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Relaxation differences using EIS through bronchoscopy of healthy and pathological lung tissue

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***Abstract*— The use of electrical impedance spectroscopy for lung tissue differentiation is an opportunity for the improvement of clinical diagnosis. The aim of this work is to distinguish among different lung tissue states by evaluating the differences among impedance spectrum parameters between two separate frequencies (15 kHz and 307 kHz) in the beta dispersion region. In previous studies we have used single frequency measurements for tissue differentiation. Differences ($P < 0.05$) are found between those tissues that undergo an increase in tissue density (neoplasm and fibrosis) and those tissues that lead to tissue destruction (emphysema). Electrical impedance spectroscopy shows its utility for lung tissue differentiation for diagnosis improvement among pathologies with different tissue structure. Further studies are necessary for the differentiation among those tissue states that are more similar to each other.

***Clinical Relevance*— Expand the diagnostic tools currently available in bronchoscopy by using minimally-invasive bioimpedance measurements to differentiate between lung patterns.

I. Introduction

The diagnosis of peripheral lung lesions in patients who are suspected of having lung cancer remains a challenge. The measurement of Electrical Impedance Spectroscopy (EIS) could allow the differentiation of pathological tissue and help in the choice of the specific sampling location and allow the selection of the biopsy area in real time.

Bioimpedance (Z) is defined as the opposition that the tissue offers to the flow of an electrical current administrated. When the administrated current is alternating current the bioimpedance is frequency dependent. When several frequencies into a wide range of frequency is used to measure bioimpedance then EIS is performed. The Z has a resistance (R) component, which is the opposition produced by the extracellular and intracellular medium and a reactance (Xc) component, produced by the capacitive behavior of the cell membranes. From these two terms, the bioimpedance module (|Z|) defined as $\sqrt{R^2 + Xc^2}$ and the bioimpedance phase angle (PA) described as $\tan^{-1}(\frac{Xc}{R})$ can be extracted. PA is produced because the capacitance causes a lag between the current and the voltage [1]–[3].

Due to the capacitive behavior of the cell membranes, between the tens of kHz and the tens of MHz the biological tissue produces a relaxation, called beta-dispersion [4]. Beta dispersion produces a drop in the permittivity (Ɛ) with an associated increase in conductivity [5]. Moreover, depending on the tissue properties the beta dispersion produces variations [6].

The aim of this study is to differentiate among different lung tissue states (neoplasm, fibrosis, pneumonia, healthy lung tissue and emphysema) by evaluating differences among impedance parameters in the beta-dispersion region of each of the tissues through minimally-invasive EIS acquired through a bronchoscopy process.

II. Materials and Methods

A. Participants

Minimally invasive EIS measurements were carried out in a total number of 102 patients (Age: 66 ± 14 yr; Weight: 74.5 ± 17.2 kg; BMI: 26.8 ± 4.3 kgm-2) with a bronchoscopy prescribed between November 2021 and August 2022 at the "Hospital de la Santa Creu i Sant Pau" of Barcelona. The number of samples divided per classes obtained were: 30 healthy lung, 29 neoplasm, 23 emphysema, 12 fibrosis and 22 pneumonia.

Ethics approval was obtained from the "Hospital de la Santa Creu i Sant Pau" (CEIC-73/2020) according to principles of the Declaration of Helsinki for experiments with human being. All patients proved signed informed consent.

B. EIS measurements

Minimally-invasive EIS measurements acquired through the 3-electrode method were obtained by injecting a multisine current signal (from 1 kHz to 1000 kHz) between a distal tetrapolar catheter electrode and a skin electrode. The injection of current induces a voltage that is measured between the distal electrode and a second skin electrode. Impedance signal is acquired using a sample frequency of 60 spectra per second during 12 seconds. A complete description of the impedance measurement system and of the calibration procedure can be found at Company-Se et al [7].

C. Measurement protocol

Minimally-invasive EIS measurements were acquired though a bronchoscopy. Radiological evaluation (chest CT or/ and PET CT) was performed before bronchoscopy. The upper airway was anaesthetized and intravenous sedation was

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provided. The acquisition of the bioimpedance data was carried out by inserting the catheter through a port of the bronchoscope. Endoscopic exploration and diagnostic procedures were indicated accordance with the guidelines.

D. Data analysis

The averaged spectra of the minimally-invasive bioimpedance measured through the 12 seconds acquisition time was used for data visualization among healthy lung tissue, neoplasm, fibrosis, pneumonia and emphysema. Data was obtained between 1 kHz and 1 MHz although 15 kHz to 307 kHz was the frequency range chosen to visualize the bioimpedance data. Low frequency values (below 15 kHz) and high frequency values (above 307 kHz) were discarded due to electrode effects and capacitive coupling induced errors respectively.

While in Company-Se et al [7] absolute values of the impedance parameters were used to differentiate between tissue states, in the current study, to perform tissue differentiation the difference between low (15 kHz) and high (307 kHz) frequency mean bioimpedance values were calculated for |Z|, PA, R and Xc.

Shapiro-Wilk test was used to assess the distribution of normality of the variables (the difference between low and high mean bioimpedance values in |Z|, PA, R and Xc). Normally distributed variables are shown as mean ± standard deviation (SD) and 95% confidence interval (CI) of the mean (lower bound – upper bound). One-way analysis of variance (ANOVA) with Tamhane t2 post-hoc test was used to determine statistically significant differences in the differences between low and high frequencies mean bioimpedance in |Z|, PA, R and Xc.

III. RESULTS

A. Multi-frequency response for minimally-invasive lung tissue measurements

Fig.1 to **Fig. 4** shows the mean impedance spectrum for bioimpedance |Z|, PA, R and Xc respectively for the frequency range of 15 kHz to 307 kHz for neoplasm (black), fibrosis (red), pneumonia (blue), healthy lung tissue (green) and emphysema (pink). Mean is represented by the continuous line and ±SD is represented by dashed lines. Impedance |Z|, PA, R and Xc show higher differences between low and high frequencies in healthy lung tissue and emphysema.

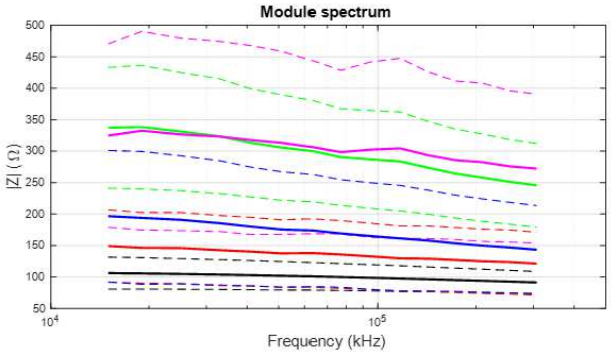

Figure 1. Modulus mean impedance spectrum for neoplasm (black), fibrosis (red), pneumonia (blue), healthy lung tissue (green) and emphysema (pink). Mean is represented by the continuous line while ±SD is represented with dashed lines.

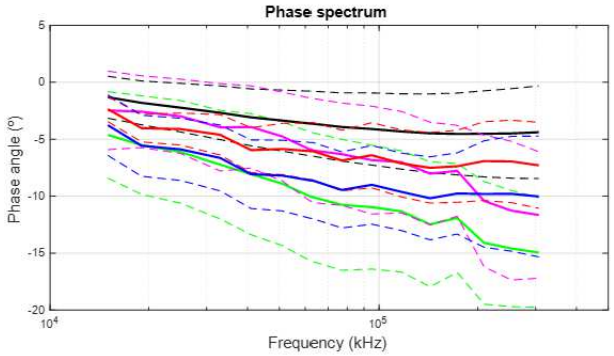

Figure 2. Phase angle mean impedance spectrum for neoplasm (black), fibrosis (red), pneumonia (blue), healthy lung tissue (green) and emphysema (pink). Mean is represented by the continuous line while ±SD is represented with dashed lines.

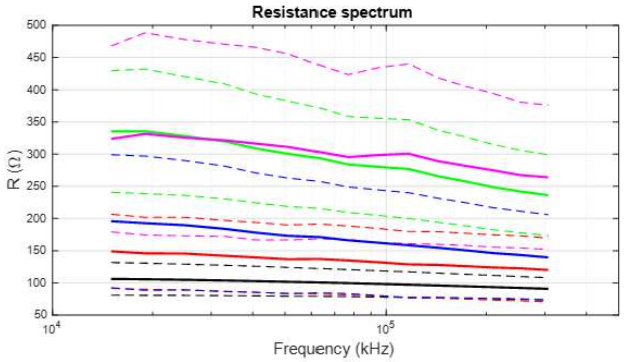

Figure 3. Resistance mean impedance spectrum for neoplasm (black), fibrosis (red), pneumonia (blue), healthy lung tissue (green) and emphysema (pink). Mean is represented by the continuous line while ±SD is represented with dashed lines.

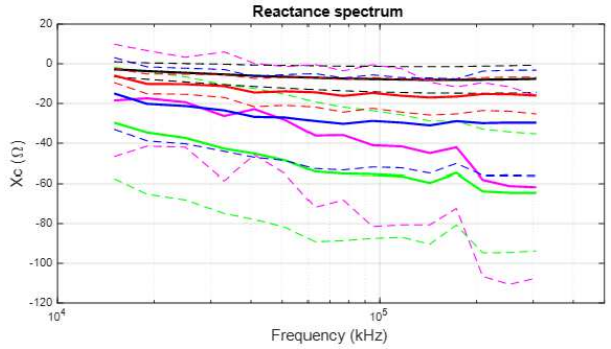

Figure 4. Reactance mean impedance spectrum for neoplasm (black), fibrosis (red), pneumonia (blue), healthy lung tissue (green) and emphysema (pink). Mean is represented by the continuous line while ±SD is represented with dashed lines.

B. Differentiation of minimally-invasive electrical impedance spectroscopy bioimpedance measurements among tissue states from the differences between high and low frequency values

Table 1 lists the descriptive parameters, specified as the mean ± SD, 95% confidence interval for mean (lower bound

Table 1. Descriptions of minimally-invasive bioimpedance measurements for healthy lung tissue, neoplasm, emphysema, fibrosis and pneumonia. The variables normally distributed are shown as mean ± SD, 95% confidence interval for mean (lower bound and upper bound) while that non-normally distributed data is shown as statistic median (interquartile range, IQR) and minimum-maximum. In addition, the statistic of the Fisher (F) coefficient for variance analysis and the statistical significance (P) are also shown.

	Mean ± SD **95% CI (lower bound – upper bound)**						
	Healthy **(n= 30)**	**Neoplasm** **(n= 29)**	**Emphysema** **(n= 23)**	**Fibrosis** **(n= 12)**	**Pneumonia** **(n= 22)**	**F**	**P**
Diff |Z| (Ω)	90.91 ± 55.82 (55.44 – 126.37)	17.84 ± 13.73 (9.12 – 26.56)	65.56 ± 63.15 (25.44 – 105.68)	27.91 ± 14.57 (18.66 – 37.17)	52.20 ± 29.69 (33.34 – 71.06)	12.73	<.001
Diff PA (°)	12.20 ± 3.05 (10.26 – 14.14)	4.37 ± 2.14 (3.01 – 5.73)	9.95 ± 2.99 (8.06 – 11.85)	5.42 ± 2.92 (3.57 – 7.27)	5.85 ± 4.43 (3.03 – 8.66)	15.24	<.001
Diff R (Ω)	100.69 ± 59.12 (63.13 – 138.25)	18.36 ± 14.14 (9.37 – 27.34)	74.13 ± 71.34 (28.80 – 119.46)	28.98 ± 15.30 (19.26 – 38.71)	54.55 ± 31.99 (34.22 – 74.87)	13.47	<.001
Diff Xc (Ω)	48.30 ± 27.85 (30.60 – 65.99)	6.83 ± 3.67 (4.50 – 9.17)	44.18 ± 24.53 (28.60 – 59.77)	10.58 ± 6.86 (6.22 – 14.94)	15.21 ± 15.12 (5.60 – 24.81)	15.68	<.001

and upper bound) of the difference between the mean values of |Z|, PA, R and Xc at 15 kHz and 307 kHz and the results of the one-way ANOVA including the Fisher coefficient (F) for healthy lung tissue (n = 30), neoplasm lung tissue (n = 29), emphysema (n = 23), fibrosis (n = 12) and pneumonia (n = 22). One-way ANOVA test shows statistical significance ($P < 0.001$) for the four parameters. Higher Fisher coefficient is obtained in PA and Xc.

Table 2 shows the Tamhane t2 test results for the multiple comparison test evaluating the difference in the mean values of |Z|, PA, R and Xc between the lowest frequency (15 kHz) and the highest frequency (307 kHz). Statistical differences are found between the following groups: healthy and neoplasm; healthy and fibrosis; healthy and pneumonia; emphysema and fibrosis; emphysema and pneumonia; neoplasm and emphysema; neoplasm and pneumonia. No statistical differences are found between healthy and emphysema; neoplasm and fibrosis and between fibrosis and pneumonia in any of the four parameters (|Z|, PA, R and Xc).

IV. DISCUSSION

This study aims to evaluate differences among different lung tissue states (neoplasm, fibrosis, pneumonia, healthy lung tissue and emphysema) through differences into the beta dispersion region.

Beta dispersion, produced between tens of kHz and tens of MHz, is due to the interfacial polarization of cell membranes, that act as barriers for the passive transport of ions between the ionic solutions that are present inside and outside the cells [4], [8]. When current penetrates the cell membranes (when frequency increases) causes reactance and phase angle to increase and resistance and modulus to decrease [1] (**Fig. 1** to **Fig. 4**). As also seen in **Fig 1** to **Fig 4**, changes in cell membranes due to lung disorders produce changes in the mean impedance spectrum obtained producing different changes in the beta dispersions based on the tissue states. Neoplasm (black) and fibrosis (red) results in a flattened spectrum, as compared with healthy lung tissue (green) and emphysema (pink).

The beta dispersion produces differences in mean impedance values between high and low frequencies, producing significant differences ($P < 0.001$) in |Z|, PA, R and Xc (**Table 1**). Tamhane t2 post-hoc test showed significant differences between: neoplasm and pneumonia (|Z|, R), healthy lung tissue (|Z|, PA, R and Xc) and emphysema (|Z|, PA, R and Xc); fibrosis and healthy lung tissue (|Z|, PA, R and Xc) and emphysema (PA and Xc); pneumonia and healthy lung tissue (PA, R and Xc) and emphysema (Xc). Non-significant differences were found ($P > 0.05$) between fibrosis and neoplasm; fibrosis and pneumonia and between healthy lung tissue and emphysema. Healthy lung tissue and emphysema have more air content than others patterns. In emphysema, the increase in inflammatory cells and oxidative stress produce the secretion of proteases which produces direct damage to structural cells and destruction of alveolar walls. The air content present in lungs in proportion to the tissue is higher compared to neoplasm, fibrosis and pneumonia. Neoplasm is characterized by a cell growth and an increase of vascularization and fibrosis is characterized by an increase of tissue non-over-vascularized. The similitude in both pathologies regarding the increment of tissue and, in turn, cell concentration makes not possible to distinguish through minimally-invasive bioimpedance measures between both pathologies. In pneumonia, the inflammatory response is initially characterized by a congestive phase with vascular hyperemia followed by an exudative phase in which the presence of neutrophils and fibrin increases, which can completely occupy the alveolar spaces. Despite the clinical differences between pneumonia and fibrosis, there are several pathological phases that could hide the differences.

Table 2. Tamhane t2 post-hoc test results for the difference between low and high frequency of the mean impedance parameters (|Z|, PA, R and Xc)

Post hoc Tamhane t2 test							
			P				**P**
Diff |Z| (Ω)	Healthy	Neoplasm	<.001	**Diff PA (°)**	Healthy	Neoplasm	<.001
		Emphysema	0.129			Emphysema	0.876
		Fibrosis	<.001			Fibrosis	<.001
		Pneumonia	0.063			Pneumonia	0.028
	Neoplasm	Emphysema	0.025		Neoplasm	Emphysema	<.001
		Fibrosis	0.161			Fibrosis	0.896
		Pneumonia	0.002			Pneumonia	0.296
	Emphysema	Fibrosis	0.336		Emphysema	Fibrosis	0.023
		Pneumonia	1			Pneumonia	0.398
	Fibrosis	Pneumonia	0.113		Fibrosis	Pneumonia	0.99
			P				**P**
Diff R (Ω)	Healthy	Neoplasm	<.001	**Diff Xc (Ω)**	Healthy	Neoplasm	<.001
		Emphysema	0.18			Emphysema	0.999
		Fibrosis	<.001			Fibrosis	<.001
		Pneumonia	0.038			Pneumonia	0.005
	Neoplasm	Emphysema	0.015		Neoplasm	Emphysema	<.001
		Fibrosis	0.159			Fibrosis	0.441
		Pneumonia	0.002			Pneumonia	0.091
	Emphysema	Fibrosis	0.207		Emphysema	Fibrosis	<.001
		Pneumonia	1			Pneumonia	0.012
	Fibrosis	Pneumonia	0.106		Fibrosis	Pneumonia	0.826

V. Conclusion

In conclusion, the study of differences in impedance parameters at separated frequencies into the beta dispersion region due to changes in lung tissue states can be used for the differentiation among different lung pathologies. The difference in the impedance parameters in the beta dispersion region is higher between those pathologies that lead to an increase of tissue (neoplasm and fibrosis) and those pathologies that lead to higher air content in lungs (emphysema). The use of minimally-invasive bioimpedance measurements to differentiate between lungs patterns aims to expand the diagnostic tools currently available in bronchoscopy. However, further studies are necessary for the differentiation among the lung disorders that are more similar to each other.

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