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A portable system for the assessment of neuromuscular diseases with electrical impedance myography

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Abstract

Primary Objective—To create a system for the acquisition of multi-angle, multifrequency muscle impedance data.

Research Design—Device development and preliminary testing.

Methods and Procedures—The system presented here employs an interrogating signal composed of multiple tones with frequencies between 10 kHz and 300 kHz. The use of a composite signal makes possible measurement of impedance at multiple frequencies simultaneously. In addition, this system takes impedance measurements at multiple orientations with respect to the muscle fibers by means of an electronically reconfigurable electrode array utilizing the linearity of muscle tissue to reduce the required measurement time.

Main outcomes and results—The system was tested in normal subjects, a patient with amyotrophic lateral sclerosis, and one with inclusion body myositis; unique impedance signatures were identified the two patients.

Conclusions—Early data suggests that this system is capable of high-quality data collection and may detect changes in neuromuscular disease; study of additional normal subjects and patients with a variety of neuro-muscular diseases is warranted.

Keywords

Bioelectrical impedance; Amyotrophic Lateral Sclerosis (ALS); Inclusion Body Myositis (IBM); Reconfigurable electrode array; Tetrapolar measurement

1. Introduction

Bioelectrical impedance has long been considered a fast, inexpensive and non-invasive approach for analysing human tissue [1]. Its basic form involves the application of high-frequency, low-intensity electrical current via two surface electrodes affixed to the skin and the resultant voltage signal measured using a second set of electrodes (so-called tetrapolar measurements). The complex ratio of the measured voltage to the applied current is the impedance of the muscle tissue. A common application of bioelectrical impedance is in commercial body composition systems, such as the ImpSFB7® from ImpediMed, Inc. that computes the fat-to-muscle ratio of a person based on impedance measurements; it can also

be used for evaluating lymphedema. Other applications include electrical impedance tomography, which uses an array of impedance measurements to create anatomical images of human body [2], [3].

There are several key challenges in bioelectrical impedance measurements. The first challenge is relating or mapping the results of impedance measurements to the physiology, structure and anatomy of the underlying tissues. Effort has been made to create equivalent circuit models of different parts of the body, and these have, for the most part, succeeded in closely reproducing measured impedance profiles [1], [4]. However, identifying a strong relationship between the capacitors, resistors, and inductors of such models and the bone, muscle, fat, blood, nerve and skin has proven more elusive. A second challenge is the difficulty in predicting and understanding the direction of current flow through this complex set of tissues. The third challenge is reducing measurement to measurement variation on a single individual. Measurements that depend on precise electrode positioning are impractical to implement in a clinical setting, unless a patient is willing to have tattoos placed to ensure consistency.

Despite these potential problems, Rutkove et al. have shown that by performing localized impedance measurements over specific muscles, clinically valuable data can be obtained, as evidenced by the results of a number of human studies in a variety of disease states [5], [6]–[15]. These data provide strong evidence of the sensitivity of localized impedance measurements to muscle health and fitness, as well as to disease status and progression. A simple reason for this is that current flows preferentially through low-resistance, high-volume muscle tissue, and thus effectively probes the relevant tissue. Moreover, a more recent enhancement to this technique utilizes the fact that muscle conducts electrical current preferentially along the direction of its fibres rather than across them. Incorporating measurement of anisotropy in muscle not only improves the reproducibility of the EIM technique, but also may assist in discriminating neurogenic from myopathic disease [16], [17], [18]. Finally, Rutkove et al. have been able to demonstrate good reproducibility of the technique [9] using adhesive electrodes and current application at a single frequency (50 kHz).

In order to transition EIM into a useful clinical tool for the evaluation of neuromuscular disease, it has become increasingly apparent that there is a need for a compact, convenient measurement system that would allow measurements to be made faster and easier. User friendliness is a fundamental requirement for the widespread adoption of any new technique intended for clinical use, and creating a prototype handheld impedance probe, for example, would be a good first step. We have previously described an early version of a first generation EIM probe prototype that required the use of bench-top equipment [19]. Here, we describe the design of a complete prototype with reconfigured circuitry for more robust behaviour and a probe head with redesigned electrode contacts. We also report the first clinical data obtained from a group of healthy subjects and two patients with prototypical neuromuscular disease.

2. Methods

2.1 Overview of EIM measurement system

The EIM system employs the tetrapolar measurement setup (shown in figure 1) that is widely used in bioimpedance measurements. Impedance measurements are taken by means of a set of four electrodes arranged parallel to each other. The two outer (current or excitation) electrodes provide the input signal (usually a current) to the tissue being investigated. This creates an electric potential distribution that is measured by the other two inner (voltage or pickup) electrodes. In contrast to a two-electrode measurement, for which

the same pair of electrodes provides the excitation current and probes the resultant voltage, the tetrapolar measurement is less likely to be corrupted by the contact resistance between the probes and the skin.

A system diagram for the redesigned EIM measurement system is shown in figure 2. The bench-top measurement and signal generation equipment used in [19] have been replaced by portable USB powered equivalents. In addition, printed circuit boards (PCBs) and integrated circuits (ICs) used for the EIM probe and reconfigurable array have also been redesigned. The new system is composed of a signal generator, a reconfigurable electrode array, a crosspoint switch network, and a data acquisition module. The excitation signal is a composite of multiple tones with 20 logarithmically spaced frequencies from 10 kHz to 300 kHz. The waveform for this signal is first synthesized using Matlab and then downloaded to a USB powered Handyscope HS3, (TiePie Engineering, The Netherlands) which has a built-in arbitrary waveform generator (AWG). A differential voltage driver converts the single-ended signal output from the AWG to a differential signal and also ensures that its amplitude ($< 5\text{mA}$) is safe for clinical use. The excitation signal from the differential voltage driver is applied to a patient's skin via an electrode array fabricated on a printed circuit board. Each electrode array element is a small solder pad that is electrically connected to one of the input/output pins of an AD2128 crosspoint switch IC (Analog Devices, Norwood, MA). Neighbouring electrode array elements are electronically connected together to operate as a single *composite* electrode using the crosspoint switch network. Both the size and position of the composite excitation and pickup electrodes can be reconfigured rapidly using inter-integrated circuit (I²C) commands sent to the crosspoint switch network by a MSP430 microcontroller (Texas Instruments, Dallas, TX). Electrical impedance measurements as a function of angle and frequency can be accomplished using this arrangement. A USB-powered Handyscope HS4 oscilloscope with 4 input channels sampling at 50 MS/s was used as the analogue-to-digital converter needed to digitize the measured voltages for further processing on a portable computer. Mechanically, the EIM system is designed to fit in the hand of a clinician so that impedance measurements of a patient's muscles can be conveniently made at a variety of sites. A photograph of the complete EIM measurement system is shown in figure 3.

2.2 Reconfigurable electrode head

The design of the electrode head is based on an electrode array concept in which neighbouring electrode elements are connected together to create a *composite* electrode. Thus, they act as a single unit that can be used for signal excitation or pickup. Figure 4 is a pictorial representation of two possible patterns of electrode elements that can be created. The four composite electrodes that need to be created to make the input signal current to flow along the major muscle fibre direction (0°) are highlighted with solid black lines. To change the current flow direction to an angle of 90° with respect the major muscle fibre direction, the old pattern is cleared and a new one is created. This new pattern is highlighted with broken grey lines.

Prior experiments (see figure 5) showed that impedance measurements taken by single solid electrodes were very similar to those taken by a series of smaller electronically connected electrodes as long as they occupy a similar spatial footprint [20]. This ensures that the impedance measurements taken by the portable EIM system are comparable to that taken by the EIM systems used in [5], [6]–[15] that used single strip electrodes.

Small solder pads on a printed circuit board serve as electrodes for the EIM system. As shown in figure 6, the electrode elements are distributed in two concentric rings. The excitation electrodes are selected from the outer ring, while the pickup electrodes are selected from the inner ring. Electrode selection is accomplished using four ADG2128

crosspoint switches (Analog Devices, Norwood, MA). Each electrode element is connected to one of the input/output pins of the ADG2128 labelled from X1 – X12 in figure 7. These devices enable any combination of electrode elements to be connected to both the excitation outputs (differential voltage driver) and the detection inputs (Handyscope HS4 oscilloscope). The commands required to control the actions of the crosspoint switches are provided by a MSP430 microcontroller (Texas Instruments, Dallas, TX) over an I²C serial interface. The MSP430 runs a firmware written in C that translates commands from the GUI running on the notebook computer into the required I²C commands for the ADG2128. Using these I²C commands, any desired pattern of interconnected electrode elements can be created. Communication between the notebook computer and the MSP430 is handled by a FT232R UART USB chip (Future Technology Devices International Ltd., Glasgow, UK). Figure 6 shows a photograph of all the chip components used in the reconfigurable electrode head mounted on a custom designed printed circuit board.

Reproducible measurement results can be obtained because the orientation of these composite electrodes with respect to the muscle fibres can be altered without physical movement of the electrode head. This makes it possible to accurately alter the direction of current propagation and improve the angular resolution of measurements. Our system can achieve an angular resolution of 15°. A system diagram and photograph of the reconfigurable electrode head is shown in figure 7 and figure 3, respectively.

2.3 Circuit design: differential voltage driver

Rather than use an actual current source to inject a signal into the tissue, we designed a low output impedance voltage driver and delivered the interrogating signal through a ‘sense’ resistor. The voltage across the sense resistor indicates the current injected. The problem with using an ideal current source is that it makes the system more susceptible to stray capacitance at the probe/skin interface. This stray capacitance causes a phase shift in the measured voltage that is not due to the tissue, and the integrity of the complex impedance measurement is compromised.

The voltage driver shown in figure 8 performs several functions. It converts the single-ended signal from the arbitrary waveform generator to a differential signal which will be used in the interrogation of the muscle. Also, for patient safety, the injected current is strictly limited by the current sources at the emitters of Q3 and Q5. The input stage consists of an emitter coupled transistor pair (Q1, Q2) that converts the single ended input signal to a differential signal. The signal then passes through the output stage, which consists of a cascode device, Q4 and an emitter follower, Q3. The base of Q4 is connected to the emitter of Q3 and the base of Q3 is connected to the collector of Q4 (Q5 and Q6 are identically connected). Using this structure, we are able to bias the base of Q4 without using another resistor chain. The output impedance of the voltage driver is the impedance looking into the emitter of Q3 (or Q5), which is quite small and given by:

$$R_{out} = \frac{1}{g_{mQ3}} + \frac{R_{C4}}{\beta_o + 1} \approx \frac{1}{g_{mQ3}} \quad (1)$$

where g_{mQ3} and R_{C4} are the transconductance and collector resistance of Q3 respectively. The small output impedance, R_{out} , of the voltage driver ensures that most of the excitation signal is dropped across the test sample. Differential signals are used to interrogate the muscle tissue to reduce common mode interference. This increases the reliability of the impedance measurements taken with the EIM system.

2.4 Signal processing

A composite signal containing a number of sinusoids with logarithmically spaced frequencies was used as the interrogating signal. By this means, impedance of the muscle group under investigation can be measured at multiple frequencies simultaneously. The fact that muscle tissue acts as a linear medium with respect to current excitation makes this approach possible. As a result, the speed of measurement is significantly increased over the proof-of-concept EIM system in [5], which takes impedance measurements at each frequency sequentially.

We next take the Fourier transform of the measured and digitized voltages, performing all required numerical computation in the frequency domain. A Matlab script was written to extract the Fourier transform values at selected frequencies at which impedance information will be measured. The current flowing through the muscle is obtained by measuring the voltage across the sense resistor, R_{sense} in figure 8. The impedance of the muscle is then computed by taking the ratio of the voltage to the current at each frequency. Figure 9 shows the time domain and frequency domain (Fourier transform) representation of a measured composite signal composed of 40 sinusoids with logarithmically spaced frequencies. The amplitude roll off shown in the frequency plot is an artefact of the finite bandwidth of the voltage driver circuit.

3. Results and discussion

In order to assess the potential clinical value of this system, institutional review board approval was obtained at Beth Israel Deaconess Medical Center and eight individuals were enrolled in the study after signing an approved consent form. The results obtained using the above system are shown in figure 10, in which data from a typical normal subject, a patient with amyotrophic lateral sclerosis (ALS) and a patient with inclusion body myositis, a type of primary muscle disease, are displayed. The data are taken at logarithmically spaced frequencies between 10 kHz and 300 kHz and at angular increments of 30° from -90° to 90° . Effort was made to orient the 0° axis of the electrode array as close to the main muscle fibre direction as possible based on the physician's knowledge of anatomy. These cases serve to demonstrate the same changes in diseased states that were observed using our earlier impedance systems which incorporated adhesive electrodes [15], [18]. As can be seen, the normal subject demonstrates a relative subtle anisotropy in both the resistance and reactance plots (x-axis). A clear frequency dependence is also present, with lower values at higher frequencies for both parameters. Table 1 displays the average and range of resistance and reactance values at select frequencies and angles for all six normal subjects. These results provide further evidence of frequency dependence and anisotropy in healthy people. In both the diseased subjects that follow in figure 10, this normal frequency dependence is altered, most notably in the reactance, where the values appear to increase at higher frequencies (note the reactance curves sloping upward and to the right). Also, in both diseased cases, the absolute value of both the measured reactance and resistance are offset considerably from those observed in the healthy subject (note the different scales).

In addition to these changes in the frequency dependence, the anisotropic character of the tissue is also altered. Since we oriented the probe such that 0° was the major muscle fibre direction in all three individuals, we would anticipate that the lowest resistance and reactance values would occur at that angle. Indeed, in the healthy subject, this general shape of the anisotropy is apparent in both the reactance and resistance traces. However, in the ALS patient, a marked distortion and accentuation of the anisotropy of the resistance is observed, with an elevation in the overall values and a minimum at -60° rather than at 0° . In the myositis patient, in contrast, the anisotropy actually appears more modest than either the normal subject or the ALS patient. Both of these findings support our earlier observations

that anisotropy will be elevated in neurogenic disease and reduced in myopathic disease [18].

The reduction in anisotropy in the myopathy patient makes intuitive sense, as in myopathic diseases the normal cylindrical structure of the muscle fibres is interrupted by isotropic materials, including fat, connective tissue, and inflammatory cells. In addition, the remaining myocytes become shortened and truncated and likely cannot conduct current as effectively in the longitudinal direction. The elevation and distortion of the anisotropy in the ALS patient remains more difficult to explain. However, one possibility is that type-grouping is occurring— islands of preserved muscle fibres are surrounded by severely atrophied fibres. These islands can serve as low-resistance paths through a muscle that is otherwise atrophied and of higher resistance. Still, this does not explain why the angle should be shifted so dramatically from 0° to -60° , though this could simply represent difficulty in accurately aligning the probe along the atrophied muscle. Clearly further data analysis and modelling will be necessary to answer these complex questions.

4. Conclusions

In this paper, we have presented a refined portable system for the assessment of neuromuscular diseases with electrical impedance myography. Significant improvements to the first generation portable system presented in [19] were implemented and results from a small group of normal subjects and a patient with ALS and another with myopathy were presented. The results show that our EIM system is capable of rapidly and accurately obtaining measurements of the complex impedance of muscle tissue. The development of a truly portable impedance measurement device will help refine EIM into an easily applied, sophisticated diagnostic tool. The simultaneous measurement of impedance at multiple frequencies using a reconfigurable electrode array will ensure that EIM measurements are robust, rapidly obtained, and highly reliable.

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Figure 1. Diagram of tetrapolar measurement setup showing equipotential (dashed lines) and current flow lines (solid lines). The shaded region represents a high-resistivity skin-fat layer. Adapted from R. Aaron et al. [16].

Figure 2.
System diagram of EIM measurement system.

Figure 3.

Photograph of complete EIM measurement system. Note the system is truly portable and does not have any components running off the AC power mains.

Figure 4. Two possible configurations of the electrode array producing the four ‘composite’ electrodes needed for tetrapolar impedance measurements.

Figure 5. Comparison of impedance plots taken with solid electrodes and electronically connected smaller electrodes with similar total spatial footprint.

Figure 6. Internal components of reconfigurable electrode array. (a) Top of electrode array PCB; (b) Bottom of electrode array PCB; (c) Analogue components PCB with differential voltage driver and contacts for oscilloscope; (d) Microcontroller and USB communication PCB.

Figure 7.
System diagram of reconfigurable electrode head.

Figure 8. Differential voltage driver. Biasing circuits are not shown for simplicity.

Figure 9.
Time and frequency domain plots of the input signal containing a number of tones at logarithmically spaced frequencies.

Figure 10. Impedance plots showing the anisotropic current conduction properties of human muscle tissue. The test was carried out on the biceps of 3 different subjects: (a) a healthy subject; (b) an ALS patient and (c) a myositis patient.

Table 1

Summary of normal subject data from biceps muscle (n=6).

Resistance			
<i>Angle</i>	<i>Frequency</i>	<i>Median</i>	<i>Range</i>
0 degrees	50 kHz	147.2	[51.2, 215.7]
	100 kHz	121.6	[38.8, 202.0]
90 degrees	50 kHz	94.8	[57.6, 239.5]
	100 kHz	68.0	[25.6, 191.7]
Reactance			
<i>Angle</i>	<i>Frequency</i>	<i>Median</i>	<i>Range</i>
0 degrees	50 kHz	32.2	[25.2, 42.2]
	100 kHz	30.9	[23.1, 46.4]
90 degrees	50 kHz	40.5	[27.1, 179.6]
	100 kHz	44.0	[22.9, 133.0]