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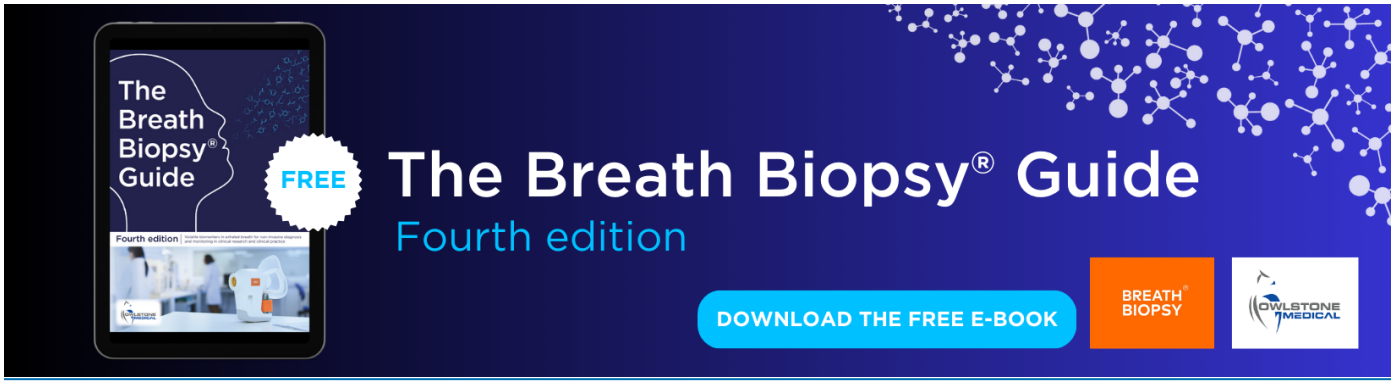

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Physiol. Meas. **25** (2004) 295–299 PII: S0967-3334(04)66698-6

Variation in breast EIT measurements due to menstrual cycle

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Received 23 July 2003, accepted for publication 30 October 2003
Published 3 February 2004
Online at stacks.iop.org/PM/25/295 (DOI: 10.1088/0967-3334/25/1/033)

Abstract

We conducted a short study on 8 volunteer subjects to establish whether physiological changes occurring as a result of the menstrual cycle affect tissue electrical properties. For this study subjects submitted to electrical impedance tomographic breast measurement four times, over two cycles at two different points in the cycle. Statistical analysis based on reconstructed values of conductivity and permittivity were conducted using the *t*-test for difference of means. The results were inconsistent, with some subjects showing a difference between the two phases and in all tests, while others showed differences only in some of the tests. At this time we can only conclude that a difference is more likely than not, although it could be a phenomenon only measurable in some individuals and not others. It seems that a larger study may be in order to establish this fact definitively.

Keywords: EIT, tissue impedance, tissue electrical properties, menstrual cycle

1. Introduction

A clinical trial is starting at our institution in which we will study the effectiveness of electrical impedance tomography as a method of screening for breast cancer. Prior to conducting this trial, we set out to study whether the menstrual cycle had an effect on the measured tissue electrical properties. Breast tissues undergo changes during the menstrual cycle, particularly in younger women who would undergo mammography in the 40–50 age group. In the context of x-ray mammography researchers found that as the menstrual cycle progresses, breast tissue becomes less fatty (transparent) and more fibrous and dense (opaque), most likely due to fluctuations in reproductive hormones. This density, which appears as increased cloudiness on a mammogram, can make it more difficult to detect tiny, early-stage malignancies among pre-menopausal women (White *et al* 1998). It was therefore logical to hypothesize that these changes may affect EIT measurements as well. A few studies have already investigated the possible effect of these changes on tissue impedance and have reported no statistically

Table 1. Schedule of examinations, showing the date of the last menses (LMP), the dates of the examinations (visits) and the number of days since last menses. Eight patients participated in the study. Each was examined four times, twice during the follicular phase 1 of the cycle (days 7–14, white cells) and twice during the secretory phase 2 (days 21–28, gray cells). In four cases (out of 32) patients were examined outside of these defined phases although close to the desired dates: examinations close to phase 1 are indicated by * and those close to phase 2 by **.

Pat ID	LMP	Visit 1	days	LMP	Visit 2	days	LMP	Visit 3	days	LMP	Visit 4	days
1051	1/28	2/5	8	1/28**	2/15**	18**	2/24	3/7	11	2/24	3/21	25
1052	2/1	2/14	13	2/1	2/25	24	3/6	3/13	7	3/6	3/28	22
1053	2/15	3/11	24	3/15	3/25	10	4/11	5/8	27	5/10	5/20	10
1054	2/18	3/14	24	5/3	5/16	13	5/29	6/6	8	5/29	6/20	22
1055	2/22*	2/28*	6*	2/22**	3/14**	20**	5/11	5/21	10	6/7**	6/27**	20**
1056	4/22	5/14	22	5/19	5/28	9	5/19	6/11	23	6/19	7/1	12
1057	5/11	5/23	12	5/11	6/6	26	6/26	7/10	14	6/26	7/23	27
1062	6/19	7/10	21	7/21	7/29	8	7/21	8/15	25	8/17	8/30	13

significant differences (Perlet *et al* 2000, Piperno and Lenington 2002). One study has shown a notable difference in the appearance of reconstructed images taken in two phases of the cycle (Cherepenin *et al* 2002), indicating that during the first phase of the menstrual cycle (days 1–10), reconstructed images exhibit a characteristic 'mosaic' appearance, while during the second phase (days 16–28), grayscale images appear more uniform in tone. These are, however, more anecdotal than quantitative results, presented as part of an extensive test of a new device, not a study designed to establish whether a significant difference should be expected. Our clinical trial is part of a larger project in which three imaging modalities are used in parallel and on the same patients to determine if effects resulting from menstrual cycle variations could be observed. The other two modalities are microwave imaging (MWI) (Meaney *et al* 2003) and near infrared (NIR) light transmission (Pogue *et al* 2004). The basic motivation for conducting this study was to answer the questions: (i) are there observable changes due to menstrual cycle variations, and, if such changes are observed, (ii) how could we account for them in breast cancer screening?

2. Study design

For this study we recruited women who were pre-menopausal with regular cycles and had had a normal mammogram within the last six months. We set out to recruit eight women, and planned to image them with all three modalities on the same day twice per cycle and for two cycles, for a total of four examinations. The timing of the examinations was intended such that each patient would be imaged within phase 1 (follicular) during days 7 through 14 of a normal cycle, and phase 2 (secretory) during days 21 through 28. During the follicular phase, it is expected that blood flow, hemoglobin content and water content will be at their lowest, while during the secretory phase they will be at their peak.

Because of practical scheduling considerations not all examinations were conducted on the planned days and so were slightly outside of the phases as we defined them. Table 1 summarizes the scheduling of the examinations and the menstrual status of the patients at the time of each examination.

The actual enrolment for this study consisted of eight women in ages ranging from 41 to 49 years (mean 45), and of average build. At each visit patients submitted to a finger stick for a hemoglobin measurement. It is interesting to note that the hemoglobin measurements

Table 2. Statistics of participants. The body-mass index (BMI, weight/height^2) usually correlates with the breast content (fatty). All the women in this study had heterogenously dense breasts. The hemoglobin readings shown in the last two columns correspond to the two measurements made during each visit. In this study they do not seem to correlate with the phase of the menstrual cycle.

Pat ID	Phase	Age	Height (m)	Weight (kg)	BMI (kg m^{-2})	Hg 1 (μ mol l^{-1})	Hg 2 (μ mol l^{-1})
1051	1	43	1.70	57	20	16	13.5
	2					13.2	13.8
1052	1	49	1.57	55	22	13.5	10.9
	2					10.2	9.7
1053	1	47	1.68	87	31	13.4	13
	2					13.1	11.7
1054	1	45	1.75	70	23	14.1	13.9
	2					15.3	14.3
1055	1	46	1.65	64	23	12.1	12.6
	2					12.4	12.5
1056	1	42	1.63	63	24	12.5	13.1
	2					14.2	13.5
1057	1	46	1.68	66	23	13	14.4
	2					13.8	14.6
1062	1	41	1.68	65	23	13.3	12.8
	2					13.5	13.8M
Average:		45	1.67	65.8	23.7	13.4	13.0

(expressed in μ mol l^{-1}) did not seem to indicate any correlation with the phases. Table 2 summarizes the participants' statistics. In all we have acquired data from eight patients, in four sessions including both breasts and on one plane each, for a total of 64 data sets.

3. Analysis and results

Impedance measurements were collected using our breast EIT system (Hartov *et al* 2000) and impedance maps of conductivity (σ) and permittivity (ε) were computed from the raw voltage and current data. Our analysis was based on these reconstructed images, which we further divided into concentric zones corresponding to 75% and 50% of the radius (see figure 1). These seem generally to correspond to the zones where the reconstructed images no longer show any electrode artifact (75%). Furthermore, the central 50% zone usually corresponds to the glandular tissue which is expected to be more influenced by the menstrual cycle. We tabulated the property values (σ and ε) for the 75% and 50% zones from the reconstructed images. To be precise, the values computed at each of the nodes within a given zone were used. Values corresponding to the same phase for a patient were grouped together for the two sessions and both breasts. Separate analyses were conducted for the 50% and 75% values.

The analysis consisted of testing the following hypotheses using statistical methods: is there a statistically significant difference between the values of conductivity, or between the values of permittivity, between the two phases, for the 75% circle and for the 50% circle? In all these cases we used the *t*-test to see if we could disprove the null hypotheses H_0: $\sigma_{\text{phase1}} = \sigma_{\text{phase2}}$ and H_0: $\varepsilon_{\text{phase1}} = \varepsilon_{\text{phase2}}$ with a confidence level of 0.01 for each patient.

A summary of the results is shown in table 3. Looking at the entire table, we rejected the null hypothesis (same means) in 21 of 32 tests (66% of the time). Looking at the conductivity

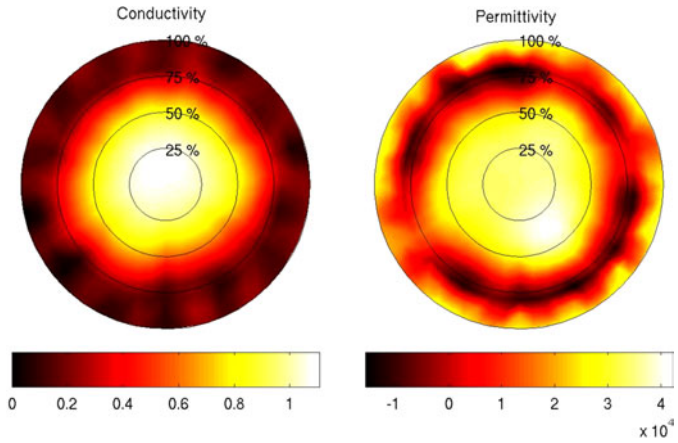

Figure 1. This figure illustrates the concentric circles defining the zones used in our analysis. Property values were averaged over the various radial zones and compared between the two phases of the cycle at which patients were examined. In these actual EIT reconstructed images, the zone between the 100% and 75% circles (outermost ring) is suspected to be the result of artifacts, either electrode mischaracterization or 2D–3D mismatch.

(This figure is in colour only in the electronic version)

Table 3. The entries in the table show the results of the individual tests. Each column compares one parameter (σ or ε) between the two phases and for a given radius zone (50% or 75%). When the *t*-test result indicated that the null hypothesis had to be rejected, the necessary conclusion was that the means of the two property sets were in fact different. This is indicated by $\mu_1 \neq \mu_2$ in the shaded cells. In these cases, the change between phase 1 and phase 2 is to be considered significant.

Pat ID	σ_1/σ_2 75%	σ_1/σ_2 50%	$\varepsilon_1/\varepsilon_2$ 75%	$\varepsilon_1/\varepsilon_2$ 50%
1051	$\mu_1 = \mu_2$	$\mu_1 \neq \mu_2$	$\mu_1 = \mu_2$	$\mu_1 \neq \mu_2$
1052	$\mu_1 \neq \mu_2$	$\mu_1 \neq \mu_2$	$\mu_1 \neq \mu_2$	$\mu_1 \neq \mu_2$
1053	$\mu_1 = \mu_2$	$\mu_1 = \mu_2$	$\mu_1 = \mu_2$	$\mu_1 \neq \mu_2$
1054	$\mu_1 \neq \mu_2$	$\mu_1 = \mu_2$	$\mu_1 \neq \mu_2$	$\mu_1 \neq \mu_2$
1055	$\mu_1 \neq \mu_2$	$\mu_1 \neq \mu_2$	$\mu_1 \neq \mu_2$	$\mu_1 \neq \mu_2$
1056	$\mu_1 = \mu_2$	$\mu_1 = \mu_2$	$\mu_1 \neq \mu_2$	$\mu_1 \neq \mu_2$
1057	$\mu_1 \neq \mu_2$	$\mu_1 = \mu_2$	$\mu_1 = \mu_2$	$\mu_1 = \mu_2$
1062	$\mu_1 \neq \mu_2$	$\mu_1 \neq \mu_2$	$\mu_1 \neq \mu_2$	$\mu_1 \neq \mu_2$

data only, we rejected the null hypothesis in 9 of 16 tests (56% of the time). Rejecting the null hypothesis, in this case means that the means are in fact different. For the permittivity data, we have rejected the null hypothesis in 12 of 16 tests (75% of the time). The most significant results occur when looking at permittivity for the 50% zone, where the null hypothesis was rejected in 7 out of 8 tests (88% of the time).

4. Discussion and conclusion

The better results were obtained in the 50% zone and for permittivity. The 50% zone is usually less affected by electrode artifacts and also corresponds generally to the glandular tissue in the central part of the breast. This may explain why it would be more likely to demonstrate evidence of changes due to the menstrual cycle.

If we look at the data on a per subject basis, we have three instances (subjects 1052, 1055, 1062) for whom all the tests indicate that there is a significant and in those cases consistent difference in property values (both σ and ε) between phases. Conversely, there are no cases in which all the tests indicate no change. We are faced with a situation where for some subjects there is a consistent difference, and not for others. In fact, for the majority of cases (subjects 1051, 1053, 1054, 1056 and 1057, 5 out of 8 times or 63%) there is no consistency in the test results. The strength of these statistical results is moderated by this inconsistency; we can, however, draw the conclusion that there seem to be a slight detectable effect overall. This effect may be more pronounced in some subjects and possibly not present in others, for reasons that we do not know. It is also apparent that the effect is most pronounced in the central part of the breast cross-section, corresponding to the glandular tissue, which is expected to be most affected by cyclic hormonal variations. We will mention here, for completeness, that the results obtained from the two other modalities were both negative (Meaney *et al* 2003, Pogue *et al* 2004); that is, no correlations were found between the phases and the tissue properties being imaged in either microwave imaging or near infrared optical tomography.

In conclusion, we must conclude that there may be a slight effect overall, more pronounced in some women than in others. The effect is most noticeable on the permittivity values, and much less so for the conductivity. We must, however, have some reservations about these claims in the light of the small number of subjects that were tested and the small number of measurements that were conducted on each subject, taking snapshots at two points in the cycle only and only twice. It is possible that a consistent effect may be confirmed in a larger study, involving more women, by following them for longer periods of time, and by making measurements at more points in the cycle.

Acknowledgment

We are grateful for support provided by NIH grant P01-CA80139.

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