Intense Focused Ultrasound (iFU) for Diagnosing Pain

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Background

Pain is often challenging to localize and properly diagnose. Back pain is especially difficult to diagnose (and therefore treat) because of its complex mechanical structure (facets, ligaments, vertebral body, discs, etc). While anatomical abnormalities may be visualized using standard imaging techniques such as MRI or CT scan, those abnormalities are often not the source of pain. For example, to assay directly for pain caused by discs in the spine, discography (Fig. 1) may be performed using long needles to inject sterile saline into the candidate painful disc. Thus, infusing the disc and evaluating the patient's response. Besides being invasive, this method can only test discs as sources of pain, which are just one of many potentially painful structures in the back. A new clinically-applicable diagnostic device is needed to non-invasively localize deep pain.

The Mourad Lab specializes in using an experimental type of ultrasound, called iFU (intense focused ultrasound) to help diagnose and therefore treat patients. iFU is different from the diagnostic ultrasound that is commonly used for imaging and it is far more powerful, and focused into a very small spot (about the size of a grain of rice) which can displace or push tissue and create heat at that focus (Fig. 2). iFU is much less intense than HIFU (high intensity focused ultrasound), used to alter the tissue's properties for therapeutic effect.

We created an inflammation the right hindpaw of rats with a complete Freyer’s Adjuvant (CFA). We then applied iFU to both hindpaws in individual pulses with increasing intensity to find the threshold for paw withdrawal from iFU was consistently lower for the inflamed paw than for the uninflected normal paw (Fig. 3), demonstrating that iFU can diagnose allodynia. We also tested two different iFU devices on the inflamed paw of rats with a shallow focus (just proximal to the surface of the device) and the other with a deep focus (6 mm below the skin surface). We found that the iFU threshold for paw withdrawal on the shallow focus device was significantly higher and more varied than the withdrawal threshold on the shallow focus device (Fig. 4). This is consistent with the distribution of peripheral nerve endings and shows that iFU can stimulate deep structures.

Diffuse Pain

Inflammatory Pain

To model neuropathic pain, we ligated the sciatic nerve in the right hind leg of rats (pSNL). This created a neuropathically sensitive paw. We then applied iFU to their hindpaws in individual pulses with increasing intensity. We found that rats which had undergone the full nerve ligation surgery had significantly lower paw withdrawal thresholds to iFU than those which had received a sham surgery or no surgery (Fig. 5 - left). Therefore, neuropathic tissue is preferentially sensitive to iFU stimulation.

Focal Pain

Second Human Study

We created a subcutaneous neuroma both away from the surgery site and accessible to testing iFU’s ability to localize a focal, subcutaneous source of pain. We adopted the tubial neuroma transposition (TNT) (Dorsi et al.) model of neuroma pain and hyperesthesia. The posterior tubial and calcaneal nerves were exposed and cut at a site proximal to the planar bifurcation (Fig. 7a). The cut nerve was then brought away from the incision under the skin, where the neuroma formed (Fig. 7b).

We are ready to try our pre-prototype device capable of imaging-guided iFU stimulation on residual limb patients at Harborview Medical Center to localize (1) their focal, subcutaneous neuromas (right) and (2) their normal peripheral nerves, the latter useful for showing that iFU can help guide needles for therapeutic injections, another anticipated application of iFU for pain.

First Human Study

To model focal pain, we created a mechanical push (a measured tissue displacement on right) and thermal stimulation (left) at its focal point alone.

Objective

The goal of our project is to test and develop a new diagnostic method that uses iFU to non-invasively quantify and localize painful tissue by way of its ability to produce focal stimulation that is deep to the skin.

Here we demonstrate that (1) damaged tissue (inflamed; neuropathic) is preferentially sensitive to iFU stimulation, (2) humans can reliably sense iFU stimulation, and (3) iFU can localize a deep pain generator. The device we use to emit iFU can be placed almost anywhere in or around the body, under MRI or ultrasound-image guidance, allowing us to focus our ‘push’ or ‘warm’ only on the possible sources of the pain.

First Human Study

We applied iFU to the finger tips of healthy volunteers to determine at what intensity they could reliably detect stimulation by iFU. With sufficiently intense ultrasound all test subjects could reliably sense iFU stimulation. Moreover, the intensity of iFU necessary to generate reliable sensations at each of 50% and 90% sensitivity scalars with the density of the peripheral nerve endings in the finger tips as measured by the two-point discriminant assay; the larger the two-point test value in millimeters, the smaller the density of the peripheral nerve endings, and the more iFU required to generate a reliable sensation (Figures 6 - right).

Second Human Study

We are ready to try our pre-prototype device capable of image-guided iFU stimulation on residual limb patients at Harborview Medical Center to localize neurons.