehensive study on the use of real-time MR monitoring to unravel often conflicting recommendations in the field of CED on the design of infusion catheters, flow rates, and other techniques to minimize variance in drug distribution. Specifically, we present here results regarding an investigation to minimize variations in drug distribution due to unwanted loss of infusate through a low pressure escape route along the exterior of the catheter, termed "backflow".

MATERIALS AND METHODS

We performed 2-4 infusions into the brains of 31 porcine subjects, typically targeting the deep basal ganglia and avoiding vascular and white matter structures that might alter distribution. Each infusion was performed with MRI guidance in a GE Healthcare MR750 3.0 T scanner (GE Healthcare; Waukesha, WI), using an in-house targeting and monitoring system [2, 3]. The interventional hardware was based on the Navigus aiming system (Medtronic, Inc.; Minneapolis, MN), which consists of a base assembly with a ball-joint pivot, an MR-visible external trajectory guide, and a remote introducer

Figure 1: Two identical infusion catheters and infusion protocols (shown in red and blue) led to substantially different drug distributions in these images from a chemotherapy trial, demonstrating the value of real-time MR monitoring.

assembly. Several catheters were tested, including FDA-approved 14 and 16 gauge SmartFlow catheters (MRI Interventions; Memphis, TN) and investigational valve-tip catheters (Engineering Resources Group; Hialeah, FL). Infusions of 5-60 µl were conducted at rates varying from 1-10 µl/min, using a PHD 22/2000 infusion pump (Harvard Apparatus; Holliston, MA) and real-time pressure monitoring system (ERG). For each animal, the target points were identified the day of the study using a 3D IR-SPGR scan. Real-time imaging was used to identify and mark a point on the skull conducive to reaching these targets. The animal was then removed from the scanner and a bilateral craniotomy was performed, with Navigus bases installed on each these. The animal was then returned to the scanner and the targeting, insertion, and infusion procedure was performed.

RESULTS AND DISCUSSION

While backflow from a simple endport catheter has been believed to increase with catheter radius in a predictable way [4] and more complicated stepped designs (narrowing at the tip) have been proposed to reduce backflow [5], it is difficult to predict how various designs will behave compared to one another. For the SmartFlow catheters, the 16G shaft had lower average backflow than the thicker 14G version. This reached statistical significance at 2.5 µl/min (p=0.040) and just missed at 5.0 µl/min (p=0.051). However, it should be noted that 6/8 of the 14G infusions reached a CSF boundary at 5.0 µl/min, putting an upper limit on their backflow distance. The remaining two reached CSF at 7.5 µl/min. In contrast, none of the 16G infusions reached CSF at 5.0 µl/min and only two did at 7.5 µl/min. In every case, the backflow was observed to reach at least to the catheter step - for the 16G catheters, backflow distances were clustered around the step, while most of the 14G infusions showed backflow reach past the step. While the differences between catheters are statistically significant for large enough trials, it should be noted that substantially larger variations are seen from experiment to experiment with a single catheter. In every case, the backflow was observed to reach at least to the catheter step, 3 mm from the tip. It cannot be said whether the variation is due to differences in shaft diameter, tip diameter, or step length. Testing of three catheters with step sizes of 0.11, 0.15, and 0.21 mm showed that mean backflow increased monotonically with decreasing step size, though experimental variation masked this effect for all except the smallest step.
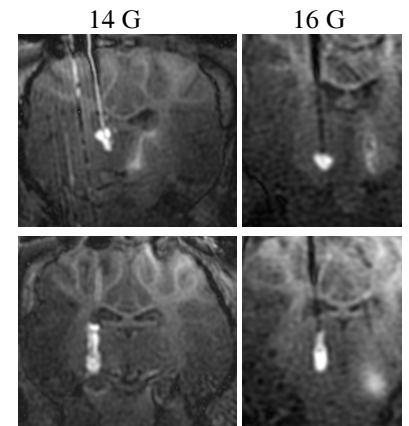
14 G   16 G

Figure 2: Substantial experimental variation is seen even with a single catheter. The left and right image pairs were created with identical SmartFlow catheters and infusion protocols. Note that significantly increased backflow in the lower images.

CONCLUSION AND FUTURE WORK

A major observation from this work is that there is a great deal of experimental variation in observed backflow that cannot be explained by any variations in methodology. Without infusion monitoring with MR or another contrast tracer, it is impossible to know where the infusate was actually delivered. This variation can lead to a great deal of confusion when trying to replicate reports from successful studies with limited sample size. It is also of concern for anyone conducting expensive drug trials, as without infusion monitoring, it is difficult to say whether a drug failed because it was ineffective or because it was not actually delivered to the target tissue. An interesting avenue for further research will be to develop an effective response to apply after large backflow is observed in order to salvage a satisfactory distribution.

REFERENCES

[1] Samson JH, et al., J. Neurosurgery 113:301 ('10) [2] Brodsky EK, et al., Proc. IEEE BSEC 3:63 ('11)
[3] Grabow B, et al., Proc. ISMRM 21:4315 ('13) [4] Morrison PF, et al., Am. J. Physiol. 277:R1218 ('99) [5] Krauze MT, et al., J. Neurosurgery 103:923 ('05)