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Interleaved imaging of cerebral hemodynamics and blood flow index to monitor ischemic stroke and treatment in rat by volumetric diffuse optical tomography

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ABSTRACT

Diffuse optical tomography (DOT) has been used by several groups to assess cerebral hemodynamics of cerebral ischemia in humans and animals. In this study, we combined DOT with an indocyanine green (ICG)-tracking method to achieve interleaved images of cerebral hemodynamics and blood flow index (*BFI*) using two middle cerebral artery occlusion (MCAO) rat models. To achieve volumetric images with high-spatial resolution, we first integrated a depth compensation algorithm (DCA) with a volumetric mesh-based rat head model to generate three-dimensional (3D) DOT on a rat brain atlas. Then, the experimental DOT data from two rat models were collected using interleaved strategy for cerebral hemodynamics and *BFI* during and after ischemic stroke, with and without a thrombolytic therapy for the embolic MCAO model. The acquired animal data were further analyzed using the integrated rat-atlas-guided DOT method to form time-evolving 3D images of both cerebral hemodynamics and *BFI*. In particular, we were able to show and identify therapeutic outcomes of a thrombolytic treatment applied to the embolism-induced ischemic model. This paper demonstrates that volumetric DOT is capable of providing high-quality, interleaved images of cerebral hemodynamics and blood perfusion in small animals during and after ischemic stroke, with excellent 3D visualization and quantifications.

Introduction

Ischemic stroke and animal models

Stroke is an emergency cerebrovascular condition and is the major leading cause of death in the United States with more than 130,000 deaths and disabilities annually (Kochanek et al., 2011). Stroke occurs when 1) blood flow to the brain is obstructed (ischemic stroke), or 2) blood vessels break and blood bleeds into brain tissues (hemorrhagic stroke). Of all patients diagnosed with stroke, more than 80% experience an ischemic stroke. Animal models are often used to help researchers better understand the pathogenesis of ischemia, to define biochemical changes in brain tissues during and after ischemia, and to discover mechanisms involved in the evolution of ischemic injury to the brain, as well as to examine therapeutic outcomes of new drugs and treatments. Among animal models, rat ischemic models have been well developed and widely utilized because the anatomy of arterial supplies to cerebral hemispheres in rats is essentially similar to that in humans. In particular, middle cerebral artery (MCA) ischemic stroke models are well established in rats mostly through occlusion of MCA using either the craniotomic or endovascular approach because ischemic stroke is often caused by occlusion of MCA and/or its branches in humans.

Non-invasive optical techniques to measure cerebral hemodynamics

Several types of non-invasive imaging techniques, such as computed tomography (CT) (von Kummer et al., 1997) and magnetic resonance

Abbreviations: 3D, three-dimensional; *BFI*, blood flow index; CBF, cerebral blood flow; CCA, common carotid artery; CT, computed tomography; DCA, depth compensation algorithm; DOT, diffuse optical tomography; DYNOT, dynamic near-infrared optical tomographic instrument; ECA, external carotid artery; FEM, finite element model; G_I, Group I to represent the suture-induced MCAO rat model; G_{II}, Group II to represent the embolism-induced MCAO rat model; HbO_2, oxygenated hemoglobin concentration; HbR, deoxygenated hemoglobin concentration; HbT, total hemoglobin concentration; ICG, Indocyanine green; ICA, internal carotid artery; MCA, middle cerebral artery; MCAO, middle cerebral artery occlusion; MRI, magnetic resonance imaging; NIR, near-infrared; NIRFAST, a FEM-based MATLAB package; NIRS, near-infrared spectroscopy; OD, optical density; $Ratio_{BFI}$, ratio between two spatially-averaged *BFI* values within ROI-2 and ROI-1; rCBF, regional CBF; ROI, region of interest; rtPA, recombinant tissue plasminogen activator; RW, real world.

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imaging (MRI), especially diffusion- and perfusion-weighted MRI (Neumann-Haefelin et al., 1999), have been used to investigate stroke and its possible treatments in experimental studies. For the last decade, researchers have been investigating non-invasive detection of cerebral hemodynamics using near infrared spectroscopy (NIRS) due to its portability, non-radiation, cost-effectiveness, and high temporal resolution. Since light in the near-infrared (NIR) range (600–900 nm) can penetrate a few centimeters into brain tissues, it can probe changes in oxygenated (HbO_2) and deoxygenated (HbR) hemoglobin concentrations in the cerebral regions. Total hemoglobin concentrations can be quantified by $HbT = HbO_2 + HbR$, serving as another hemodynamic contrast in proportion to the cerebral blood volume.

Specifically, with single or limited source–detector pairs, several NIRS measurements were performed in investigating cerebral hemodynamics during cerebral ischemia (Liu et al., 2008; Xia et al., 2007) using a suture-induced rat MCA occlusion (MCAO) model. With multiple source–detector pairs and a similar rat MCAO model, researchers (Chen et al., 2000, 2002) showed two dimensional (2D) topographic maps of HbT after performing spatial interpolation among the multi-channel NIRS readings. Their results exhibited good correlations with MR images and histological brain slices of the animals. Moreover, diffuse optical tomography (DOT), which utilizes diffusion theory to reconstruct tomographic images of multi-channel NIRS with a relatively large number of source–detector pairs, has demonstrated the feasibility of three dimensional (3D) image reconstruction of cerebral hemodynamics during cerebral ischemia in rat MCAO (Culver et al., 2003a) or common carotid artery (CCA) occlusion models (Bluestone et al., 2004b).

Non-invasive techniques to measure cerebral blood flow

Assessment of cerebral blood flow (CBF) is also important and useful for understanding and interpreting hemodynamic kinetics and cerebral physiology of acute ischemic stroke, especially for embolism-induced ischemia. Continuous observation of regional CBF (rCBF) for patients receiving thrombolytic treatment is crucial because ischemic tissues may be non-functional or dying due to different levels of blood reperfusion, which may cause a severe neurological and fatal deficit in the brain. Studies have shown that infarct volume highly depends on reduction of CBF during cerebral ischemia and perfusion recovery from ischemia (Soriano et al., 1997). There are several techniques providing rCBF measurements, including single photon emission tomography (SPECT) (Kwiatek et al., 2000; Pavics et al., 1999), CT, positron emission tomography (PET) (Johnson et al., 1999; Tuominen et al., 2004), perfusion-weighted MRI, diffuse correlation spectroscopy (DCS) (Shang et al., 2011; Zhou et al., 2006), and laser Doppler flowmetry (Liu et al., 2008; Tonnesen et al., 2005). All of these techniques have been adopted in human and animal studies.

Furthermore, measurements of rCBF by tracking the kinetics of an intravenous tracer or contrast, namely, indocyanine green (ICG), with NIRS have been reported when evaluating reduction of rCBF for patients with acute ischemic stroke (Terborg et al., 2004). The ICG-tracking technique allows repetitive and minimally invasive (due to the injection of ICG solution) measurements in a very short period of time because of rapid clearance of ICG from the blood stream. Researchers have shown that a blood flow index (*BFI*) derived from ICG kinetics is significantly correlated with the cortical blood flow (Kuebler et al., 1998), and thus allows rCBF assessment with good reproducibility (Keller et al., 2003; Wagner et al., 2003). Using the NIRS topographic technique, researchers have also shown the feasibility of generating 2D CBF images of infant patients with infarcts and hemorrhages; those images had good correlation with SPECT images (Kusaka et al., 2001).

Motivation and organization of this paper

The aim of this study was to investigate changes in cerebral hemodynamics and CBF kinetics during and after ischemic stroke, with and without thrombolytic therapy for an embolic MCAO model, using three-dimensional diffuse optical tomography (3D DOT). We have achieved interleaved 3D imaging of hemispheric hemodynamic changes and CBF kinetics after integrating conventional DOT with our recently developed depth compensation algorithm (DCA). The novelty of this paper includes 1) design and implementation of an interleaved method to quantify two sets of changes in both hemoglobin concentrations and *BFI* during and after MCAO in rat, 2) integration of DCA with a volumetric mesh-based rat head model to generate volumetric DOT on a rat brain atlas, and 3) longitudinal imaging and quantification of cerebral hemodynamics and CBF index before, during, and after a thrombolytic therapy for an embolic MCAO model.

This paper will provide details on several aspects of the study in the following order: First, we will modify and combine our recently developed DCA with a volumetric mesh-based rat head model to generate volumetric DOT on a rat brain atlas/template for improved depth localization and better visualization of MCAO effects in the rat brain. Second, we will describe how a suture-induced MCAO rat model was achieved and measured by a high-density DOT system one hour during and one hour after MCAO. The suture-induced MCAO model is studied mainly for validation of our experimental setup, measurement methodology, and volumetric image reconstruction as this model has been well established and documented. Third, we will introduce how our newly established embolism-induced MCAO rat model was utilized and measured with the same experimental setup and procedures. Next, interleaved data collection, analysis and volumetric image reconstruction will be described for longitudinal monitoring of cerebral hemodynamics and CBF index during and after MCA embolization. We will also discuss the effect of thrombolytic treatment. This work will demonstrate the feasibility of interleaved volumetric DOT to monitor longitudinal progress of cerebral hemodynamics and blood perfusion during and after cerebral ischemia in rats with and without therapeutic treatments. Results will be illustrated through high-quality 3D visualization and quantifications.

We will also discuss the influence of ICG injections on the quantification of hemodynamic variables and effect of thrombolytic treatment. This work will demonstrate the feasibility and limitation of interleaved volumetric DOT to monitor longitudinal progress of cerebral hemodynamics and blood perfusion during and after cerebral ischemia in rats with and without therapeutic treatments.

Materials and methods

Animal preparation

Male Sprague–Dawley rats weighing 350–400 g were purchased from Charles River (Wilmington, MA) and housed in a 12 h light and 12 h dark cycle with free access to water and food. All surgical procedures were approved by the Institutional Animal Care and Use Committee of the University of Texas at Arlington and the University of North Texas Health Science Center.

In this study, we created and measured two types of ischemic stroke rat models: suture-induced (Longa et al., 1989; Xia et al., 2007) and embolism-induced MCAO model (Ren et al., 2012), respectively. We briefly describe the procedures here.

1. Suture-induced ischemic model: The rat was anesthetized with isoflurane (2–2.5%); the left MCA was occluded by monofilament silicon-coated suture introduced throughout the left internal carotid artery (ICA), as shown in Xia et al. (2007). The time period for