Measurement of the Electrical Bio-Impedance of Breast Tumors

T. Morimoto, Y. Kinouchi, T. Iritani, S. Kimura, Y. Konishi, N. Mitsuyama, K. Komaki, Y. Monden

*Second Department of Surgery, School of Medicine,
**Department of Electrical and Electronic Engineering, Faculty of Engineering, and
*Department of Electronic Engineering, College of Industrial Technology, University of Tokushima, Japan

Key Words. Electrical bio-impedance · Breast tumor · Diagnostic modality · Measurement in vivo

Abstract. A new impedance analytical system was developed, and measurements were performed over a frequency range of 0–200 kHz by the three-electrode method. The three electrodes consist of a coaxial needle electrode inserted into the tumor and a large reference electrode on the upper abdominal wall. The electrical bio-impedance was measured in 54 patients with breast tumors. The biological tissue can be regarded electrically as an equivalent consisting of extracellular resistance (Re), intracellular resistance (Ri), and electrical capacitance of the cell membrane (Cm). These three parameters were calculated from the measured values of electrical bio-impedance by the curve-fitting technique using a computer program. It was found that Re and Ri of breast cancers were significantly higher than those of benign tumors (p < 0.01), and that Cm of breast cancers was significantly lower than that of benign tumors (p < 0.01). Measurement of the electrical bio-impedance of breast tumors may have value in the differential diagnosis of breast lesions.

Introduction

It is well known that the electrical properties of biological tissues differ significantly depending on their structure [1, 2]. This has been reported by investigators studying the application of differences in the electrical properties of tumors to the clinical aspect. Electrical properties of malignant breast tumors have been investigated by Fricke and Morse [3]. They found significantly higher permeability of the tumor tissue at 20 kHz compared to normal or nonmalignant tissues. Similar results have been reported by several other investigators [4–7]. Recently, Surowiec et al. [8] studied the electrical properties of breast carcinoma and surrounding tissues at frequencies from 20 kHz to 10 MHz using an automatic network analyzer.

We developed a new measurement system of the electrical bio-impedance of various tumors. In this study, the impedance of breast tumors was measured in vivo, and the usefulness of impedance information for tumor diagnosis was investigated.
Materials and Methods

Principle of Measurement

The pulse response method using a pulse current containing multiple-frequency components was used in this study. Assuming the applied pulse current to be \( i(t) \), the response voltage to be \( v(t) \), and their Fourier transformation to be \( I(o) \) and \( V(o) \), respectively, the impedance, \( Z(o) \), is expressed by the following equation:

\[
Z(o) = \frac{V(o)}{I(o)}
\]

In actual measurement, the pulse current \( i(t) \), defined by the following function, was used:

\[
i(t) = Im \sin \left[ \frac{\pi(t-2\tau)/\tau}{\pi} \right] \times \cos \left[ \frac{2\pi(t-2\tau)/\tau}{\pi} \right] \times \frac{1}{1 - \left[ \frac{2(t-2\tau)/\tau}{\pi} \right]^2}
\]

where \( Im = 10 \mu A, \beta = 0.5, \tau = 2.5 \mu s \), and \( 0 \leq t \leq 4\tau \). Since the frequency spectrum of \( I(o) \) is 0 at 300 kHz, it was possible to measure the impedance up to about 200 kHz.

In the measurement, a host computer (PC9801E, NEC, Tokyo, Japan) and a slave computer (Microprocessor 8086, Intel Co., USA) were used. The host computer was used for the generation of pulse current waveform data, calculation of impedance, display of vector trajectory and other data processing. The slave computer was used for controlling measurement circuits and eliminating noise from the measured data by using the synchronous addition method (256-fold addition). In the measurement circuits, pulse currents were applied, and the data was sampled at high speed (0.2 \( \mu s \)). It took about 1 min to calculate the impedance of each measurement.

Electrode Configuration

Figure 1 shows the arrangement for a three-electrode method. The coaxial needle electrode was inserted into the tumor tissues, and a plate electrode was placed on the upper abdominal wall. A pulse current with a peak value of 5 \( \mu A \) was applied between the outside conductor of the needle electrode and the plate electrode, and the response voltage between the inside conductor and the plate electrode was measured with an instrument we developed. The plate electrode was a counterelectrode plate (80 \( \times \) 160 mm\(^2\)) of an electrosurgical knife. The impedance was calculated with a personal computer (PC9801E, NEC, Tokyo, Japan).

The coaxial needle electrode was fabricated by inserting a silver wire 0.2 mm in diameter into a stainless steel tube 0.5 mm in diameter and 40 mm in length. The lumen and outside were insulated with epoxy resin, and only the end section was used as an electrode. The area of this end electrode was about 0.63 mm\(^2\) outside and about 0.1 mm\(^2\) inside, and the current density on the outside of the electrode was about 0.8 mA/cm\(^2\).

Measurement Method

Immediately before biopsy was performed, under general or local anesthesia, the coaxial needle electrode was inserted into the fatty tissue, mammary tissue and breast tumor through a surgical incision, and in each patient, 3-5 measurements were carried out by the method stated above.

Investigation

Individual cells and biological tissue can be ideally modeled with a simple equivalent circuit (fig. 2) in which \( R \) and \( R_i \) represent extracellular and intracellular resistance and \( C_m \) cell membrane capacitance [9]. In this study, from the measured impedance value, \( R \), \( R_i \) and \( C_m \) were calculated on the basis of a bio-equivalent circuit by means of the curve-fitting technique [9] using a computer program. The frequency impedance trajectory of the circuit in figure 2b is a semicircle on a complex plane intersecting the real axis at points \( R \) and \( R_i / (R + R_i) \). In the computer program, a measured trajectory is curve-fitted to a semicircle by a least-square method, and the intersections of the semicircle and the real axis give \( R \) and \( R_i \). \( C_m \) is calculated basically from an impedance value measured at a frequency \( \omega \) by using \( R \) and \( R_i \) obtained above. Here, calculated values of \( C_m \) for every frequency are averaged. These three parameters were compared between the fatty tissue, mammary tissue and breast tumor.

All resected materials were fixed in 10% formalin solution, and the tissues were sectioned on cut surface with the longest axis in the primary tumor, embedded in paraffin and stained with hematoxylin-eosin and Azan-Mallory. The tissue slice specimens were used for histological study. Histological classification was according to the rules established by the Japanese Breast Cancer Society [10]. The areas of epithelial and stromal components were measured by means of an analyzer system (Color Image Analyzer 102, Olympus, Tokyo, Japan), the area ratio of the stroma was
Fig. 1. Electrode configuration and coaxial electrodes.
Fig. 2. a Equivalent circuit of biological tissue. b Simple equivalent circuit. Rm = Cell membrane resistance; Ce = extracellular capacitance; Ci = intracellular capacitance.
Table 1. Patient characteristics

<table>
<thead>
<tr>
<th></th>
<th>Breast cancer</th>
<th>Fibroadenoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cases</td>
<td>31</td>
<td>13</td>
</tr>
<tr>
<td>Median age, years (range)</td>
<td>52 (29–77)</td>
<td>38 (21–58)</td>
</tr>
<tr>
<td>Cases with tumor size</td>
<td></td>
<td></td>
</tr>
<tr>
<td>up to 0.9 cm</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>1.0–1.9 cm</td>
<td>11</td>
<td>9</td>
</tr>
<tr>
<td>2.0–4.9 cm</td>
<td>16</td>
<td>3</td>
</tr>
<tr>
<td>5.0– cm</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>median (range)</td>
<td>2.2 (0.9–6.0)</td>
<td>1.5 (0.9–3.3)</td>
</tr>
<tr>
<td>Histological classification of cases</td>
<td></td>
<td></td>
</tr>
<tr>
<td>papillotubular carcinoma</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>solid-tubular carcinoma</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>scirrhous carcinoma</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td>pericanalicular type</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>intracanalicular type</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>mixed type</td>
<td>5</td>
<td></td>
</tr>
</tbody>
</table>

Calculated for each case using the formula $S/(S + E) \times 100\%$, where $S =$ area of stromal components and $E =$ area of epithelial components. The stromal ratio was compared to the values of Re, Ri and Cm.

Statistical analyses were conducted using Wilcoxon's test and analysis of variance, and values $< 0.05$ were considered significant. Values were expressed as the mean $\pm$ SD.

**Materials**

This study was based on 54 patients having undergone resection of a breast tumor at the Second Department of Surgery, School of Medicine, The University of Tokushima, between April 1986 and December 1987 (Table 1). There were 31 cases of breast cancer, 13 cases of fibroadenoma and 10 cases of mastopathy. The median tumor size of breast cancer and fibroadenoma was 2.2 and 1.5 cm in diameter, respectively. The former ranged from 0.9 to 6.0 cm, the latter from 0.9 to 3.3 cm (Table 1).

**Results**

The impedance at 10 kHz ($Z$ at 10 kHz) was $1,271 \pm 508 \Omega$ in breast cancer, $806 \pm 144 \Omega$ in fibroadenoma, $674 \pm 157 \Omega$ in 'normal breast tissue', and $5,668 \pm 3,166 \Omega$ in fatty tissue. The data of 'normal breast tissue' comprised the values of mastopathy and mammary tissue around the tumor. There were no significant differences between fibroadenoma and 'normal breast tissue'. Compared to these values, breast cancer had a significantly higher value ($p < 0.01$). Furthermore, the fatty tissue recorded higher values than breast cancer ($p < 0.01$; fig. 3).

The value of Re was $1,445 \pm 586 \Omega$ in breast cancer, $954 \pm 156 \Omega$ in fibroadenoma, $772 \pm 203 \Omega$ in 'normal breast tissue', and $6,044 \pm 3,388 \Omega$ in fatty tissue. These Re values are the same as the tendency for $Z$ at 10 kHz, that is, breast cancer demonstrated significantly higher values in comparison with fibroadenoma and 'normal breast tissue' ($p < 0.01$), and the fatty tissue showed higher values than breast cancer ($p < 0.01$; fig. 3).

The value of Ri was $2,493 \pm 1,490 \Omega$ in breast cancer, $1,179 \pm 446 \Omega$ in fibroadenoma, $1,955 \pm 1,414 \Omega$ in 'normal breast tis-
sue' and 8,622 ± 4,210 Ω in fatty tissue. Thus, the value of Ri showed nearly the same tendency as the Re value (fig. 3).

The value for Cm was 3,525 ± 1,879 pF in breast cancer, 6,171 ± 2,365 pF in fibroadenoma, 5,946 ± 3,194 pF in 'normal breast tissue' and 554 ± 262 pF in fatty tissue. Fibroadenoma and 'normal breast tissue' had high Cm values, with no difference between them. The lowest Cm value was recorded for fatty tissue. The value for Cm in breast cancer was significantly lower than the values for fibroadenoma and 'normal breast tissue' (p < 0.01; fig. 3).

When the values of Z at 10 kHz, Re, Ri and Cm were compared as a function of the histological type of breast cancer, there were no differences between papillotubular carcinoma, solid-tubular carcinoma and scirrhous carcinoma.

The stromal ratio was 55.8 ± 18.7% in breast cancer, which was significantly smaller than the 86.4 ± 7.2% in fibroadenoma (p < 0.01). There was no correlation between the stromal ratio and the values of Re, Ri and Cm in 34 cases of breast cancer and 11 cases of fibroadenoma, respectively (fig. 4, 5).

Discussion

At radio frequencies, the electrical properties of biological matter are basically determined by the changing of the cell membrane through a combined impedance of the intracellular and extracellular media. They also depend on the chemical composition of the tissue [2]. In general, the electrical properties of biological tissues show three dispersions (al-
Electrical Bio-Impedance of Breast Tumor

Fig. 4. Correlation between value of Re and stromal ratio.
Fig. 5. Correlation between value of Cm and stromal ratio.

pha, beta and gamma), and the beta-dispersion is said to express the tissue structure as estimated by the cell level relaxation phenomenon [1, 2]. Our system can measure a frequency range of 0–100 kHz, and this region of the measurement is within the limits of beta-dispersion, and hence it was considered that the electrical properties of tissues were compared.

According to Cole [11], the bio-impedance draws an arc called the Cole-Cole distribution when expressed on a complex plane, and the impedance spectrum trajectory determined in this study closely followed a Cole-Cole distribution. By assuming this impedance trajectory to be a semicircle having its center at the real axis, the values of Re, Ri and Cm expressed in the bio-equivalent circuit can be calculated [9]. In this study, these values were calculated and compared between breast tumors, and a significant difference was detected depending on the disease. That is, the values of Re and Ri in breast cancer were significantly higher than those in benign tumor, and the value of Cm in breast cancer was significantly lower than that in benign tumor. The stromal ratio of breast cancer was significantly smaller than that of fibroadenoma. In this study, the relationship between the stromal ratio and
the values of Re, Ri and Cm were investigated. There was no correlation between the stromal ratio and these values. These results suggest that the significant differences of these values between breast tumors are not dependent on only the stromal ratio. Surowiec et al. [8] reported that significant differences in electrical properties between the breast cancer tissues and the surrounding tissues can be associated with the cellular heterogeneity and structural differences. In our data also, these significant differences between breast cancer and benign tumor can be expected to be associated with the structural and cellular inhomogeneities of the tumor tissue. These results seem to indicate that measurement of the electrical bio-impedance can be relevant to biological characterization of benign and malignant tumors, especially in the breast.

Recently, fine-needle aspiration cytology in the diagnosis of palpable breast tumors tends to become the most valuable diagnostic technique [12]. In this study the needle electrode was inserted into the tumor through a surgical incision of biopsy. It is possible to insert the needle electrode into the tumor through the skin. Therefore, this procedure can potentially be used as a diagnostic modality for breast tumors in combination with fine-needle aspiration.

Acknowledgement

This work was supported in part by a grant-in-aid for scientific research (60570592) from the Ministry of Education, Science and Culture, Japan.

References


Received: June 12, 1989
Accepted: December 8, 1989

Tadaoki Morimoto, MD
Second Department of Surgery
School of Medicine
The University of Tokushima
Karamoto-cho 3
Tokushima 770 (Japan)