ORIGINAL

Basic study of new diagnostic modality according to non-invasive measurement of the electrical conductivity of tissues

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Abstract : The purposes of this study were to estimate the electrical conductivity of tissues by non-invasively measuring the electrical bio-impedance, to develop a new method for tissue diagnosis, i.e., electrical impedance tomography (EIT).

Tissue models were first designed taking into consideration the distribution of the fat tissue, muscle and bone in the human forearm, and then the intra-tissue distributions of electrical potential and field, and the electrical impedance in the models was theoretically analyzed by the three-dimensional finite element method. The electrical impedance of both forearms was measured in healthy human subjects, and estimated the electrical conductivity of individual local tissues. The results of the analysis showed that the distributions of electrical potential and field were affected by the presence of fat tissue but not by the presence or absence of bone. In addition, as a result of calculation of the electrical resistance of the extracellular fluid (Re) in each model, it was found that the value of bio-impedance was influenced by the presence of fat tissue, and the value of bio-impedance was increased by the intervention of a fat layer.

The electrical conductivity estimated by fitting the observed values to the values obtained by finite element analysis was 0.40 S/m and 0.15 S/m for male muscle and fat tissue, and 0.35 S/m and 0.11 S/m for female muscle and fat tissue, respectively. The sex difference in the slope of linear approximation in the estimation of electrical conductivity of the males and females was thought to be due to sex differences in the properties and structure of fat tissue.

These results suggest that local tissues can be diagnosed differentially and electrically by percutaneous measurement of local bio-impedance and subsequent estimation of the electrical conductivity of each tissue. **J. Med. Invest. 51 : 218-225, August, 2004**

Keywords : *electrical bio-impedance, electrical conductivity, measurement, non-invasive electrode, soft tissue*

Received for publication April 28, 2004; accepted July 20, 2004.

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INTRODUCTION

To obtain information on biological tissues, X-rays, ultrasound and magnetic resonance are utilized, and diagnostic modalities based on these technologies are conventionally used in clinical medicine. Imaging based on density distribution is the basis of these diagnostic methods. On the other hand, the electrical bio-impedance measured over a frequency band (1 kHz to 1MHz) in the β-dispersion region reflects the structure and physiological function of biological tissues at the cellular level and is therefore expected to provide different bio-information compared to that obtained by the conventional methods. In our previous basic and clinical studies, we demonstrated that bio-impedance information obtained by using invasive needle electrodes is useful for estimation of ischemic structural changes in hepatic cells and tissues (1) and for differential diagnosis of benign and malignant breast and lung tumors (2-4). We have also reported that benign and malignant superficial tumors, including breast cancer, can be differentiated by percutaneous measurement of the local impedance using four non-invasive electrodes (5).

In the present study, tissue models for the forearm were designed by taking into account the distributions of fat tissue, muscle and bone, and then the intra-tissue distributions of electrical potential and electrical field and the electrical impedance were analyzed by the three-dimensional finite element method. Furthermore, actual electrical bio-impedance values measured in humans and the values obtained by tissue model analyses were used for simulation to estimate the electrical conductivity of individual subcutaneous tissues. The purposes of the present study were to estimate the electrical conductivity of tissues and to diagnose subcutaneous tissues differentially by measuring the local bio-impedance percutaneously using non-invasive electrodes, to explore the possibility of imaging conductivity differences and to achieve development of Electrical Impedance Tomography (EIT).

MATERIALS AND METHODS

1) Simulation study

① Forearm models

Based on MRI images, the forearm was regarded as a tube which has the radius and the ulna at its center, which is surrounded by antebrachial muscle and fat tissue. Then the following four models were designed by varying the compositions : Model A was based on the assumption that the forearm is composed entirely of muscle, model B was model A plus bone alone, model C was model A plus fat tissue alone, and model D was model A plus bone and fat tissue (Fig.1 a).

② Analysis of forearm models by the three-dimensional finite element method

Prior to theoretical analysis, the electrical conductivity values of the muscle (σm), bone (σb) and fat tissue (σf) were defined as 0.4S/m, 0.005S/m and 0.15S/m, respectively, based on the data reported previously.[2, 3] Then, the distributions of the electrical potential and electrical field and the value of the electrical impedance

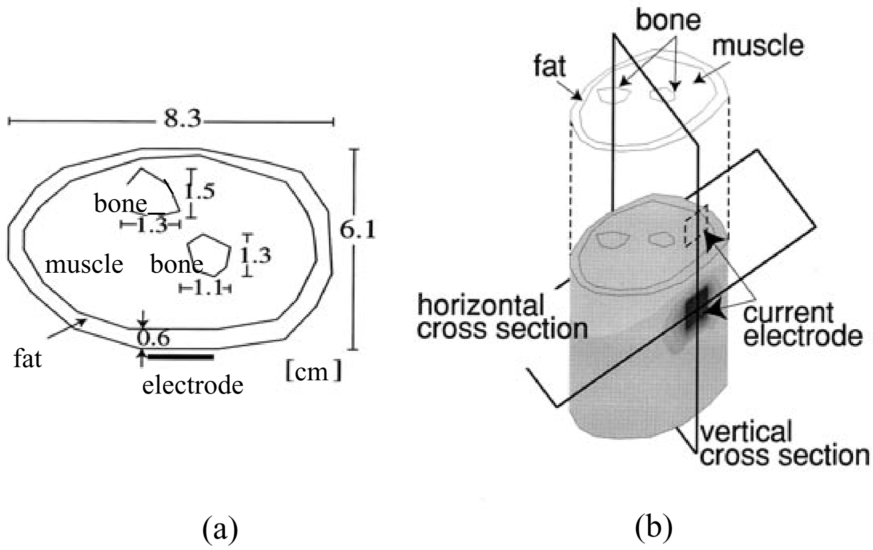


Figure 1.(a) Human forearm models. Model A : the forearm was assumed to contain muscle alone ; model B : model A plus bone ; model C : model A plus fat tissue ; and model D : model A plus bone and fat tissue. (b) Three-dimensional figure of analysis of human forearm models. A pair of electrodes for supplying electrical current is shown in top and bottom of a human forearm model. We analyzed each electrical potential distribution and electrical field distribution about horizontal cross section and vertical cross section in a figure.

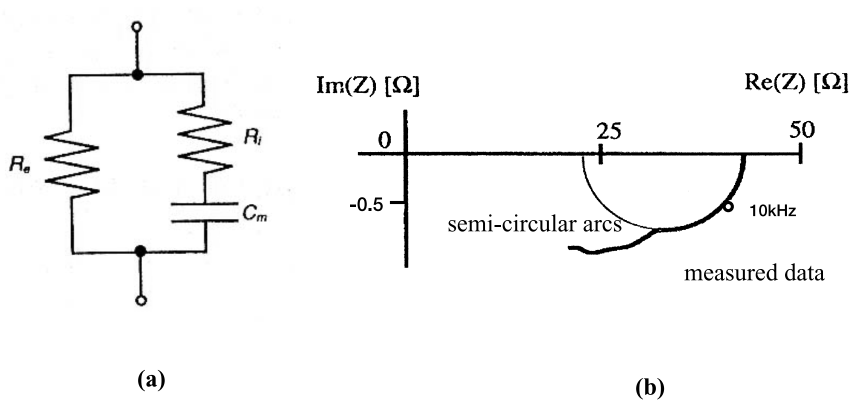


Figure 2. **An example of impedance trajectories in healthy subjects. The solid line shows observed values in a frequency range from 0 to 100 kHz. The impedance trajectory was approximated to a semi-circle using the values observed in a frequency range from 0 to 35 kHz, and the three parameters corresponding to the equivalent circuit of tissue, i.e., extracellular fluid resistance (Re), intracellular fluid resistance (Ri) and cellular membrane capacity (Cm), were calculated.**

were analyzed by the three-dimensional finite element method. Since the distribution of electrical potential is symmetrical around the cross section at the electrode center (Fig.1b), a 1/2 model was used for actual analysis. Voltages of ± ν (ν=1V in actual analysis) were applied to the current-supplying electrode, and the central cross section of both the left and right current-supplying electrodes was set to be 0V. The analytical software used was an electrical field program by the finite element method, MAGNA/FIM (CRC General Research Institute, Tokyo).

2) Bio-impedance measuring

① Measuring equipment

A bio-impedance measuring device using the pulse response method was developed in cooperation with a manufacturer (6, 7). This equipment uses a pulse waveform with an approximate raised cosine spectrum, which enables measurement of the impedance in a β-dispersion region reflecting biological tissue structures. The duration of measurement was 2 seconds, and the measurement error was less than 1%. Using this device, the electrical bio-impedance of the forearm was measured in healthy human subjects.

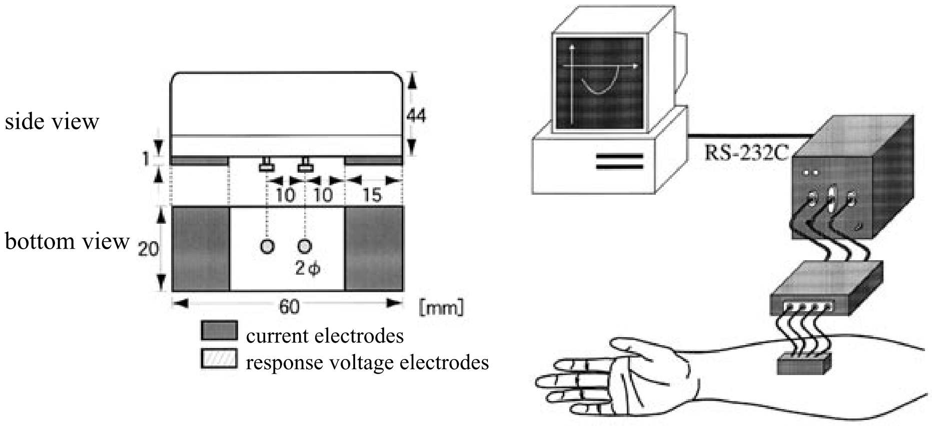
The impedance trajectory actually obtained over a frequency range of 0 to 100kHz using four electrodes is shown in Fig.2. The impedance trajectory over a low frequency range of up to 35kHz formed a part of a circular arc having its center on the real axis. Therefore, the following three parameters correspond to the equivalent circuit of tissues : extracellular fluid resistance (Re), intracellular fluid resistance (Ri) and cellular membrane capacitance (Cm) tentatively assigned. These parameters were able to be calculated by approximating the trajectory measured in the low frequency region give semi-circular arc (5).

② Measuring electrodes

As shown in Fig.3a, electrical bio-impedance in humans was measured non-invasively using four electrodes consisting of a pair of electrodes for supplying electrical current and another pair for detecting the response voltage. These electrodes were attached firmly to the measurement site on the skin surface, and pulse currents (0 to 200kHz) were applied between the disc electrodes on both ends. Response voltage signals were measured between the two central spring electrodes and subjected to Fourier transformation to calculate the electrical impedance (6, 7). Since the electrode surface was deformed locally when it was pressed onto the skin surface, a spring was equipped inside the voltage-detecting electrode, and a gel-state pad containing a sticky electrolyte was attached to the current-supplying electrode to prevent local deformation and to ensure contact with the skin (5).

③ Electrical impedance of human forearm, and ultrasonic measurement of the thickness of subcutaneous fat

The electrical impedance of both the left and right forearms was measured in 18 healthy human subjects (12 males, aged 22 to 25 years, and six females, aged 20 to 23 years). After cleaning the forearm skin with ethanol and smearing on electrode gel, the electrodes were attached and the local electrical impedance was measured (Fig.3b). The thickness of subcutaneous fat(Ts) beneath the measurement site on the forearm was measured using MRI and an ultrasonic device. Prior to these measurements, written informed consent had been obtained from each of the 18 subjects.



(a) (b)

Figure 3. Measuring system and four measuring electrodes. (a) Electrical bio-impedance in humans was measured non-invasively using four electrodes. These electrodes were attached firmly to the measurement site on the skin surface, and pulse currents (0 to 200 kHz) were applied between the disc electrodes on both ends. Lateral and bottom views are shown. (b) The two outer electrodes are current-supplying electrodes, and the two inner electrodes are response voltage-detecting electrodes.

3) Estimation of the electrical conductivity of muscle and fat

Given each electrical conductivity of muscle (σm), fat tissue (σf) and bone (σb), and a model of the tissue structure, it is possible to calculate the Re by finite element analysis. However, as $\sigma b=1/80\times\sigma m$ is set from the data reported previously and the published literature, the electrical conductivity of both σm and σf is estimated. Here, their electrical conductivity was estimated using the method following. That is, using three models of the tissue structure corresponding to Ts=2 mm, Ts=6 mm and Ts=10 mm, setting σm and σf arbitrarily, the Re value was estimated by finite element analysis. The error between the estimated Re values and the observed Re values obtained by equation (1)(see below) was calculated. This error is a function of σm and σf, which were obtained as the least square sum of error in the three structural models. These values were determined as the estimated values of the electrical conductivity.

The above method for estimating the electrical conductivity was applied to measurement data for the male and female subjects, and the electrical conductivity was estimated. In addition, in the case of zero thickness (Ts=0), the Re value of fat tissue in the absence of real measurement data can be obtained by finite element analysis using a structural model of Ts=0 and the electrical conductivity estimated by the above methods.

4) Statistical analysis

The unpaired t-test, paired t-test and Spearman's rank correlation coefficient method were used for statistical analyses.

RESULTS

1) Results of analyses by the three-dimensional finite element method

The results of analyses of the distribution of the electrical potential on the horizontal and vertical cross sections are shown in Fig.4, respectively. The high potential portion on the left side of each model in Fig.4 was the site of attachment of the current-supplying electrode. No difference was observed in the potential distribution when the analytical results were compared between model A and model B, whereas a clear difference was observed when model B was compared with model D. Little differences in the potential distribution was observed between model C and model D. The depth where the applied voltage (1V) was halved was 0.9 cm from the skin surface for models A and B, while it was 0.5 cm for model D.

The distribution of the electrical field was concentrated in the skin surface, namely, in the vicinity of the electrode contacting a measurement site (Fig.5). Similarly to the distribution of electrical potential, there was no difference in the electrical field distribution between models A and B, whereas a clear difference was observed between model B and model D. Little differences were observed between model C and model D. It was assumed that the region where 90% of the total electrical current from the current-supplying elec-

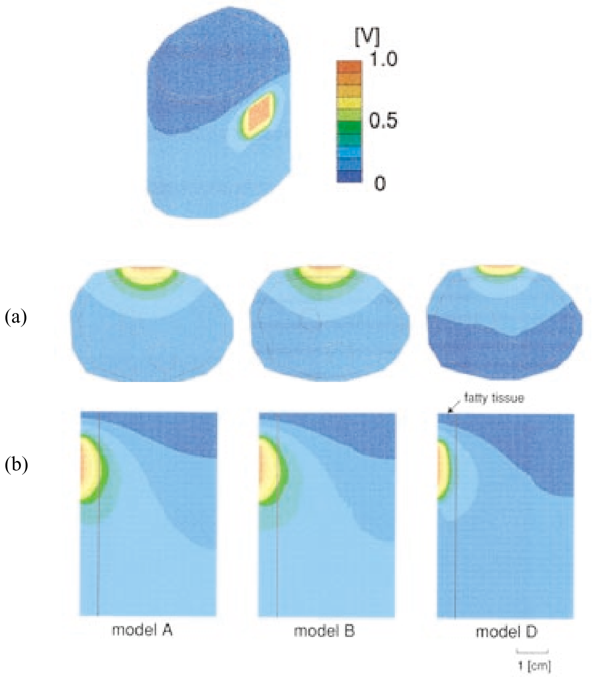


Figure 4. **The analyzed distribution of electrical potential on a horizontal cross section (a) a vertical cross section (b)**

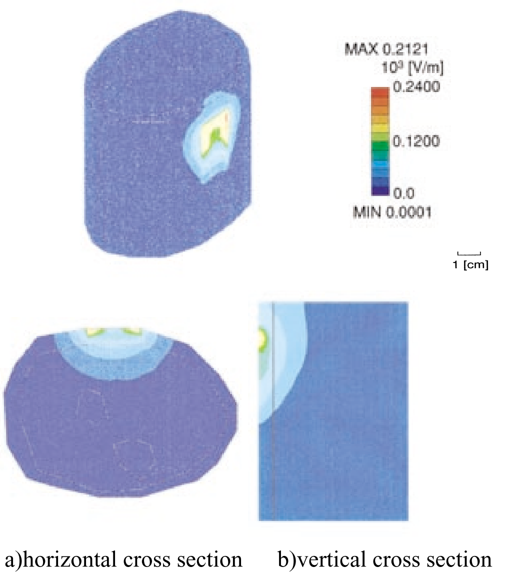


Figure 5. **The analyzed distribution of electrical field on a horizontal cross section (a) and a vertical cross section (b)**

Table 1. **Comparison of extracellular fluid resistance (Re) values in individual models**

	Model A	Model B	Model C	Model D
Voltage electrodes [V]	0.151	0.150	0.110	0.107
Current electrodes [mA]	7.37	7.28	3.88	3.85
Re [Ω]	41.0	41.2	56.7	55.6

trode is flowing into the body is the measurement region, and such a region was found to be 3cm below the skin surface (the surface in contact with the electrode).

The extracellular fluid resistance (Re) was then calculated from the values of the current-supplying electrode and the voltage-detecting electrode for each model (Table 1). Since the distribution of electrical potential is symmetrical around the cross section at the electrode center, a 1/2 model was used for actual analysis. Therefore, Re value becomes a value of double of analysis value. The obtained Re values were 41.0 Ω, 41.2Ω, 56.7Ω and 55.6 Ω for models A, B, C and D, respectively.

2) Measurement results in healthy human subjects

The electrical impedance values (Re, Ri and Cm) obtained from healthy human subjects are shown in Table 2. The Re, Ri and Cm values of male forearms were 48.5±9.6Ω, 90.0±100.6Ω and 0.53±0.20pF, respectively, and the Re, Ri and Cm values of female forearms were 64.8±10.5Ω, 182.2±70.4Ω and 0.37±0.10 pF, respectively. Significant differences were observed between the male and female subjects for the Re, Ri and Cm values ($p<0.0001$). In this study, only the Re value was further investigated, as described below.

Table 2. **Observed values (Re, Ri and Cm) of electric impedance in healthy subjects**

Measured site	Electrical impedance (Re, Ri, Cm)
Forearm (female)	Re=64.8±10.5 Ω a)
	Ri=182.2±70.4 Ω b)
	Cm=0.37±0.10 pF c)
Forearm (male)	Re=48.5±9.6 Ω d)
	Ri=90.0±100.9 Ω e)
	Cm=0.53±0.20 pF f)

a) vs d) : $p<0.0001$; b) vs e) : $p<0.0001$; c) vs f) : $p<0.0001$

The relationship between the antebrachial Re value and the thickness of subcutaneous fat (Ts) was able to be expressed by the following linear approximation equations (Fig.6) :

Males : $Re=3.92\ Ts+30.7$ ·········· Equation (1)
($R=0.974$, $p<0.0001$)

Females : $Re=6.14\ Ts+30.1$ ········ Equation (2)
($R=0.963$, $p<0.0001$)

The thickness of subcutaneous tissue (fat layer) can be estimated using these equations when the electrical impedance is measured non-invasively via the skin

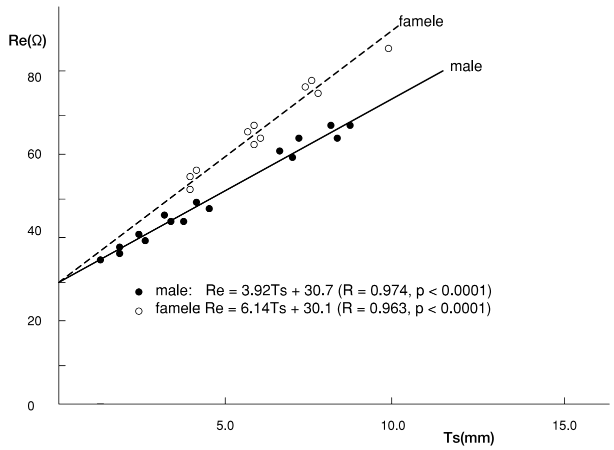


Figure 6. Relationship between the impedance values (Re) obtained from human forearms and the thickness of subcutaneous fat (Ts) at the forearm site of measurement.

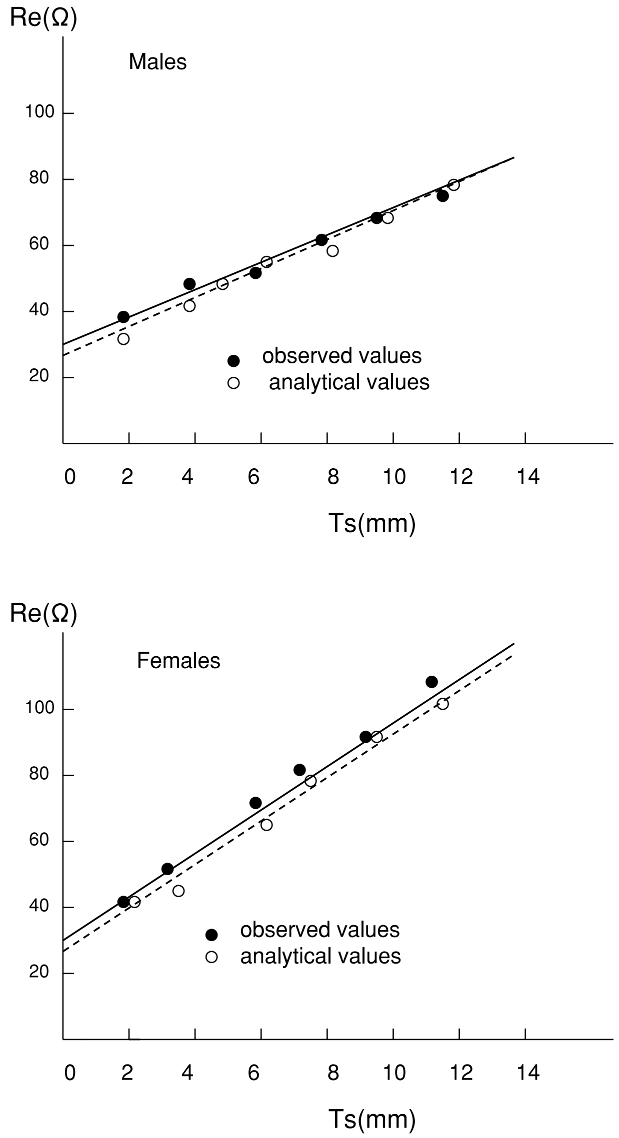


Figure 7. Observed values (Re) and linear approximation of analytical values in male and female data points.

surface. A sex-based difference was observed in the slope of the above linear approximation lines.

3) Comparison between observed and analytical values

The values obtained by finite element analysis were compared with the observed values. Each of the male and female data points was approximated linearly in Fig.7. The electrical conductivity estimated by fitting the observed values to the values obtained by finite element analysis was 0.40S/m and 0.15S/m for male muscle and fat tissue, and 0.35S/m and 0.11S/m for female muscle and fat tissue, respectively.

DISCUSSION

The electrical bio-impedance measured at a frequency band of 1kHz to 1MHz in the β-dispersion region is considered to provide information on the structure, composition and function of the tissue being measured (8, 9). We have demonstrated that the electrical bio-impedance measured using an invasive needle electrode can be utilized for differential diagnosis of benign and malignant breast and lung tumors (2-5).

The present study aimed to elucidate the differences in tissue electrical conductivity among individual local subcutaneous tissues and to develop a new method for tissue diagnosis, i.e., Electrical Impedance Tomography.

First, we used MRI images to prepare four model patterns of the human forearm according to the presence or absence of bone and fat tissue. The conductivity values of muscle and fat tissue were assumed on the basis of previously reported observed values (2, 3), and the electrical conductivity of bone was estimated using the equation, $\sigma b=1/80x\ \sigma m$, taken from the literature. Thus, the electrical conductivity was set at $\sigma m=0.4S/m$ for muscle, $\sigma b=0.005\ S/m$ for bone and $\sigma f=0.15\ S/m$ for fat tissue. Then the distributions of the electrical potential and electrical field, and the electrical impedance values were analyzed by the three-dimensional finite element method.

The results of the analysis showed that, when the region where 90% of the total electric current from the current-supplying electrode is flowing into the body was assumed to be the measurement region, such a region was found to be 3 cm below the skin surface (the surface in contact with the electrode). Accordingly, the measured bio-impedance actually provides bio-information at this measuring region.

It was also shown that the distributions of the electrical potential and electrical field were influenced by the existence of fat tissue but not by the presence or absence of bone. In fact, the extracellular fluid resistance (Re) estimated from values from the current-supplying electrode and the voltage-detecting electrode did not differ between model A (muscle alone) and model B (muscle plus bone). Model C (muscle plus fat tissue) and model D (muscle plus fat tissue plus bone) showed similar Re values. Significant differences were observed, however, between models A and B and models C and D. Since the distribution of the electrical potential was concentrated in a region right beneath the electrode because of the structure of the electrode used, it was thought that bone which is present at a depth of 2.3 cm showed little influence on model A (muscle alone), whereas a fat layer affected the impedance in models C and D. Thus, the presence or absence of bone did not affect the bio-impedance, while the presence of fat tissue affected the bio-impedance.

The relationship between the measured impedance (Re) of the human forearm and the thickness of subcutaneous fat (Ts) measured by MRI and ultrasonography in the forearm region could be approximated linearly as shown below.

Males : $Re=3.92\ Ts+30.7$ ········Equation (1)

Females : $Re=6.14\ Ts+30.1$ ······Equation (2)

Using the above equations, the thickness of a subcutaneous tissue (fat) can be estimated from the extracellular fluid resistance (Re) obtained by non-invasive measurement of electrical impedance via the skin surface. The sex-based difference in the slopes of approximated linear plots was thought to be due to the sex-based difference in the property or structure of the fat layer. When the condition of Ts=0mm is assumed as a state in which no fat layer is present but muscle is present homogenously, the Re values calculated with Equations (1) and (2) nearly agreed with each other. This indicates that fat tissue is more responsible for the sex-based difference in impedance (Re) than muscle.

The linear approximation of data points for males and females is shown in Fig.7. The linear gradient of the analytical values almost accorded with the observed values in the males and females, respectively.

By fitting the observed values to the values obtained by finite element analysis, the electrical conductivity was estimated to be 0.40S/m and 0.35S/m for male and female muscles, respectively, and 0.15S/m and 0.11 S/m for male and female fat tissues, respectively. As noted above, sex-based differences in the property and structure of fat tissue were thought to affect the slope of linear approximation. The electrical conductivity of individual tissues will be able to be estimated more accurately if a more practical biological model is constructed which takes into account the skin and blood flow in addition to the bone and fat tissue.

To increase the usefulness of bio-impedance information for tissue diagnoses, technologies of an EIT have been developed, where conductivity distributions in the tissue are imaged by using bio-impedance data measured non-invasively on the body surface (11-14). Though there are several problems to be solved, our results suggest that tissue electrical conductivity can be estimated by measurement of local bio-impedance using non-invasive electrodes and also show the possibility of using image conductivity differences to develop EIT as a new diagnostic modality (15, 16).

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