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Research Article

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Posted Date: July 28th, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-745218/v1>

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Bioelectrical impedance phase angle as a diagnostic indicator in thyroid cancer

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Abstract

Background: Bioelectrical impedance spectroscopy (BIS) is a non-invasive and easy-to-use technique to distinguish tissue properties. Phase angle, determined by BIS, detects changes in tissue electrical properties. We aimed to study the feasibility and validity of phase angle in diagnosis of thyroid cancer for the first time.

Methods: 226 invitro thyroid specimens in 210 patients from Department of Thyroid in West China Hospital of Sichuan University from March to November 2013 were collected. According to the location from thyroid cancer, thyroid specimens were divided into four groups: A, B, C and D. All of the groups were analyzed with phase angles respectively. The results were compared with final

pathologic diagnosis.

Results: Results showed that the phase angle is the characteristic parameter. The rank-sum test showed, the significant difference between the four groups and between two groups ($P < 0.05$), with statistical significance. Our study showed 86% sensitivity and 72% specificity of mean phase angle difference (MPAD). The corresponding positive and negative predictive values were 78% and 82%, overall accuracy was 80%, the area under the ROC curve is 0.838.

Conclusions: The study demonstrated that phase angle can be used to diagnose thyroid cancer. With further research, the phase angle may be a potential diagnostic indicator for the thyroid cancer.

Key words: electrical impedance spectroscopy; phase angle; thyroid cancer; ultrasound-guided fine-needle aspiration; receiver operating characteristic

Introduction

Thyroid cancer incidence is increasing the second fastest among solid tumors¹, and it is already the first most common malignancy in adolescents and young adults (ages 15 to 29 years) in the United States². Therefore, thyroid cancer seriously affects human health. Currently, Ultrasound and Ultrasound-guided fine-needle aspiration (US-FNA) are widely accepted as the primary diagnostic tools for the evaluation of thyroid nodules and diagnosis of thyroid cancers. However, some patients worry that the puncture might cause needle tract implantation metastases³. Furthermore, in some primary hospital US-FNA is unavailable and lack of pathologists, this can be a big challenge. Even if the hospital is equipped with US-FNA and pathological diagnosis, 5-

20% of US-FNA results are non-diagnostic⁴. Additionally, the false-negative rate of thyroid nodules with a benign FNA result reaches 13.6-56.6% when the thyroid nodules have suspicious features on ultrasound⁵. Therefore, for these nodules with non-diagnostic cytology results, patients are required either close observation or surgical excision for definite diagnosis. Some patients would choose surgery for fear of cancer, but they have to face a series of surgical risks and complications, including recurrent laryngeal nerve injury, hypoparathyroidism, and lifelong thyroid hormone replacement, etc.⁶, which affect the quality of life seriously. Although immunohistochemistry and genetic testing are now available to assist diagnosis, they are not yet universally available in all hospitals. A less common tool to assess thyroid nodules properties and diagnose thyroid cancer, called Electrical Impedance Spectroscopy (EIS), which can overcome some of these challenges and diagnose thyroid cancer in electrophysiological and pathological perspectives. EIS is an easy-to-use, non-invasive, and reproducible technique to diagnose thyroid cancer. Therefore, the paper introduces the diagnostic technique-EIS. EIS measures the ratio of voltage to current in an alternating current signal, or the phase angle of impedance in function of frequency. The body can be considered as a composite volume conductor comprising a number of spatially distributed tissues with differing electrical properties⁷. EIS measurements are based upon tissue-specific electric field distribution on the surface of the body at the region of interest. In biological tissue, the resistance and the related electrical impedance are associated with the electrical properties of the tissues, which depend on the structure of tissues⁸. Biological tissues are complex electrical impedance system, which is a function of frequency of electrical

current applied, because tissues contain components that have both resistive and charge storage (capacitive) properties⁹. Both theory¹⁰ and practice¹¹ have demonstrated that different tissue structures are associated with impedance in different frequency bands¹². There are three major relaxation regions, called α , β , and γ , at frequencies of approximately 100 Hz, a few kHz to 1MHz and 1 GHz. These regions are related to extracellular surface polarizations of large cells (α region), to increasing capacitive charging and discharging of cell membranes (β region) and to the relaxation of the water molecules (γ region), respectively. For many applications the α and β dispersion regions are particularly interesting, since most changes between normal and pathological tissue seem to appear in this frequency range⁹. Therefore, it is more practical to design a measuring system dedicated to the low frequencies. At low frequencies, the current pass extracellular space. Because the current has to pass around the cells with path of least resistance, the resistance to flow depends on the cell spacing and how they are arranged, whereas with increasing frequencies current can penetrate the membrane and hence passes through both intracellular and extracellular spaces⁹. Cellular changes alter the flow of electrical current through living tissue, and a number of literatures indicated differences in human electrical impedance between benign and malignant tumors [breast^{13,14}, thyroid¹⁵⁻¹⁷, prostate¹⁸, bladder¹⁹, colon²⁰]. Previous studies have confirmed the feasibility of EIS in diagnosis of thyroid cancer. However, due to the low specificity¹⁵⁻¹⁷, in order to screen better diagnostic parameters and improve specificity, we found that phase angle is a good diagnostic indicator. To the best of our knowledge, no investigation was reported that phase angle is a diagnostic indicator in thyroid cancer.

Phase angle reflects the relative contributions of fluid (resistance) and cellular membranes (reactance) of tissues. By definition, phase angle is positively associated with reactance and negatively associated with resistance²¹. Lower phase angles suggest cell death or decreased cell integrity, while higher phase angles suggest large quantities of intact cell membranes²². The primary objective of the preliminary study is to evaluate the feasibility and significance of phase angle derived EIS in diagnosis of human thyroid cancer.

Materials and Methods

In this study, 226 invitro human thyroid tumors from 45 man and 165 women hospitalized at Department of Thyroid Surgery, West China Hospital of Sichuan University from March to November 2013 were collected. we presented a preliminary study of four electrodes alternating current impedance method in freshly excised thyroid specimens. We constructed, validated and experimented with a four electrodes probe used in conjunction with an impedance analyzer to record bioimpedance measurements on thyroid specimens in the operating room immediately following thyroidectomy. The measured results were compared with the pathology results. The study protocol was approved by the Ethics Committee of Sichuan University and relevant institutions for the use of human subjects in research. All patients provided written informed consent.

Electrical Impedance Spectroscopy System (Figure 1)

EIS instrument was designed to measure electrical properties of thyroid specimens for distinguishing the malignant form benign thyroid nodules. When we apply an alternating current to tissue, the impedance can be measured by the potential and current.

Bioimpedance measurements were made with a pen probe of 4 mm in diameter, with two gold and silver electrodes (1 mm diameter) mounted flush with the face of the probe and spaced equally on a 1 mm diameter circle (Figure 2). The probe was connected through a set of 4 shielded cables to a laptop computer (HP, CQ40-607AU, Chengdu, China) controlled the Reference 600 electrochemical comprehensive tester (Gamry instruments, Philadelphia, the United State) (Figure 3). A probe collected impedance from the tissue and propagated it to the Reference 600, which outputted the impedance spectrum to the laptop computer for record and further analysis. The collection and record of impedance spectrum of a single fresh specimen took less than one minute.

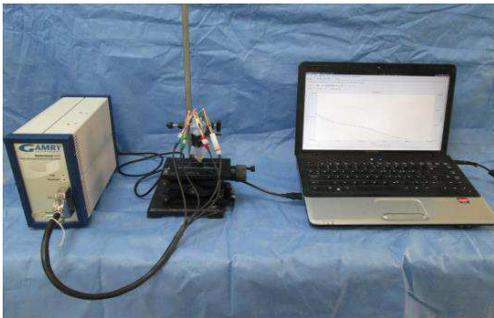


Figure 1 Electrical Impedance Spectroscopy System



Figure 2 A pen probe of the first generation



Figure 3 Reference 600

Patient Selection and *Ex Vivo* Measurement

Spectroscopy measurement and analysis

EIS data of ex vivo thyroid specimens were collected from patients arranged for surgical thyroidectomy in the operating room within 5 minutes of surgical removal and prior to pathological examination. Written informed consent was obtained from all patients for using tissue samples. All aspects of the study were approved by the ethics committee of the West China Hospital of Sichuan University and were carried out in accordance with the approved guidelines.

The EIS of different pathological results were measured from 200 patients. The ratio of the measured potential to the amplitude of the imposed current determines a transfer impedance. In order to reduce the polarization effect of low frequency, measurement frequencies ranged from 1MHz to 100Hz with 10 times intervals (1MHz, 100kHz, 10kHz, 1kHz, 100Hz) at 40 different frequencies. A current of 10 μ A peak-to-peak was passed between gold electrodes, and the resulting voltage was measured between the two remaining silver electrodes. Before each measurement, the probe was regularly calibrated using the known conductivity of saline solutions, and ultrasonically

cleaned, then removed moisture and surface oxidation film on electrode front-end with non-woven. The fresh specimens were made by size of 2 cm*2 cm* 0.5 cm, of which surface must be uniformly flat to facilitate measurement, hemorrhage, degenerative cyst, and necrotic tissues were avoided. Then, according to the distance from thyroid cancer, the resection specimens were divided into four groups: A,B, C and D, represented 10mm distance from the edge of malignance (normal thyroid tissue proved by pathology), benign tumor(proved by pathology), malignant tumor(proved by pathology) and malignant tumor margin(1mm distance from the edge of malignance) respectively, and four groups were measured, then EIS data were acquired from three separate sites in the same group in order to check the reproducibility. The measured data were recorded in the laptop for further analysis. The entire collection and recording of impedance spectrum of a single fresh specimen took less than 30 minutes. Lastly, all the groups were fixed in formalin separately and sent for pathological examination. Our analysis results were compared with pathologic diagnosis.

All data were analyzed by SPSS 22.0 software, the Kruskal-Wallis test was applied to assess whether difference among four groups, with $p < 0.05$ statistically significant. The receiver operating characteristic curve was used to screen optimal threshold, and obtain the optimal diagnostic value in diagnosis of thyroid cancer, and then yielded corresponding the sensitivity, specificity, positive predictive value, negative predictive value and accuracy.

Results

The pathologic result of groups

A total of 226 thyroid nodules were sampled from 210 sequential patients who

underwent surgical thyroidectomy, 1662 valid impedance data were obtained and analyzed. All the specimens were compared with the pathological results. The four groups were A: 226 specimens, 678 impedance data; B: 104 specimens, 312 impedance data; C: 122 specimens, 366 impedance data; D: 122 specimens, 366 impedance data. The benign nodules included 44 cases of nodular goiter, 44 cases of nodular goiter with adenomatous nodules, 7 cases of thyroid adenoma, 10 cases of Hashimoto's thyroiditis versus malignant nodules were consisted of 117 cases of papillary thyroid carcinoma, 2 cases of follicular thyroid carcinoma, 3 cases of medullary thyroid carcinoma. The frequency distribution table in pathological result of group B and group C pathological type was shown in Table 1. In each case, the repeated measurement data of the same group were highly consistent, the dispersion coefficient was less than 10%.

Table 1 Thyroid pathological type and percentage

The results of pathology	Cases	Percents
PTC	117	51.7
FTC	2	0.9
MTC	3	1.3
Nodular goiter	44	19.5
Nodular goiter with adenomatous nodules	44	19.5
Thyroid adenoma	7	3.1
Hashimoto's thyroiditis	9	4.0
Total	226	100.0

Statistical analysis of four groups

By studying the impedance data, we found that the phase angle between 1K and 31.64K fluctuated significantly, so we used the mean of the phase angle difference (MPAD)

as a reference index. Mean \pm standard deviation of MPAD were 14.2 ± 4.3 , 10.8 ± 5.2 , 4.9 ± 2.9 and 12.7 ± 4.0 degrees in four groups (A, B, C, D), and their histograms (Figure 4) and box plot (Figure 5). The Kruskal-Wallis rank of MPAD among four groups and between two groups have statistical significance ($P < 0.01$). MPAD in the same group has no statistical significance ($P > 0.05$). Statistics showed in order of descending MPAD among four group: group A, group D group, group B and group C.

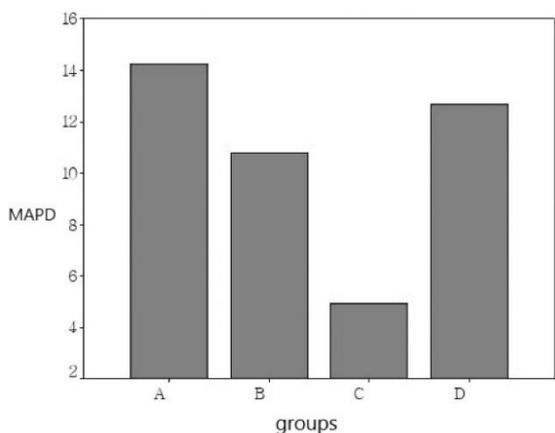


Figure 4 Histograms of MPAD among four groups

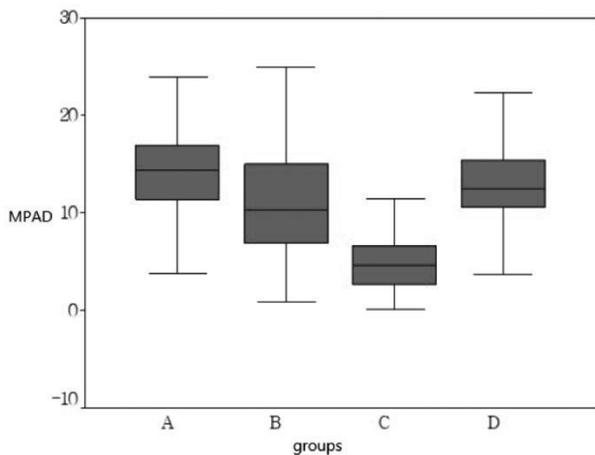


Figure 5 Box plot of MPAD among four groups

Compared with pathological diagnosis, MPAD was defined as a test variable and ROC curve (Figure 6) was plotted, thereby Area under the curve (AUC) of the test variable was 0.838 (95% confidence interval 0.785 0.891). The sensitivity and specificity in

different cutoff points on ROC curve were analyzed to determine the optimal threshold for thyroid cancer diagnosis on basis of the maximum Youden index (YI). The test variables of MPAD for thyroid cancer diagnosis was 7.59 degrees, which was optimal diagnostic critical point, this means that MPAD of tumors with greater than or equal to the value was benign, the opposite was malignant tumors. The corresponding sensitivity, specificity, positive predictive value, negative predictive value and accuracy were 86%, 72%, 78%, 82% and 80%, thereby MPAD were analyzed by diagnostic test fourfold table (Table 2). In addition, the false positive and false negative results (Table 3, 4). In the false negative result, thyroid papillary carcinoma accounts for more than 88%, and in the false positive result, nodular goiter with adenoma nodules constitute more than 52%.

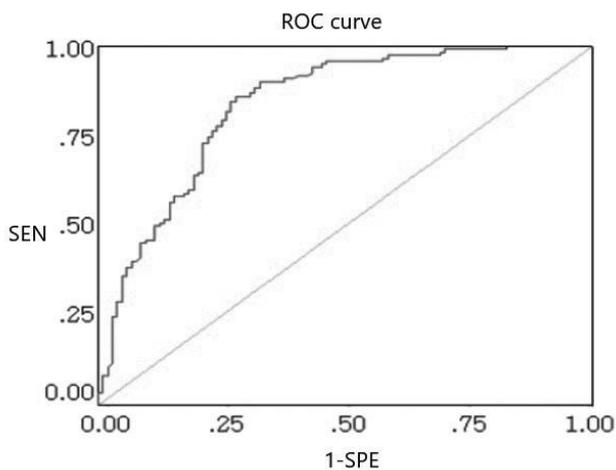


Figure 6 ROC curve

Table 2 MPAD results

EIS test	Pathology diagnosis		Total
	Malignant	Benign	
Positive	105	29	134
Negative	17	75	92
Total	122	104	226

Table 3 MPAD false positive results

Pathology	false positive results (cases)	constituent ratio (%)
Nodular goiter	7	24%
Nodular goiter with adenomatous nodules	17	59%
Hashimoto's thyroiditis	2	7%
Thyroid adenoma	3	10%
Total	29	100%

Table 4 MPAD false negative results

Pathology	false negative results (case)	constituent ratio (%)
PTC	15	88%
MTC	2	12%
Total	17	100%

Discussion

The aims of this research are to study the relation between EIS and *ex vivo* human thyroid tissues, and explored more effective and accurate diagnosis parameter to differentiate malignant from benign thyroid nodules. Until now, there American research teams have proved that the EIS is effective in classification of the thyroid nodule in vivo studies with a certain accuracy¹⁵⁻¹⁷. It was difficult to diagnose benign thyroid tumors with a relatively low specificity (61%)¹⁷. However, none of researches was reported that phase angle is a diagnostic indicator in thyroid cancer in the published literature. In our study, we had demonstrated phase angle a promising marker for differentiating malignant from benign thyroid nodules with high sensitivity and negative predictable value.

Currently, ultrasound and FNA are commonly used in the diagnosis of thyroid cancer. However, FNA demands for high proficiency of operators, besides, a majority of patients worry about that the operation may cause cancer metastasis, as well as other objective factors, so that the technology was not popularized in clinical. In addition, the diagnostic principle of ultrasound and FNAB were established on the basis of structure and morphology²³, but when disease occurs, functional changes of tissues or organs often are prior to structural and morphological changes, after a certain functional compensatory or latent period, it develops into organic lesions, structural changes of tissues and organs, therefore it is difficult for potential cancers or precancerous lesions to realize early diagnosis and real-time monitoring for ultrasound and FNA. Instead, EIS has these advantages. EIS is based upon tissue-specific conductivity and permittivity, it reflects electrical properties of tissues. Once tissues alter physiologically or pathologically, their electrical properties may change accordingly²⁴. The change may reflect the internal information of tissues in a functional perspective.

In this study, electrical properties of four groups were measured by constant current EIS system equipped with four electrode probes. The acquired data were mainly affected by the following two factors, the property of tissue and environmental interference (including ambient temperature, air humidity and electromagnetic radiation). Since each sample were tested under the same condition, so the EIS data primarily reflected the electrical property of thyroid specimens.

Among EIS parameters, such as impedance modulus, the real and imaginary part of the impedance and phase angle), the phase angle-frequency curve demonstrated a

potential to distinguish thyroid property, therefore, all the results were analyzed and discussed in phase angle perspective. Between 1kHz and 31.64kHz, phase angles of four groups changed drastically, so we defined MPAD as the test variable to distinguish four groups. MPAD is the absolute value of mean phase angle difference between 31.64kHz and 1kHz (Figure 5). From the experimental results, MPAD changed with different pathological tissues, which reflected mainly the property of thyroid tissues.

From the cytology and electricity perspectives, MPAD significant differences of specific frequency domain were the result of the difference response of different thyroid cells to electric field. It is known that at lower frequencies the current flows mainly through the extra-cellular space, whereas at higher frequencies the current flows both through the extra-cellular space as well as through the intracellular space⁹. Additional, because of ion channels on the cell membrane, which make the cell a leakage capacitor, and cell membrane permeability and arrangement density of cells, based on these cell structural characteristics, none or a few of current with the frequency of 1KHz crossed normal cells and benign lesion cells, all or most passed through the extra-cellular space. At the same time, the stronger membranes polarization, the more intense the current resisted from cell membranes, therefore, phase angle increased with the reactance. Whereas the current frequency reached 31.64KHz, the current crossed cells increase, so reactance decreased, the phase angle decreased with a larger varied amplitude. This phenomenon is due to intact structures, tight junctions, stable electrical properties¹⁰, the strong charge storage capacity of normal cells and benign tumor cells, on the contrary, different electrical properties of malignant cells with respect to healthy and benign cells are attributed to increased cellular

water and salt content, altered (high) membrane permeability, changed packing density, extra-cellular space, orientation of cells and the lack of tight junction⁴⁻⁶, so that cancerous cells can be related to a resistor with a lower resistance or a higher conductance, respectively, than its surrounding⁴, it attracts current and thus enhances the current density through the cancerous cell, and the low frequency current easily penetrated cancerous cells, so that when frequencies increased, the current across the cell changed inconspicuously, the phase angle and its amplitude decreased, so these principles can be used to analyze MPAD differences of different pathological thyroid tissues, and that is why thyroid tissues with same pathology results produced similar MPAD. Other results showed significant differences between group C and D, between group A and D, the MPAD of malignant marginal thyroid tissue located between thyroid cancers and normal thyroid tissues, which may indicate that peritumoral tissues has changed in electrical properties before cancerization. The measured interest points might be precancerous lesions, the result may provide reference value for the range of surgical resection.

MPAD of thyroid was defined as a test variable which was compared with pathologic examination, based on ROC curve analysis, AUC of test variable was 0.838 [with a 95% confidence interval of 0.785–0.891], which demonstrated a certain accuracy. In addition, the optimal diagnostic critical value was 7.59 degrees, namely, when the MPAD of thyroid tumor is greater than or equaled to 7.59 degrees, it is benign; otherwise, it is malignant, and the result showed 86% sensitivity and 72% specificity of MPAD in differentiating malignant from benign thyroid tumors, respectively, the corresponding positive and negative predictive values were 78% and 82%, overall accuracy was 80%. Therefore,

MPAD can be used to diagnose thyroid cancer. Our study results were consistent with Nissan A research team (87% sensitivity, 71% specificity, positive and negative predictive values were 76% and 84%, overall accuracy was 79%).

In addition, statistics showed MPAD in order of descending among four groups: A, D, B and C, the difference may be due to cell electric physiological or pathological causes, whether it reflected thyroid tumor cancerization continuing process, the hypothesis need further studying.

Two cases of FTC were correctly diagnosed by MPAD, however, FNAB and intraoperative frozen hardly give a definite diagnosis, whether MPAD showed an excellent diagnostic role in FTC, which still need a large sample experiments to confirm our result because of our insufficient samples.

Further analysis of reasons of false negative and false positive results. In the false negative results, PTC consisted of 88%. Three causes may explain it, firstly, because of large cases of PTC, which accounted for 95% of group C, besides, measurement errors and limitations of the EIS. Nevertheless, subtypes of PTC need analyzing furtherly and find the reasons from cytology to improve diagnostic technique for a higher accuracy. Other two cases of MTC accounting for 67% of MTC measured, which may result from EIS defect and small sample, but the final reason requires deep-going research from electricity and cytology. In false positive cases, nodular goiter with adenomatous nodules constituted 59%, the reason may be due to the limitations of the experimental conditions, or technical reasons such as measurement error or random error. However, nodular goiter with adenomatous nodule may be a precancerous lesion, whose electrical properties had

changed prior to morphology, whether the result can predict that the benign disease is a kind of precancerous lesion, but no literatures were reported, the above assumption need further experiments.

In summary, our study has demonstrated the diagnostic significance of phase angle in thyroid cancer. EIS is a useful technique to distinguish the property of *in vitro* human thyroid tissue and this can be a complementary method for evaluation of the thyroid tumor. However, the test variable with a wide frequency goes against screening single frequency value and rapid measurement, therefore, it is necessary to screen the phase angle of a single frequency for diagnose thyroid cancer in the future. In addition, besides of conductivity, permittivity, time constant and other parameters may be preferable electrical impedance characteristic parameters in diagnose thyroid cancer, these ideas need further experimental studies to validate.

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Acknowledgements

The authors would like to thank all patients who participated in this study, without whom this investigation would not have been possible.

Funding/Support

None

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Contributions

ZHD and ZWX conceived and designed the study. ZHD performed the experiments.

ZWX and JQZ provided the experimental materials. ZHD wrote the paper. ZHD, JQZ and ZWX reviewed and edited the manuscript. All authors read and approved the manuscript.

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Conflict of interest/Disclosure

The authors have no related conflicts of interest to declare.