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In vivo evaluation of needle force and friction stress during insertion at varying insertion speed into the brain

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HIGHLIGHTS

- Friction stress can be evaluated in vivo, in real time, by measuring forces during needle insertion and retraction.
- Faster needle insertion produced less friction stress which matches greater track damage from our previous study.
- Smaller friction stress was measured within white matter regions compared to gray matter regions.

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ABSTRACT

Background: Convection enhanced delivery (CED) infuses drugs directly into brain tissue. Needle insertion is required and results in tissue damage which can promote flowback along the needle track and improper targeting. The goal of this study was to evaluate friction stress (calculated from needle insertion force) as a measure of tissue contact and damage during needle insertion for varying insertion speeds.
New method: Forces and surface dimpling during needle insertion were measured in rat brain in vivo. Needle retraction forces were used to calculate friction stresses. These measures were compared to track damage from a previous study. Differences between brain tissues and soft hydrogels were evaluated for varying insertion speeds: 0.2, 2, and 10 mm/s.
Results: In brain tissue, average insertion force and surface dimpling increased with increasing insertion speed. Average friction stress along the needle–tissue interface decreased with insertion speed (from 0.58 ± 0.27 to 0.16 ± 0.08 kPa). Friction stress varied between brain regions: cortex (0.227 ± 0.27 kPa), external capsule (0.222 ± 0.19 kPa), and CPu (0.383 ± 0.30 kPa). Hydrogels exhibited opposite trends for dimpling and friction stress with insertion speed.
Comparison with existing methods: Previously, increasing needle damage with insertion speed has been measured with histological methods. Friction stress appears to decrease with increasing tissue damage and decreasing tissue contact, providing the potential for in vivo and real time evaluation along the needle track.
Conclusion: Force derived friction stress decreased with increasing insertion speed and was smaller within white matter regions. Hydrogels exhibited opposite trends to brain tissue.

1. Introduction

Modern clinical techniques developed to diagnose or treat neurological diseases have come to include the insertion and implantation of devices like needles, probes, and electrodes in affected central nervous system (CNS) tissues. With implantation, surrounding soft brain tissue is mechanically damaged, e.g. torn, stretched, or compressed. Thus, the mechanics of insertion can have a direct effect on the resulting tissue–implant interface. In addition, localized injury such as edema, hemorrhage, and glial reaction is introduced (Edell et al., 1992; Manaenko et al., 2011; White et al., 2011; Xue and Del Bigio, 2003). In this study, we are focusing on convection-enhanced delivery (CED) which is one of few local drug delivery methods that bypass the blood brain barrier (BBB) and

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provides large distribution volumes for macromolecular agents. It is an infusion-based method in which a cannula or needle is surgically implanted and infusate is pumped directly into CNS tissues to enhance extracellular transport (Bobo et al., 1994). For controlled flow rates, this procedure has been conducted without side effects or histological evidence of major tissue damage (Degen et al., 2003). However, localized tissue damage changes tissue-infusate interactions around the needle and this can influence drug targeting, e.g. the extent of infusate that flows back along the needle track (backflow) (Chen et al., 1999; Raghavan et al., 2006). Therefore, insertion tissue damage may limit the potential of CED treatment and new methods to evaluate insertion events in real time are needed.

The extent of brain tissue damage is dependent on the mechanics of the needle insertion. Needle force measurement is a useful tool to evaluate tissue response to deformation and damage as a function of insertion depth and speed (Andrei et al., 2012; Peidong et al., 2012; van Gerwen et al., 2012; Welkenhuysen et al., 2011). High insertion forces are generally associated with a larger extent of tissue damage across tissue types (Mahvash and Dupont, 2010; Peidong et al., 2012; van Gerwen et al., 2012). Therefore, monitoring of insertion force may be a simple way to evaluate the influence of insertion parameters on damage in vivo and in real time. In brain tissue, increased insertion force has been previously observed with high speed insertion of neural probes (Andrei et al., 2012). Also with needle insertion, the surface of the brain is primarily displaced downward in the axial direction before surface puncture. This surface dimpling (surface deformation before puncture) introduces large deformations of tissue under the needle tip (DiMaio and Salcudean, 2003) and corresponding stored energy is released with puncture. Therefore, tissue dimpling may also predict the extent of tissue damage introduced with implantation. Previous electrode insertion studies have found surface dimpling to increase with increasing insertion speeds (Andrei et al., 2012).

Insertion factors like needle diameter, needle tip geometry and insertion speed affect tissue damage and insertion force (Alterovitz et al., 2003; Peidong et al., 2012). Relatively few studies have looked at how insertion speed affects local tissue damage in CNS (Polikov et al., 2005). Previous ex vivo electrode insertion studies by Bjornsson et al. show less vasculature rupture at higher insertion speeds which suggests less tissue damage with increasing insertion speed (Bjornsson et al., 2006). Other electrode insertion studies find greater insertion force and increasing tissue deformations for a higher speed (0.1 mm/s) in comparison with lower insertion speed (0.05 and 0.01 mm/s) suggesting greater tissue damage for fast insertion (Andrei et al., 2012). In contrast, electrodes inserted at slower speeds have shown better performance, which is thought to be due in part to less initial tissue damage (Nicolelis et al., 2003).

In previous studies by our group, the influence of needle insertion speed on tissue damage and local tissue stresses was evaluated in a tissue phantom material and in rat brain (Casanova et al., 2012, 2014). Holes left in tissue slices were used to evaluate damage and corresponding changes in the compressive radial stress at the needle–tissue interface (pre-stress) for varying insertion speeds. Pre-stress provided a spatially-varying measure of tissue compression at the needle interface. Tissue damage increased while pre-stress decreased for increasing insertion speed. Under the same conditions, the effect of needle insertion speed on damage and CED backflow in hydrogels (Casanova et al., 2012) was found to be opposite that in brain tissue (Casanova et al., 2014). Local tissue swelling also increased pre-stress with time. Therefore, to better characterize the influence of needle insertion speed on acute tissue damage, pre-stress or an equivalent measure should be evaluated during in vivo insertion.

Brain tissue is heterogeneous. Therefore, mechanical response and acute tissue damage are influenced by differences in tissue composition in different regions along the needle pathway, e.g. gray matter vs. white matter regions (Elkin et al., 2011; Lee et al., 2014). In our previous study (Casanova et al., 2014), we found that the heterogeneity of brain tissue affected tissue damage and interfacial pre-stresses. Greater damage (larger holes) and smaller pre-stresses were found in white matter regions compared to gray matter regions, possibly due to pre-existing tensile residual stresses in white matter regions (Xu et al., 2009). During insertion, needle forces, deformation, pre-stresses, and damage are also expected to vary regionally due to differences in stiffness (Elkin et al., 2011; Lee et al., 2014) and failure strength (Franceschini et al., 2006).

In this study, needle insertion force was used to provide improved understanding of the influence of speed and brain region on the mechanics of brain tissue penetration. Measurements were performed in vivo in rat brain. Force measurements were used to calculate friction stress (product of pre-stress and friction coefficient) at the needle–tissue interface (Sharp et al., 2009). Similar to our previous measures of pre-stress, friction stress values were used to evaluate variation in tissue contact at different insertion speeds and in different brain regions along the needle track. Friction stress was then evaluated as a quantitative indicator of local tissue damage by comparing results with measures of tissue damage from histology and a previous study with the same insertion conditions (Casanova et al., 2014). In addition, the magnitude of surface deformation before needle penetration (surface dimpling) was measured. Agarose hydrogel has been used as a tissue phantom for needle insertion and brain infusion studies (Chen et al., 2004; Raghavan et al., 2010). In our previous studies (Casanova et al., 2012; Casanova et al., 2014), we have also evaluated insertion damage in tissue surrogate hydrogels. Insertion force, friction stress and dimpling were further tested as indicators of the extent of tissue contact and damage in this material with different failure behavior. Overall, this study provides a new methodology to evaluate the mechanics of insertion in real time and as a function of insertion speed and depth. In CED, acute tissue damage at the needle–tissue interface can result in flow of the infusate back along the needle track. This backflow phenomenon is directly dependent on the extent of tissue contact and damage at the needle–tissue interface, with lower friction stress resulting in the likelihood of more backflow. In future studies, established metrics may be used to predict extent of interfacial tissue stress. These data may also be used to improve insertion processes for needles or electrodes in the brain.

2. Methodology

2.1. Animal preparation and surgical procedures

Experiments were performed on 15 young male Sprague-Dawley rats (300–350 g) using protocols and procedures approved by the University of Florida Institutional Animal Care and Use Committee. Anesthesia was initiated with xylazine (10 mg/kg, SQ) and isoflurane (4%) in oxygen delivered at 1 L/min. The head was shaved and disinfected with iodine/alcohol cotton swabs. Then animals were placed on a stereotaxic frame (model 900, David Kopf Instruments, Tujunga, CA), and inhalation anesthesia (1.5% in 0.5 L/min of oxygen) was delivered via a nose mask. Body temperature was maintained (~37 °C) by means of a heating pad during the entire procedure. The skull was exposed by a mid-sagittal incision that began between the eyes and extended caudally to the level of the ears to expose bregma and lambda. Two holes with 2 mm diameter were drilled into the skull above the right and the left caudate putamen (CPu) (AP = 0.5, ML = ±3, DV = −5). In this way, bilateral needle insertions were conducted on each rat. The CPu region was chosen because it is a relatively homogeneous region composed mainly of gray matter and has been used previously in CED backflow studies