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In vivo performance of a microfabricated catheter for intraparenchymal delivery

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HIGHLIGHTS

- We tested a new type of catheter made with microfabrication techniques.
- Small molecule to virus-sized particles were infused into living porcine brain.
- No backflow was observed along the shaft at flow rates up to 30 μL/min.
- The design principles allow future construction of smart catheters with biosensors.

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ABSTRACT

Background: Convection-enhanced delivery (CED) is currently the only effective clinical technique to deliver biological therapeutic agents that would otherwise not cross the blood–brain barrier. Despite the promise of CED, several technical problems have limited its effectiveness.
New method: Brain infusions into a large mammal (pig) were performed with a catheter that was fabricated using micro-electro-mechanical systems (MEMS) technology (Olbricht et al., 2010). The performance of the catheter was evaluated for infusions at increasing infusion rates. Magnetic resonance (MR) images were acquired in real time to examine the distribution of infused tracers in the parenchyma.
Results: Both backflow and the distribution of CED of infusates into a variety of cytoarchitectures in porcine brain were quantified. Concentration profiles were determined for several MR contrast reagents as well as a fluorescent dye that are the sizes of small molecules, therapeutic proteins and an adeno-associated virus (AAV). The reagents can serve as surrogates for assessing the convective distribution of active molecules. Infusion rates up to 20 μL/min were attained without evidence of backflow along the catheter.
Comparison with existing methods: The device performed well in terms of both backflow and infusion, superior to that of many studies reported in the literature on other catheters. All infused molecules had comparable ratios of distribution to infusion volumes.
Conclusions: The catheter described in this report appears able to target tissue structures with precision, deliver therapeutics at high infusion rates, and resist backflow that can compromise the efficacy of CED therapy. The technology allows development of "smart" catheters for future applications.

1. Introduction

Convection enhanced delivery (CED) is an advanced technique used to distribute therapeutic agents into targeted regions of the brain (Bobo et al., 1994; Prabhu et al., 1998). CED involves the direct infusion of compounds into brain parenchyma through a

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catheter implanted in the brain through a hole in the skull. The technique shows promise for treating a variety of neurological disorders, including glioblastoma, epilepsy, and Parkinson's disease. However, practitioners have been continually plagued with unreliable delivery of infused therapeutics, which may have resulted in the failure of pivotal clinical trials (Sampson et al., 2010; Morrison et al., 2007; Salvatore et al., 2006).

In recent years, CED practitioners have focused on the design of new catheters that mitigate or eliminate backflow. Backflow, or reflux, refers to the tendency of infused fluid to flow up the external surface of the catheter instead of flowing into the parenchyma surrounding the catheter. Several innovative designs have been tested, such as catheters consisting of multiple cylindrical tubes in series with stepwise reductions in tube diameter toward the distal tip of the catheter, which have been shown to reduce backflow (Krauze et al., 2005). Another design involves a tube whose wall is porous at the end of the catheter so that fluid is released into the parenchyma along the length of the porous segment instead of release at a single outlet (Oh et al., 2007). These examples and similar designs are fabricated using traditional machining techniques.

An alternative strategy is to use micro-electro-mechanical systems (MEMS) technology to fabricate catheters that contain microfluidic circuits to deliver fluid into tissue. Microfabricated catheters not only can contain the desirable step reductions in diameter to reduce backflow, but also can contain features that are difficult to incorporate using tubes and standard mechanical fabrication. For example, a microfabricated catheter containing multiple microfluidic channels on an insertable silicon shank was used to deliver multiple therapeutics sequentially in rodent studies (Olbricht et al., 2010). The outlets of the channels were recessed from the leading edge of the shank to prevent clogging of the channels by soft tissue when the device was inserted into the brain. Similar microfabrication methods have been used to build a flexible catheter made completely from parylene, a soft polymer (Olbricht et al., 2010). The flexible catheter was coupled to a rigid biodegradable shank for insertion into the rodent brain. Beyond the conformational features demonstrated in these devices, electronic features could be included in a microfabricated device, such as integrated sensors that could provide information about the efficacy of the infusion and measure biochemical or electrical conditions in the surrounding tissue to assess the effectiveness of therapy.

The devices mentioned above were designed for use in rodents, so the microfabricated component was only a few millimeters in length. Scale-up of a microfabricated device to carry out CED in humans is a significant challenge. Although it may be possible to microfabricate a device of sufficient length for use in humans, it may not be necessary, cost-effective, or otherwise advantageous to do so. Instead, the advantageous features described above could be realized by fitting a small microfabricated device to the distal end of a "standard" cannula that is modified to accommodate the microfabricated tip. This is the strategy used in this study to assess the performance of a microfabricated device suitable for use in humans. Here, results are reported for intraparenchymal infusions into the brains of live, anesthetized pigs. The distributions of infused molecules of various sizes are characterized using real-time magnetic resonance imaging (MRI). The primary outcomes of the study are backflow and infusate distribution measurements for CED into a variety of cytoarchitectures.

2. Equipment and materials

The design characteristics of the class of microfabricated devices have been described elsewhere (Olbricht et al., 2010). Fig. 1 shows the microcatheter (Alcyone Lifesciences, Inc., Concord, MA) that is used in this study. The device consists of four parts. The most proximal part (far left in Fig. 1) is the catheter shaft, which is a 1.6-mm diameter tube. A custom-designed transition called the "bullet nose" connects the catheter shaft to a fused silica tube with a length of 4 mm and a diameter of 350 μm. The bullet nose is designed to prevent backflow, and the narrow tube provides additional strength and a backflow stopping step to the microfabricated tip. The tip, which is 7 mm long, is fitted into the fused silica tube so that 3 mm of the tip remains exposed (far right in Fig. 1). The silicon tip narrows to a point at its distal end to ease insertion of the device into the brain. Two parallel microfluidic channels, each having a cross-section of 30 μm × 30 μm (a few of the experiments used a 30 μm × 53 μm section, but the outer dimensions which determine backflow were the same in all cases), are etched into the top of silicon tip. A thin layer of silicon is bonded to the top surface of the tip to cover the microfluidic channels over most of their length. The inset of Fig. 1 shows a magnified view of the tip. The uncovered distal ends of the microfluidic channels, which are visible in the inset, are the channel outlets. The proximal end of each microfluidic channel is connected to a microtube (not visible in the photograph) that resides inside the narrow tube and catheter body. Each microtube is connected to a syringe pump through a standard Luer fitting. Thus, the fluid delivery systems for the two microfluidic channels are completely independent of each other.

The small cross-sectional dimensions of the tip may reduce tissue trauma during insertion and allow more precise therapeutic delivery in smaller cytoarchitectural targets. The independent fluidic channels in the device can be used to deliver two therapeutic compounds or a therapeutic compound and an imaging agent in programmed sequences. The side-facing outlets of the microfluidic channels are intended to diminish the possibility of occlusion by tissue during insertion of the device into the brain. The bullet nose transition between the catheter shaft and the narrow tube and the change in size from narrow tube to the microfabricated tip are designed to help reduce backflow at higher infusion rates.

3. Methods

Infusion experiments were performed at the University of Virginia. The animal use committee at the University of Virginia approved all protocols. The general methods for catheter placement and navigation to target have been described in Brady et al. (2011) and Emborg et al. (2010).

3.1. Animal preparation and catheter navigation and device insertion

On the day of the infusion, each animal had free access to water for 12 h before the experiment. Initial sedation was by intramuscular injection of ketamine (25 mg/kg) and xylazine (1–2 mg/kg). Anesthesia was maintained by inhalation of isoflurane (≈1%) using a ventilator.

Pre-infusion imaging on the anesthetized animal was then performed in a 3 Tesla Clinical MR scanner (Trio, Siemens, Malvern, PA) to characterize the normal brain and plan for the infusions. Among other sequences detailed below, these included a high-resolution 3D T1-weighted FLASH and a 3D MPRAGE to distinguish anatomy. The images were used to plan trajectories on the MRI console workstation based on the targets planned for the animal. The x–y coordinates for skull burr hole placement were measured relative to the inion.

The anesthetized animal was then placed on a surgical table and the scalp in the midline incised and retracted widely. Burr holes were placed bilaterally in the skull at locations determined by the pre-operative planning. A disposable MR-compatible