The alpha parameter of the Cole-Cole model as an indicator of fibromyalgia

C A González-Correa¹, E Colina-Gallo² and D A Miranda-Mercado³

¹Universidad de Caldas / Research Group of Electrical Bio-impedance, Cll 65 # 26-10, Manizales, Colombia
²Universidad de Caldas / Department of Human Physical Activity, Cll 65 # 26-10, Manizales, Colombia
³Universidad Industrial de Santander / CIMBIOS, Cra 27 Cll 9 Bucaramanga, Colombia

evelyn.colina@ucaldas.edu.co

Abstract. Introduction: Fibromyalgia (FM) is a condition characterized by chronic widespread pain and generalized tenderness accompanied by fatigue, disturbed sleep and cognitive difficulties. Several types of muscle abnormalities have been reported in FM at tissue, cellular and subcellular level, which could eventually alter the passive electrical response of the muscle. Methods: We evaluated the brachial musculature of 41 women, 21 with FM and 20 without, using multi-frequency electrical impedance myography and the characteristic parameters of the Cole-Cole model were obtained ($R_0$, $R_\infty$, $\tau$ and $\alpha$). Results: The alpha parameter of the FM group was statistically different ($0.21 \pm 0.05$ against $0.17 \pm 0.05$ p = 0.008). Discussion: The higher values of alpha parameter in the FM group may suggest that the behaviour of the cell membrane in FM is more permeable to the ions than in the non FM group and, therefore, less resistive.

1. Introduction

In fibromyalgia (FM), various muscular abnormalities have been associated with chronic widespread pain and generalized tenderness, accompanied by fatigue, disturbed sleep and cognitive difficulties that characterize this condition [1]. Among these, we can mention: low levels of ATP (adenosine triphosphate) [2], increased levels of lactate and pyruvate [3], reduced blood flow [4], increased cytokines [5], DNA fragmentation [6], mitochondrial dysfunction, decrease in mitochondrial membrane potential and increased mitophagy, that could contribute to cell-bioenergetic imbalance [7], functional abnormalities of the muscle membrane, with higher muscle fiber conduction, maybe related to fast/hyper-excitable muscle membrane [8]. A possible link between some of these abnormalities could be: reduced blood flow $\rightarrow$ hypoxia $\rightarrow$ mitochondrial dysfunction $\rightarrow$ diminution of ATP production $\rightarrow$ increased lactate and pyruvate concentration as well as low Na⁺-K⁺-ATPase activity $\rightarrow$ pain, inflammation and leaky membrane.

In a previous study, we have explored the use of Electrical Bio-Impedance Spectroscopy (EBIS) as a potential tool for the diagnosis of FM [9]. EBIS is a safe, easy to use, non-invasive and objective method that can give information about local tissue, organs, body segments or even the whole body. Changes either in the architecture or the composition of different biological structures (at ultrastructural, microscopic or gross level), or all, (‘both’ solo se refiere a dos, aqui hay 3?) can affect the passive electrical response of the studied structure.
The main assumption behind EBIS is that, when we applied a spectrum of alternating electrical currents to a volume where we have cells surrounded by a liquid matrix, at low frequencies, these currents flow through the extracellular fluid, while, at high frequencies, they also flow through the intracellular space. This flow of current is mainly explained by the presence of cell membranes, a component that, in principle, practically do not allow the movement of ions in the interior of the cells at low frequencies. At the same time, the cell membrane has a capacitive property, which allows it to store electrical charges of opposite voltage on its two sides, acting as a capacitor. Nevertheless, it is not a perfect capacitor and, in the electrical model of biological tissues by Cole and Cole, eq. (1), this fact is accounted for by the presence of what is known as a “constant phase element” (CPE). In the mathematical expression of the physical (electrical) model of biological structures, we end up, therefore, with four parameters [10]: $R_0$ “static” resistance, i.e., resistance at 0 Hz (assumed to be the resistance of the extracellular fluid), $R_\infty$, or resistance at “infinite frequency” (assumed to be the resistance of the whole volume when current is flowing through both compartments), $\tau$ (tau) or a generalized relaxation time (associated with the time it takes for the tissue to polarize and depolarize) and $\alpha$ (alpha, part of an exponential as shown in equation 1), a dimensionless parameter that accounts for the “imperfection” of cell membranes to act as pure capacitors. $\alpha$ ranges between the two extreme values of 0 (zero) and 1 (one), where, in the first case, the membrane ought to be a pure capacitor, and, in the second case, the membrane ought to be a perfect resistor.

$$Z = R_\infty + \frac{R_0 - R_\infty}{1 + (j\omega \tau)^{1-\alpha}}$$

(1)

We hypothesize; therefore, that either $\alpha$, $\tau$ or both, could be affected in individuals with FM. From this perspective, we report in this article on the analysis of preliminary data that has been obtained to date. Initially, the use of raw data did not give statistically significant differences between a group of people with FM and a matching group of individuals without FM [9]. However, for further analysis, we calculated the four parameters of the Cole-Cole model by inverse modeling, using the Miranda & Rivera algorithm [11], and found that the comparison of the parameter $\alpha$ between the two groups suggests the possibility of using it as a biomarker of FM.

2. Materials and Methods

Materials and methods are basically those already referred to in [9], which we briefly summarize now.

2.1. Subjects

Initially, we had a group of 26 volunteers with FM and 23 control individuals without FM. Data from 5 subjects with FM and three without FM were disregarded because the root-mean-square error (RMSE) of these individuals was too high (cut off point: an RMSE > 0.09), meaning that the fit was not very good, something that also can be visually detected (see figure 1). Basic data of the subjects remaining in both groups is shown in Table 1. All participants gave their informed written consent based on the guidelines of the Ethical Committee of the University of Caldas (Manizales, Colombia).
Figure 1. The first graphic, identified as PMG001, is an example of a good fit (RMSE=0.008). The second one, identified as PEC001, is an example of a poor fit (RMSE=0.41).
Table 1. Average (SD) physical characteristics of the participants.

|               | Age(y) | Weight (kg) | Height(m) | BMI$^a$ (kg/m$^2$) | BF$^b$ (%) | Muscle area(m$^2$) |
|---------------|--------|-------------|-----------|--------------------|------------|-------------------|
| **FM group**  | 47.1   | 66.7        | 1.56      | 27.4               | 34.4       | 0.00328           |
| (N=21)        | (8.3)  | (9.6)       | (0.05)    | (4.2)              | (6.5)      | (0.00076)         |
| **Control group** | 51.7  | 69.6        | 1.55      | 27.8               | 35.4       | 0.00324           |
| (N=20)        | (9.4)  | (11.6)      | (0.06)    | (4.4)              | (5.6)      | (0.00068)         |

$^a$Body Mass Index
$^b$Body Fat

2.2. Anthropometric measurements
The following variables were measured: height (SECA station 284, SECA GMBH & Co Hamburg Germany), body fat percentage (TANITA BC-418 model analyzer, TANITA Corporation, Tokyo, Japan), the circumference of the midarm (midway between the tip of the acromion and the olecranon process, measured with a cloth tape), biceps and triceps skinfolds (Slim Guide Skinfold Caliper, SKINDEX, Albuquerque, USA). This data is also shown in Table 1.

2.3. FM variables
For the diagnosis of FM we applied the modified preliminary diagnostic criteria of the American College of Rheumatology (ACR) [12]. Tender points were also evaluated using a digital algometer (FORCE TEN™ FDX, Wagner Instruments, Greenwich, USA). Diagnosis of FM was established when 11 or more tender points were present according to the 1990 ACR classification criteria [13].

2.4. Bioimpedance measurements and model parameterization
Arm segmental measurements of raw resistance (R) were performed using a 4000B Bio-Impedance Spectrum Analyzer System (XITRON Technologies, San Diego, USA) at 50 frequencies in a log spectrum ranging from 5 kHz to 1 MHz, with a nominal current of 400µA RMS. Injecting electrodes were placed on the distal third of the dorsal metacarpus and the dorsal metatarsus, at the dominant side of each subject. Voltage electrodes were placed on the ventral side of the dominant arm over the biceps brachii, 5 cm proximal and 5 cm distal to the midpoint between the tip of the acromion and the olecranon process. For all participants in the study, total body bioimpedance readings were also registered, in one of the usually recommended ways [14]. The parameters of the Cole-Cole model, equation (1), were obtained from the raw data using a least square data fitting with the algorithm proposed by [11].

2.5. Data analysis
The Student’s t-test was used for assessing the statistical significance of the difference between means of the Cole-Cole parameters estimated for each group. $P$ values of less than 0.05 were accepted for significance. We also explored the possible sensitivity and specificity of $\alpha$ parameter as a possible biomarker for FM, using the receiving-operating curve (ROC) obtained from the data.

3. Results
The two groups were homogeneous in all physical characteristics, and the application of the diagnostic criteria allowed an adequate differentiation between the FM and the control group (see Table 1).
Table 2 shows the four Cole-Cole parameters estimated for both groups, with the data obtained from measurements on the arm.

|                | RMSE^a | \( R_0 (\Omega) \) | \( R_\infty (\Omega) \) |
|----------------|--------|---------------------|--------------------------|
| **FM** group   | 0.024  | 58                  | 45.1                     |
| (N=21)         | (0.018)| (10)                | (7.8)                    |
| **Control** group | 0.040  | 61.1                | 48.7                     |
| (N=20)         | (0.026)| (8.5)               | (7.0)                    |
| **p value**    | 0.29   | 0.12                |                          |

^aRoot Mean Square Error

The ROC curve obtained with the data used in this analysis is shown in Figure 2. Values of \( \alpha > 0.177 \) would be considered as positive, with a sensitivity of about 0.81 and a specificity of 0.70.
4. Discussion
As mentioned in the introduction, α parameter takes a numerical value in the range of the two extreme values of 0 and 1, i.e. zero representing a hypothetical perfect capacitor and one, a hypothetically perfect resistor. There are two situations of interest: firstly, normal membranes and, secondly, “leaky” membranes. Because the main subject of this paper is FM, we will describe the “leaky” membranes.

“Leaky” membranes allow more inward movement of Na⁺ ions, or, in the case of malfunctioning of the membrane Na⁺- K⁺ ATPase, where it cannot pump adequate quantities of Na⁺ ions out of the cells. This would probably have a manifold effect: a) a decrease in transmembrane rest voltage, b) a lower capacitance of the cell membrane and c) a more prominent role of its resistive properties, which would increase the value of α parameter. Any of these situations would alter both muscle and nerve cells.

Some of the muscle alterations associated with FM reported in scientific literature suggest one of the hypothetical scenarios mentioned in the previous paragraph: hypoxia due to poor capillarization [4,15-20], mitochondrial alterations [7,16], lower concentration of high energy phosphates [2], presence of lactate and pyruvate in free nerve endings [3], and, in sum, alteration in membrane resting potential [8].

An alteration of the Na⁺- K⁺ pump would also mean a prolongation in the time it takes cell membranes to stabilize after an external electrical stimulus. This would mean an alteration in the parameter τ of the Cole-Cole model, but the experimental data did not corroborate this.

The presence of irritative substances in the free nerve endings like lactate, pyruvate or substance P [3], could also produce a neurogenic inflammatory condition [21], also described in people with FM. These changes should imply a decrease in the extracellular resistance due to edema, as was reported in participants with acute lumbago [22], but, again, there were no statistically significant differences in the parameter R₀.

Studies carried out in FM using superficial EMG have shown an increase, in resting conditions, of the electrical activity in anti-gravity muscles like lumbar erectors [23], an increase in conduction velocity of muscle fibers [24], and even in low affected muscles like the biceps brachii [8,25]. This finding has been correlated with alteration at cell membrane level, reflected in continuous muscle activation between contractions, prolonging the period of facilitated post depolarization [8]. Although this ionic alteration at membrane level in FM has not been completely elucidated, it leads to thinking about an increase in membrane permeability and, possibly, a less electronegative resting potential. If this is the case, the excitatory cells would more easily reach the threshold potential, i.e., they would depolarize more easily, even with stimuli that, under normal conditions, would not depolarize these cells.

Finally, as already mentioned, the parameter α (0≤ α ≤ 1) of the Cole-Cole model tends to 1 (one) if the cell membrane behaves more like a resistor than as a capacitor. i.e., the cell membrane decreases its ability to act as an insulator (and therefore, diminishes its capacitive property). The observed differences in α parameter between the normal group and the group with FM, where the mean of subjects with FM is higher than the mean of those without FM, suggest a relation between this parameter with the membrane biochemical anomalies that would make it easier for the external charges to flow into the cell. When the parameters obtained for the whole body readings were compared, there were no statistically significant differences between both groups (data not shown).

5. Conclusion
The analysis of the experimental data of this study shows a statistically significant difference between the means of the parameter α in the brachial readings of the two groups considered. The results of this research lead to the hypothesis of an alteration in the functioning of the cell membrane in subjects with FM. This alteration could, probably, be associated with a failure in the Na⁺- K⁺ pump, produced
by low availability of ATP, due, in turn, to alterations in the number or functioning of mitochondria. These biochemical anomalies would be equivalent to an increase in cell membrane permeability.

The differences in the parameter $a$ in brachial segmental readings seem to be a promising finding, although larger studies are needed to confirm the possibility of using this as an objective biomarker for FM. This is interesting, as the diagnosis of fibromyalgia is clinical and, so far, there are no objective confirmatory diagnostic methods.

References

[1] Buskila D 2009 Developments in the scientific and clinical understanding of fibromyalgia *Arthritis. Res. Ther.* **11** 242
[2] Bengtsson A, Henriksson KG and Larsson J 1986 Reduce high-energy phosphate levels in the painful muscles of patients with primary fibromyalgia *Arthritis. Rheum.* **29** 817-21
[3] Gerdele B, Söderberg K, Salvador Puigvert L, Rosendal L and Larsson B 2010 Increased interstitial concentrations of pyruvate and lactate in the trapezius muscle of patients with fibromyalgia: a microdialysis study *J. Rehabil. Med.* **42** 679-87
[4] McIver KL, Evans C, Kraus RM, Ispas L, Sciotti VM and Hickner RC 2006 NO-mediated alterations in skeletal muscle nutritive blood flow and lactate metabolism in fibromyalgia *Pain* **120** 161-69
[5] Wallace DJ, Linker-Israeli M, Halleluga D, Silverman S, Silver D and Weisman MH 2001 Cytokines play an aetiopathogenetic role in fibromyalgia: a hypothesis and pilot study *Rheumatol. (Oxford)* **40** 743-9
[6] Sprott H, Salemi S, Gay RE, Bradley LA, Alarcón GS, Oh SJ, et al. 2004 Increased DNA fragmentation and ultrastructural changes in fibromyalgic muscle fibres *Ann. Rheum. Dis.* **63** 245-51
[7] Cordero MD, de Miguel M, Carmona-López I, Bonal P, Campa F and Moreno-Fernández AM 2010 Oxidative stress and mitochondrial dysfunction in fibromyalgia *Neuroendocrinol. Lett.* **31** 169-73
[8] Klaver-Król EG, Rasker JJ, Henriquez NR, Verheijen WG and Zwarts MJ 2012 Muscle fiber velocity and electromyographic signs of fatigue in fibromyalgia *Muscle. Nerve.* **46** 738-45
[9] Colina-Gallo E, González-Correa CA, Miranda-Mercado DA 2016 Correlation between Algometry and Electrical Bioimpedance in Subjects with and without Fibromyalgia.In: Simini F., Bertemes-Filho P. (eds) II Latin American Conference on Bioimpedance. IFMBE. *Proc.* **54** 72-5 Springer, Singapore
[10] Cole KS and Cole RH 1941 Dispersion and Absorption in Dielectrics I. Alternating Current Characteristics *J. Chem. Phys.* **9** 341
[11] Miranda DA and Rivera SL 2008 Determination of Cole-Cole parameters using only the real part of electrical impedance measurements *Physiol. Meas.* **29** 669-83
[12] Wolfe F, Clauw DJ, Fitzcharles MA, Goldenberg DL, Häuser W, Katz RS, et al. 2011 Fibromyalgia criteria and severity scales for clinical and epidemiological studies: a modification of the ACR Preliminary Diagnostic Criteria for Fibromyalgia *J. Rheumatol.* **38** 1113-22
[13] Wolfe F, Smythe HA, Yunus MB, Bennett RM, Bombardier C and Goldenberg DL 1990 The American College of Rheumatology 1990 criteria for the classification of fibromyalgia: report of the Multicenter Criteria Committee *Arthritis. Rheum.* **33** 160–72
[14] González-Correa CH and Caicedo-Eraso JC 2012 Bioelectrical impedance analysis (BIA): a proposal for standardization of the classical method in adults *J. Phys. Conf. Ser.* **23** 407:012018
[15] Lund N, Bengtsson A and Thorborg P 1986 Muscle tissue oxygen pressure in primary fibromyalgia *Scand. J. Rheumatol.* **15** 165-73
[16] Lindman R, Hagberg M, Bengtsson A, Henriksson KG, Bengtsson A and Henriksson KG 1995
Capillary Structure and Mitochondrial Volume Density in the Trapezius Muscle of Chronic Trapezius Myalgia, Fibromyalgia and Healthy Subjects J. Musculoskelet. Pain. 3 5–22

[17] Lindh M, Johansson G, Hedberg M, Henning G and Grimby G 1995 Muscle fiber characteristics, capillaries and enzymes in patients with fibromyalgia and controls Scand. J. Rheumatol. 24 34–7

[18] Morf S, Amann-Vesti B, Forster A, Franzcek UK, Koppensteiner R, Uebelhart D, et al. 2005 Microcirculation abnormalities in patients with fibromyalgia measured by capillary microscopy and laser fluxmetry Arthritis Res Ther. 7 R209–16

[19] Kasikcioglu E, Dinler M and Berker E 2006 Reduced tolerance of exercise in fibromyalgia may be a consequence of impaired microcirculation initiated by deficient action of nitric oxide Med. Hypotheses. 66 950–2

[20] Katz DL, Greene L, Ali A and Faridi Z 2007 The pain of fibromyalgia syndrome is due to muscle hypoperfusion induced by regional vasomotor dysregulation Med. Hypotheses. 69 517–25

[21] De Stefano R, Selvi E, Villanova M, Frati E, Manganelli S and Franceschini E 2000 Image analysis quantification of substance P immunoreactivity in the trapezius muscle of patients with fibromyalgia and myofascial pain syndrome J. Rheumatol. 27 2906–10

[22] Ching CTS, Chen YC, Lu LH, Hsieh PF, Hsiao CS, Sun TP, et al. 2013 Characterization of the muscle electrical properties in low back pain patients by electrical impedance myography PLoS. One. 8 e61639

[23] Anders C, Sprott H and Scholle HC 2001 Surface EMG of the lumbar part of the erector trunci muscle in patients with fibromyalgia Clin. Exp. Rheumatol. 19 453–5

[24] Gerdle B, Ostlund N, Gronlund C, Roeleveld K and Karlsson JS 2008 Firing rate and conduction velocity of single motor units in the trapezius muscle in fibromyalgia patients and healthy controls J. Electromyogr. Kinesiol. 18 707–16

[25] Casale R, Sarzi-Puttini P, Atzeni F, Gazzoni M, Buskila D and Rainoldi 2009 Central motor control failure in fibromyalgia: a surface electromyography study BMC Musculoskelet. Disord. 10 78