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The use of bioimpedance in the detection/screening of tongue cancer

Tai-Ping Sun [a,b,1], Congo Tak-Shing Ching [a,b,1,*], Chi-Sheng Cheng [c,1], Su-Hua Huang [d], Yi-Juai Chen [e], Chin-Sung Hsiao [f], Ching-Haur Chang [f], Shiow-Yuan Huang [f], Hsiu-Li Shieh [b], Wei-Hao Liu [a], Chia-Ming Liu [a], Chung-Yuan Chen [b]

[a] *Graduate Institute of Biomedicine and Biomedical Technology, National Chi Nan University, Nantou, Taiwan*
[b] *Department of Electrical Engineering, National Chi Nan University, Nantou, Taiwan*
[c] *Department of Oral and Maxillofacial Surgery, Taichung Veterans General Hospital, Taichung, Taiwan*
[d] *Department of Biotechnology, Asia University, Taichung, Taiwan*
[e] *Department of Oral and Maxillofacial Surgery, Chung Shan Medical University Hospital, Taichung, Taiwan*
[f] *Department of Photonics and Communication Engineering, Asia University, Taichung County, Taiwan*

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ABSTRACT

Oral cancers are the 11th most common malignancy reported worldwide, accounting for 3% of all newly diagnosed cancer cases, and one with high mortality ratios among all malignancies. The objectives of this study were therefore to study the electrical properties of cancerous tongue tissue and normal tongue tissue, as well as to investigate a new approach for low-cost, noninvasive, and real-time screening of oral cancer. Twelve tongue cancer patients and twelve healthy subjects participated in this study. A disposable probe with four silver electrodes was used to measure the electrical properties of patient's and healthy subject's tongue tissues at six different frequencies, which were 20 Hz, 50 kHz, 1.3 MHz, 2.5 MHz, 3.7 MHz and 5 MHz. The amplitude of the applied voltage was limited to 200 mV. Four measurement parameters of impedance, phase angle, real part of impedance, and imaginary part of impedance of tongue were assessed to see if significant difference in values obtained in patient's and healthy subject's tongue tissues existed. Intraclass correlation coefficient showed that all measurements had good reliability and validity (ICC > 0.95 for all measurements). Significant differences were found at 20 Hz ($p < 0.05$–0.001 for the four measurement parameters) and 50 kHz ($p < 0.001$ for the four measurement parameters) between patient's and healthy subject's tongue tissues. In conclusion, bioimpedance at a particular frequency is a potentially promising technique for tongue cancer screening.

1. Introduction

Oral cancer is one of the 11 most frequently occurring cancers worldwide and has a higher proportion of deaths per number of cases than breast cancer or cervical cancer because of late detection. Diagnostic delay has been shown to be a significant factor in disease progression. The time between diagnosis of premalignant lesion and malignant transformation is relatively short. Studies have demonstrated transformation occurred as soon as 6 months from time of biopsy to definitive cancer diagnosis [1].

The term oral cancer encompasses a diverse group of tumors arising from the oral cavity (i.e., lip, tongue, floor of the mouth, gums, and soft palate). The most common sites for oral cancer are the tongue and floor of the mouth. Oral cancer is a major public health issue in almost all countries of the world. Cancers of the oral cavity accounted for 274,000 cases worldwide in 2002, with almost two thirds occurring in men [2]. According to the figures reported in 2004 by Bureau of Health Promotion, Department of Health, R.O.C. (Taiwan), the prevalence of oral cancer in Taiwan increases 160% in the past 10 years and the mortality increases 110% with the average age of 53. Incidence rates in men are high in Western Europe, Southern Europe, Southern Asia, Southern Africa, and Australia/New Zealand [2]. In females, incidence is relatively high in southern Asia [2].

The routine clinical practice to detect oral cancer is initially made by visual inspection, followed by biopsy of any suspicious lesions found. However, oral cancer can go unnoticed and therefore visual inspection is incapable of effectively screening or detecting cancerous changes in the oral cavity. Such delay in diagnosis may adversely affect patient prognosis. That is why most oral cancer patients present with advanced disease, have secondary tumours and suffer from other co-morbidities. On the other hand, biopsy is

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[*] Corresponding author at: Graduate Institute of Biomedicine and Biomedical Technology, National Chi Nan University, No. 1 University Rd., Puli, Nantou County 54561, Taiwan. Tel.: +886 492910960x4774; fax: +886 492912434.
E-mail address: tsching@ncnu.edu.tw (C.T.S. Ching).

[1] These authors contributed equally to this work.

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an invasive method and this approach increase the emotional trauma to the patient waiting for a diagnosis. New methods for reliable, low-cost, noninvasive, and real-time screening or detection of oral cancer are thus warranted.

In recent times, 'light biopsy' with various optical methods, such as Fluorescence [3,4], Raman [5] and Elastic Scattering [6] spectroscopy, have been investigated to establish techniques for the screening or detection of oral cancer. However, none of these techniques has been proved to be totally reliable in screening or detecting oral cancer and limitations still exist. For example, Fluorescence spectroscopy can be significantly hindered by the presence of tissue scattering and absorption and fail to account for confounding factors such as inflammatory changes that may produce fluorescence emission spectra, resulting in false-positive results. Raman spectroscopy shares the major limitation of other point-detection methods in that only a very small tissue volume is interrogated and it can be very sensitive to mucosal movement. Also, Raman spectroscopy technique is expensive, complex and difficult to adapt for *in vivo* use due to superimposed optical fiber and auto-fluorescence complicating the spectra. Elastic Scattering spectroscopy is insensitive and imaging is very difficult. Source and detector fibers need to be sufficiently separated for the diffusion approximation to be valid, i.e., >0.5 cm, but at this distance would be insensitive to the size and shape of scattering centers. The intention of this study was therefore to investigate a new approach, namely bioimpedance, for reliable, low-cost, noninvasive, and real-time screening or detection of tongue cancer.

Bioimpedance is the measurement of the bioimpedance signal, which is obtained by injecting low-level sinusoidal current in the tissue and measuring the voltage drop generated by the tissue impedance. Bioimpedance signal gives information about electrochemical processes in the tissue and can hence be used for characterizing the tissue or for monitoring physiological changes. The electrical properties of tissue vary with the frequency of the applied electric field as seen from α-, β- and γ-dispersion [7]. The α-dispersion occurs at low frequencies (10 Hz to 10 kHz) and is mainly affected by the ionic environment that surrounds the cells. The β-dispersion (10 kHz to 10 MHz) is a structure relaxation. At higher frequencies, the γ-dispersion is found related to water molecules. The α- and β-dispersion regions are more interesting in medical applications, since most changes between pathological and normal tissue occur in this range [8]. In this study the electrical properties of tongue tissue were measured at α- and β-dispersion regions.

Bioimpedance is well established and has been introduced into clinical investigation of breast cancer [9–12] and cervical cancer [13–15]. In 1999, TransScan TS2000 (TransScan Medical Ltd., Sweden), an impedance-imaging device for breast cancer detection, was approved for use by the American Food and Drug Administration as an adjunct to mammography for the evaluation of equivocal breast lesions [16]. At present, no studies using bioimpedance for the screening or detection of cancerous changes in the oral cavity was reported in the literature. Many *in vitro* [17–20] and *in vivo* [9–12] studies showed that there are significant differences in electrical impedance between normal and malignant human breast tissues; malignant breast tumors have typically lower electrical impedance than surrounding normal tissues. The changed electrical impedance of malignant tissue with respect to surrounding healthy tissues are attributed to increased cellular water and salt content, altered membrane permeability, changed packing density, and orientation of cells [21]. Studies [9,11,18,22] also demonstrated that there are significant differences in electrical impedance between benign and malignant breast tumors. Therefore, the hypothesis of this study was that cancerous tongue tissue has lower impedance compared with surrounding normal tongue tissue.

The aim of this study was to investigate the electrical properties of cancerous tongue tissue and normal tongue tissue, in order to establish a new approach, namely bioimpedance, for reliable, low-cost, noninvasive, and real-time screening or detection/screening of tongue cancer.

2. Materials and methods

Twelve tongue cancer patients (7 men and 5 women; age: 51 ± 5-year old; T1 and T2 stages of oral squamous cell carcinoma) and twelve healthy subjects (6 men and 6 women; age: 48 ± 6-year old) were recruited in this study. The study was approved by The Institutional Review Board of Taichung Veterans General Hospital and the Asia University Medical Research Ethics Committee. Informed consent was obtained from each patient and healthy subject.

Four electrical properties of tongue tissue were measured and they were impedance (Z), phase angle (θ), real part of impedance (R), and imaginary part of impedance (X). Measurements were made using a disposable probe (Fig. 1) with four 1-mm-diameter silver electrodes (2 mm between electrode centers) mounted in square configuration on a plastic bar (5 mm width × 3 mm thick × 100 mm long). The disposable probe was connected to an impedance analyzer (Precision Impedance Analyzer WK6420C, Wayne Kerr Electronics Ltd., United Kingdom) for all measurements. On the other hand, the probe was evaluated in saline of known electrical conductivity and has the accuracy of $\pm 0.2\ \Omega$ on measuring resistance.

2.1. Measurement procedures

For patient measurement, the disposable probe was placed in two separate positions on the patient's tongue: (1) Cancerous Tongue Tissue (CTT) and (2) Normal Tongue Tissue (NTT). The definition of patient's NTT is defined as the tongue tissue 10 mm away from the regional edge of the CTT.

For healthy subject measurement, the disposable probe was placed in two separate positions on the healthy subject's tongue: (1) NTT 1 and (2) NTT 2. The definition of healthy subject's NTT 2 is defined as the tongue tissue 10 mm away from the NTT 1.

At each position, electrical properties of tongue tissue measurements were made at six frequencies of 20 Hz, 50 kHz, 1.3 MHz, 2.5 MHz, 3.7 MHz and 5 MHz, with the amplitude of the applied voltage limited to 200 mV. In all cases, three separate sets of measurement of a position were made in succession in order to check reliability of the measurements.

Before and after experiment, patient's and healthy subject's oral temperatures were orally measured using body-temperature thermometer (Terumo Digital Clinical Thermometer C402, Terumo Corporation Tokyo, Japan).

2.2. Statistical analysis

Intraclass correlation coefficient (ICC) was used to evaluate intrarater reliability (ICC 3,1) for the measurement of Z, θ, R, and X. Paired-sample t test (within group) and independent-samples t test (between groups) were used to determine whether there were significant differences between patient's and healthy subject's

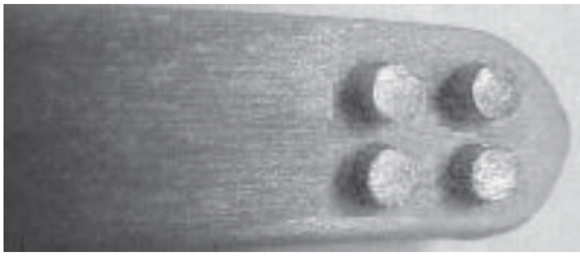

Fig. 1. The four-electrode disposable probe.

Table 1
The oral temperature of patients and healthy subjects before and after experiment.

	Oral temperature (°C)			
	Patients		Healthy subjects	
	Before experiment	After experiment	Before experiment	After experiment
Subject 1	36.6	36.6	36.8	36.8
Subject 2	36.7	36.8	36.7	36.7
Subject 3	36.8	36.8	36.7	36.6
Subject 4	36.6	36.6	36.8	36.8
Subject 5	36.7	36.7	36.6	36.7
Subject 6	36.8	36.8	36.7	36.7
Subject 7	36.8	36.8	36.7	36.7
Subject 8	36.7	36.7	36.8	36.8
Subject 9	36.6	36.6	36.7	36.7
Subject 10	36.8	36.7	36.7	36.7
Subject 11	36.7	36.7	36.7	36.7
Subject 12	36.7	36.7	36.6	36.6

Table 2
Estimation of intrarater reliability (ICC 3,1) for the measurement of impedance, phase angle, real part of impedance, and imaginary part of impedance of patient's and healthy subject's tongue tissues.

	Impedance	Phase angle	Real part of impedance	Imaginary part of impedance
ICC 3,1	0.97	0.96	0.97	0.97

tongue tissues for the test parameters of Z, θ, R, and X at each frequency and oral temperature. All statistical analyses were carried out using SPSS software with the level of statistical significance set at 0.05.

3. Results

Twelve tongue cancer patients and twelve healthy subjects participated in this study. Their pre- and post-experimental oral temperatures were recorded and summarized in Table 1. Their oral temperature ranged from 36.6 °C to 36.8 °C. No statistical significant difference was found on patients' pre- and post-experimental oral temperatures as well as on healthy subjects' pre- and post-experimental oral temperatures. Also, no statistical significant difference was found between the pre-experimental oral temperatures of patients and that of healthy subjects as well as between the post-experimental oral temperatures of patients and that of healthy subjects.

ICC for the intrarater reliability (ICC 3,1) for the measurement of electrical parameters (Z, θ, R, and X) of tongue tissues at different frequencies were summarized in Table 2. ICC ranged from 0.96 to 0.97.

The electrical properties of tongue tissues at different frequencies were summarized in Figs. 2 and 3. It was found that the impedance of patient's and healthy subject's tongue tissues decreased as measurement frequency increasing. Moreover, the impedance of patient's CTT was found to be significantly smaller than that of patient's and healthy subject's NTT at 20 Hz ($p < 0.001$) and 50 kHz ($p < 0.001$).

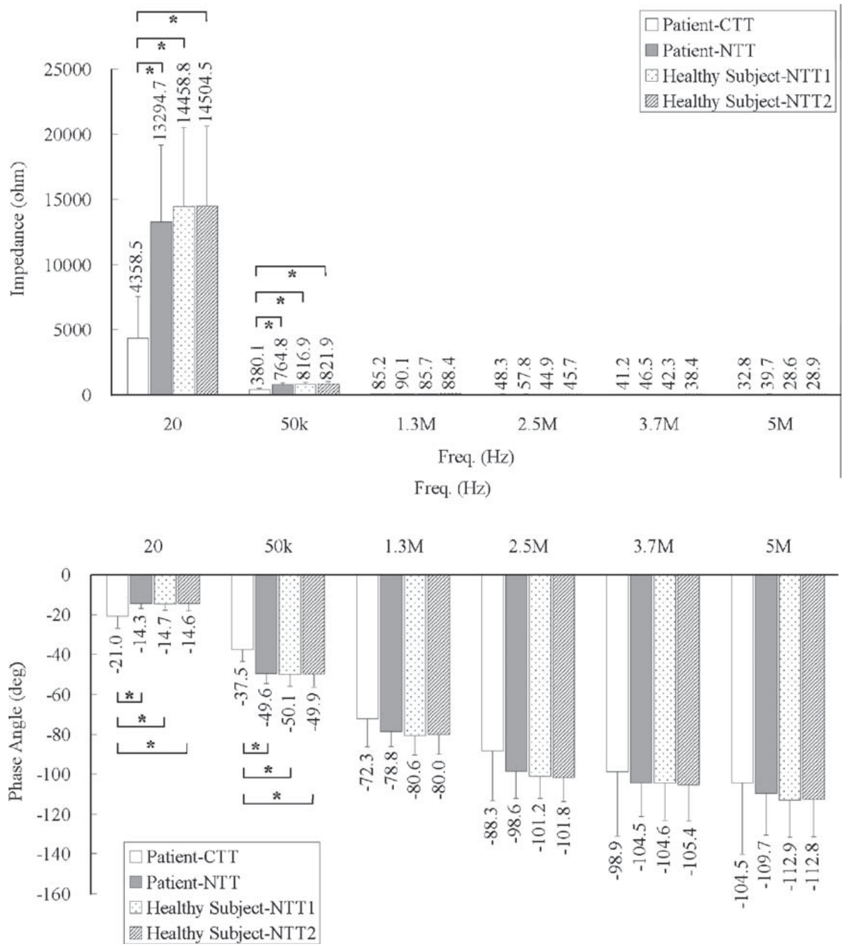

Fig. 2. Impedance and phase angle of patient's and healthy subject's tongue tissues measured at different frequencies. Patient-CTT and Patient-NTT represents the patient's cancerous tongue tissue and normal tongue tissue, respectively. Healthy Subject-NTT1 and Healthy Subject-NTT2 represents the healthy subject's normal tongue tissue 1 and normal tongue tissue 2, respectively. Results were expressed as means and standard deviations. Statistically significant differences were shown, with $p < 0.001$ represented by *.

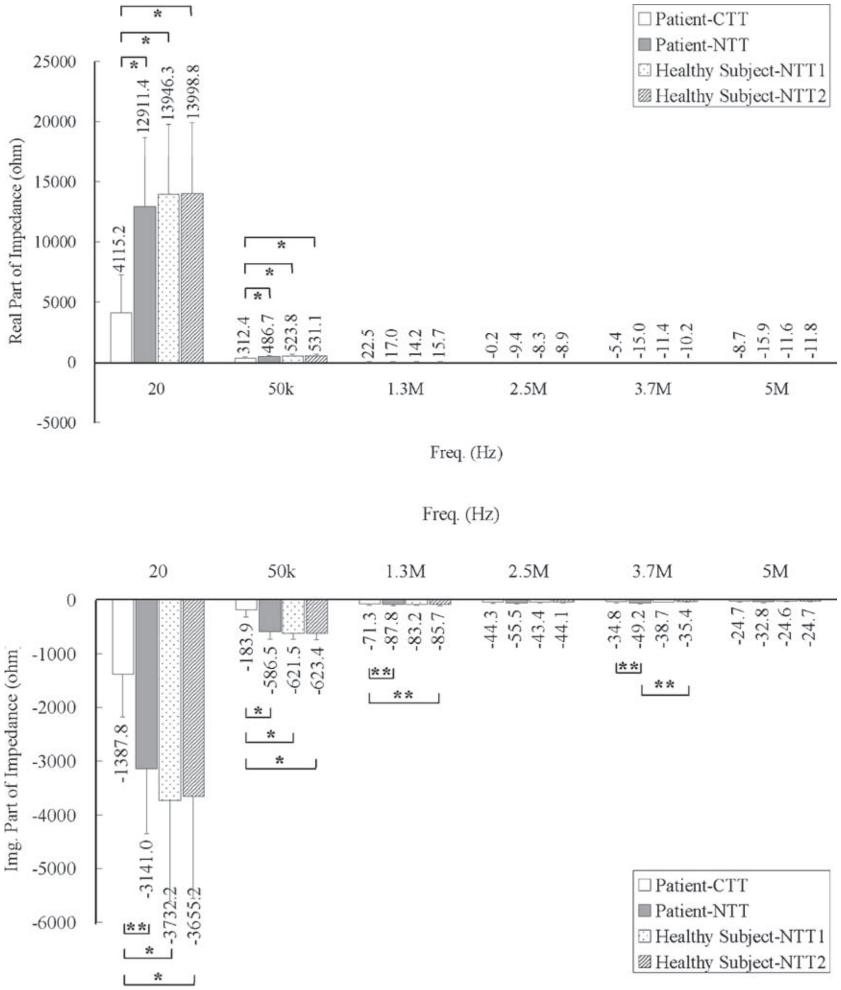

Fig. 3. Real part and imaginary part of impedance of patient's and healthy subject's tongue tissues measured at different frequencies. Patient-CTT and Patient-NTT represents the patient's cancerous tongue tissue and normal tongue tissue, respectively. Healthy Subject-NTT1 and Healthy Subject-NTT2 represents the healthy subject's normal tongue tissue 1 and normal tongue tissue 2, respectively. Results were expressed as means and standard deviations. Statistically significant differences were shown, with $p < 0.001$ represented by * and $p < 0.05$ represented by **.

On the other hand, it was found that the phase angle of patient's and healthy subject's tongue tissues reduced as measurement frequency rising. Furthermore, the phase angle of patient's CTT was found to be significantly smaller than that of patient's and healthy subject's NTT at 20 Hz ($p < 0.001$), but significantly larger than that of patient's and healthy subject's NTT at 50 kHz ($p < 0.001$).

The real part of impedance of patient's and healthy subject's tongue tissues was found to decline as measurement frequency increasing. It was also found that the real part of impedance of patient's CTT was significantly smaller than that of patient's and healthy subject's NTT at 20 Hz ($p < 0.001$) and 50 kHz ($p < 0.001$).

The imaginary part of impedance of patient's and healthy subject's tongue tissues was found to increase as measurement frequency increasing. In addition, the imaginary part of impedance of patient's CTT was found to be significantly larger than that of patient's and healthy subject's NTT at 20 Hz ($p < 0.05$–0.001) and 50 kHz ($p < 0.001$).

4. Discussion

In this study, the oral temperature of patients and healthy subjects before and after experiment were measured as impedance of tissue varies with temperature [23]. Results showed that only patient number 2 and 10 as well as healthy subject number 3 and 5 has changed in oral temperature after experiment. There were 2 possible reasons for such temperature change (0.1 °C). It might be due to the patient's and healthy subject's real oral temperature change. Also, it might be due to the instrumentation error during measurement as the body-temperature thermometer has the accuracy of ±0.1 °C. For the other patients and healthy subjects, their oral temperature was constant before and after experiment. Among the patients, the lowest and the highest oral temperature were 36.6 °C and 36.8 °C respectively, with the temperature difference of only 0.2 °C. Among the healthy subjects, the lowest and the highest oral temperature were also 36.6 °C and 36.8 °C, respectively, with the temperature difference of only 0.2 °C. Because the oral temperature difference among patients and healthy subjects was not large, the effect of temperature on patients' and healthy subjects' impedance was assumed to be minimal.

The ICC is a measure used to quantify the reproducibility of a variable and together a measure of the homogeneity within groups of replicate measurements relative to the total variation between groups. It has been suggested that ICC values above 0.75 are indicative of good reliability and those below 0.75 should be considered as poor to moderate [24]. Moreover, Portney and Watkins [25] state; "For many clinical measurements reliability should exceed 0.90 to ensure reasonable validity". All the ICC(3,1) measurements in this study exceeded 0.90 which suggests they have exceeded the threshold for both good reliability and reasonable validity.

A four-electrode, rather than two-electrode, impedance measurement was employed because this could lead to the measured impedance essentially independent of the contact impedance between electrode and tissue. Because four-electrode configuration was utilized in this study and human tongue is small, the disposable probe and its sensing area should be as small as possible. In this study, the sensing area of the probe was about 9 mm^2 (3 mm × 3 mm) with the probe size of 5 mm width × 3 mm thick × 100 mm long. This could ensure the probe to be capable of placing in most of the part of the human tongue.

Tongue cancer is usually associated with the squamous cell carcinoma (SCC) [26]. SCC is a malignant neoplasm of mucosal origin [27] and often causes abnormality of the covering mucosa of the oral cavity [28]. In this study, α- and β-dispersion regions (20 Hz to 5 MHz) for tongue tissue electrical properties (Z, θ, R, and X) measurement was conducted. Our findings showed that not all the frequencies within the α- and β-dispersion regions could be able to use for distinguishing the CTT and NTT. Only electrical properties (Z, θ, R, and X) measurement at 20 Hz and 50 kHz could significantly distinguish the CTT and NTT. Results also showed that Z and R of patient's CTT were significantly smaller ($p < 0.001$ for all cases; Z: 3-fold at 20 Hz and 2-fold at 50 kHz; R: 3-fold at 20 Hz and 1.7-fold at 50 kHz) than that of patient's and healthy subject's NTT. This might be due to the abnormality of the covering mucosa of the patient's CTT. A possible explanation for the changes observed is as follows. At low frequency (<1 MHz) most of the current flow around the cell without being able to penetrate into the cell and the measured values of Z and R are dominated by contributions from the most superficial layer of the oral mucosa. In NTT, cells are well packed and attached to each other, therefore the current at low frequency has a very narrow and tortuous intercellular route to follow, which therefore has high resistance. However, cancer cells normally have a phenomenon of metastases, which have opposite effects on resistance. CTT has widening extracellular space because of the loss of intercellular connections, a universal characteristic of cancer leading to metastases, and this would be expected to decrease resistance.

Both 20 Hz and 50 kHz resulted in significant separation of CTT from NTT on the 4 electrical properties (Z, θ, R, and X) measurement. Therefore, both 20 Hz and 50 kHz was suggested as the optimum frequency for distinguishing the CTT and NTT.

There are several advantages of this method as a potential screening test over the current screening methods. It is relatively low-cost. Also, it provides real-time results. The potential advantages of real-time screening tests include a reduction in patient anxiety, improved patient compliance and ability to repeat inadequate tests immediately. Last but not least, it requires little training, and thus can be easily used in primary care or in the developing countries where the organizational structure and economical factors limit national screening programs.

In conclusion, significant separation of CTT from NTT could be achieved at both 20 Hz and 50 kHz electrical properties (Z, θ, R, and X) measurement. ICC showed that all measurements had good reliability and validity. The advantage of this method as a potential screening test is that it can provide an immediate result and may be used by those with minimal training in the setting of primary care or in the developing world.

Conflict of interest statement

This is no conflict of interest for this work.

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