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Tongue electrical impedance in amyotrophic lateral sclerosis modeled using the finite element method

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HIGHLIGHTS

- Computer modeling shows electrical impedance myography (EIM) values reflect changes in intrinsic muscle electrical properties.
- Tongue thickness, unrelated to tongue health, has limited impact on the EIM data.
- Given these findings, EIM of the tongue appears to hold potential to serve as a useful biomarker of disease progression in ALS clinical trials.

ABSTRACT

Objective: Electrical impedance myography (EIM) of the tongue has demonstrated alterations in patients with amyotrophic lateral sclerosis (ALS) compared to normal subjects. Whether these differences are due to reduced tongue size or diseased-associated alterations in the electrical characteristics of intrinsic tongue muscles is uncertain.
Methods: We employed computer simulations using the finite element method, inputting data from healthy and ALS mouse muscle, to help answer that question, comparing our modeled results to human data.
Results: The models revealed that much of the electrical current flows superficially in the tongue and that tongue thickness only begins to have a major impact on the measured impedance when substantial atrophy is present. Modeled values paralleled the human tongue data.
Conclusions: These findings suggest that the observed changes in tongue impedance in ALS are mainly due to alterations in the electrical properties of the tongue and are not a mere consequence of tongue volume loss.
Significance: Further development of EIM for evaluation of bulbar dysfunction in ALS may provide useful information on drug efficacy and could serve as a biomarker in future clinical trials.

1. Introduction

The development of quantifiable indices of bulbar muscle deterioration due to amyotrophic lateral sclerosis (ALS) and other neuromuscular disorders remains a major research challenge. Because approximately 20–25% of ALS patients initially present with bulbar dysfunction (Gubbay et al., 1985; Caroscio et al., 1987), including dysarthria and dysphagia, diagnostic tools are needed as biomarkers for objectively detecting early tongue involvement and for documenting its progression over time. Needle electromyography of tongue remains one of the most frequently used approaches to help establish a diagnosis of bulbar involvement due to ALS (Jenkins et al., 2013; Tankisi et al., 2013). This approach, however, has significant limitations including that it is not easily quantifiable and that it requires full relaxation of the tongue. Motor unit number estimation, while potentially valuable in quantifying progression in appendicular muscles (Shefner et al., 2011), cannot be readily applied to the tongue given challenges in stimulating the

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hypoglossal nerve and recording from the tongue. Assessments of tongue function during speech and swallowing are also available for quantifying bulbar motor deterioration. These include instrumentation-based measures of lingual strength and kinematics (Langmore and Lehman, 1994; Yunusova et al., 2012; Green et al., 2013), measures of speech and swallowing decline (Robbins, 1987; Yorkston et al., 2007), and functional severity rating scales, such as the bulbar subscore on ALS functional rating scale revised (Cedarbaum et al., 1999). One disadvantage of these approaches, however, is that they can be affected by a variety of factors including effort, fatigue, and cognitive status.

One technique that potentially overcomes some of the limitations of existing approaches to quantifying bulbar muscle disease is electrical impedance myography (EIM). EIM has been shown to be sensitive to disease progression in appendicular muscles in ALS, in both human patients (Rutkove et al., 2012) and animal models (Wang et al., 2011b; Li et al., 2013b). More recently, a pilot study of tongue EIM was also completed (Shellikeri et al., 2015), in which an EIM electrode array was created by affixing four electrodes to a plastic tongue depressor wired directly to an impedance-measuring device. Significant differences could be detected between healthy individuals and those with ALS.

One unexplored possibility is that these EIM changes are driven by reductions in tongue volume that occur due to lingual muscle atrophy. Presumably, reductions in tissue volume could directly impact the measured resistance and reactance, the two major basic EIM parameters. Surface EIM data may also be influenced by disease-related alterations in the electrical material properties of the tongue. These properties, including the conductivity (the ability for charge to flow freely through the tissue), and permittivity (the ability for a polarized electrical field to develop within the tissue) are altered in ALS (Li et al., 2014), and thus could directly impact the obtained data. Thus, in this study, we performed a series of *in silico* analyses using the finite element method (FEM) to determine the interplay between disease-related tongue changes and EIM results, incorporating a combination of both animal tissue data and human tongue dimensions. We then compared those modeled values to a small set of human tongue data.

2. Methods

2.1. Developing a FEM-based tongue model

There are several major tasks that need to be completed in order to develop a FEM-based model of the tongue following upon previous efforts made to create models of both human and animal muscle (Wang et al., 2011a; Jafarpoor et al., 2013). First, the electrical material properties (i.e., the conductivity and permittivity) of tongue tissues need to be obtained. These properties are critical to model development and have both a frequency and directional-dependence called anisotropy. Because the tongue is made up of several tissues, including epithelium and muscle, separate parameters for each tissue should be included in the model.

Second, an accurate geometric representation of the tongue using computer-assisted design techniques needs to be developed, including layers for the muscle and epithelium. This model should take into account not only the tongue's shape and size in its healthy state but also capture changes in the thickness with disease progression. The model also needs to include the electrode array itself placed on the surface of the tongue. Third, using commercial modeling software, the model is divided into a vast array of thousands of finite linear elements termed a "mesh," each of which helps approximate a boundary condition for that region of the model via numerical linear algebra, with the electrical material properties being input as parameters for these calculations. Having offered this overview, we now provide a more detailed description of the model development pursued here.

2.2. Electrical material properties

Ideally fresh cadaveric human tongue would be used for these analyses; however, this tissue was unavailable. Thus, for these analyses, we used data that was available—namely, mouse gastrocnemius muscle data from our previously reported studies in healthy and ALS animals (Li et al., 2014). While the gastrocnemius may seem far removed from the tongue, the basic pathological processes of motor neuron loss and subsequent cell atrophy should hold for both muscles. For the overlying epithelial layer's electrical properties, we used an online data resource (Institute of Applied Physics (IFAC), 2007) based on previously published work by others (Gabriel et al., 1996). The *ex vivo* muscle data were obtained after mice were sacrificed at the end of the study via the use of an impedance measuring cell, as previously described (Jafarpoor et al., 2013). The muscle data obtained included anisotropic information, with separate longitudinal (conduction along the length of the fibers) and transverse values (conduction across the fibers). The epithelial layer data were isotropic. Institutional animal care and use committee approval had been previously obtained for all studies.

2.3. FEM development and analysis

The basic FEM model was based on available human anatomic tongue morphological data (Hopkin, 1967; Oliver and Evans, 1986) and was developed and analyzed using the AC/DC Module, Electric Currents Physics in Comsol Multiphysics software (Comsol, Inc, 5.0 Burlington, MA), as shown in Fig. 1A. The proximal end of the model extended toward the base of the tongue and the distal end extended to and included the tip of the tongue. The basic structure consisted of a superficial epidermal layer and an underlying muscle layer. More distant structures, such as the sublingual arteries and veins were not included, since, based on past work, electrical current would not be expected to penetrate that deeply (Jafarpoor et al., 2013). The model included anisotropic data: longitudinal values in the sagittal plane and transverse data in both the

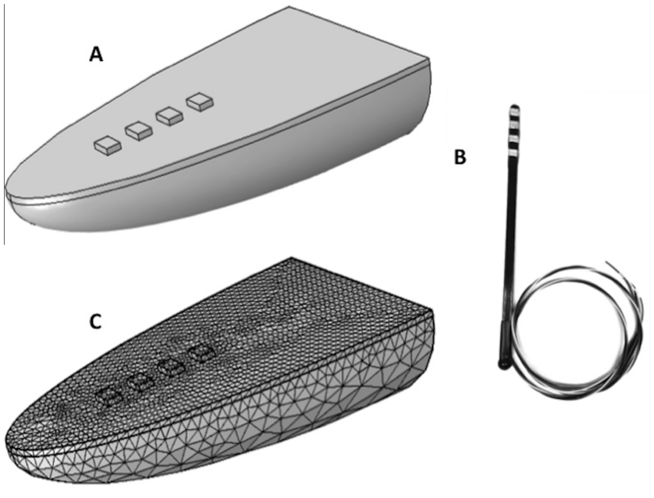

Fig. 1. (A) Basic geometric model of tongue with electrodes on surface. (B) Tongue electrode array used in the developed finite element model, using the same design as in McIlduff et al. (2016). (C) Same model as in (A), now with finite element mesh added.