Electropotential evaluation as a new technique for diagnosing breast lesions

Mark Faupel* *, Daniel Vaneld, Volker Barth, Richard Davies, Ian S. Fentiman, Roland Holland, Jean Louis Lamarque, Virgilio Sacchini, Ingrid Schreer

*Biofield Corp, 1225 Northmeadow Parkway Suite 120, Roswell, GA 30076, USA
bDepartment of Radiology, Institut Gustave Roussy, 39, rue Camille Desmoulins, 94805 Villejuif, France
cEasingen Hospital, Easingen, Germany
dHackensack University Medical Center, UMD-New Jersey Medical School, Hackensack, New Jersey, USA
eGuy’s Hospital, London, UK
fNational Expert and Training Center for Breast Cancer Screening, Nijmegen, Netherlands
h1st Illinoisio di Oncologia, Milan, Italy
iInstitut Montpellierain d’Imagerie Médicale, 209 rue des Apothicaires, Parc Euroniedicine, 34196 Montpellier, France
jStrahleninstitut Prof. Dr. Med. W. Hoeffken, Cologne, Germany

Received 5 September 1996; revised 5 September 1996: accepted 5 September 1996

Abstract

A new approach, termed the Biofield test, may have the potential to augment the process of diagnosing breast cancer. This technique is based on the analysis of skin surface electrical potentials measured by an array of specially designed sensors which are placed on the breasts. Measurements are recorded noninvasively and then analyzed using pattern recognition algorithms to produce an immediate and objective assessment of breast tissue in vivo. Initial clinical trials suggest that the test can achieve a sensitivity of approximately 90% and a specificity of 40—50%, which indicates that the test might be useful for excluding cancer when it is, in fact, absent. Although research to date has focused on the differential diagnosis of suspicious breast lesions, future applications could include breast cancer screening, close surveillance and diagnosis of recurrent cancers in breasts previously treated with conservative therapy, and monitoring the effectiveness of breast cancer therapies. Improvements and new applications are expected to occur as additional research and validation in actual clinical settings is performed. Copyright © 1997 Elsevier Science Ireland Ltd.

Keywords: Electrical potentials; Breast cancer, diagnosis; Non-invasive breast cancer

1. Introduction

The detection and diagnosis of breast cancer can be represented by a three-tiered model of breast disease management encompassing screening, diagnosis, and disease staging (Fig. 1). The ultimate objective of screening is to reduce mortality and there exists reasonable agreement that mammography screening programs

* Corresponding author. Tel.: +1 770 7408180; fax: +1 770 7401832.

Fig. 1. Stages of breast cancer disease management.
can reduce mortality by about 30% for women aged 50 or over [1,2]. Physical examination is the other method by which breast cancers are initially discovered, although it is more difficult to demonstrate a mortality reduction once a malignancy is palpable. In order for screening to achieve a reduction in mortality, approximately 3–10% of patients are recalled for additional evaluation.

Once an abnormality has been detected by screening or physical examination, diagnosis of the abnormality occurs, as represented in the second stage of the model. A primary objective at this point is to localize and characterize the suspicious lesion so that a decision to biopsy can be made. Many approaches have been adopted for this purpose including ultrasound, fine needle aspiration (FNA) biopsy and magnetic resonance (MRI) scanning. Nevertheless, about 30–50% of the open biopsies performed in women over age 50 at specialized European centers are found to be benign, and this number is higher in younger women and in North America, where the ratio of benign to malignant biopsies is about 4:1 [3].

The final tier of the model, disease staging, involves a tissue sample to determine disease management from the perspective of prescribing appropriate treatment. However, because the aforementioned techniques have limitations, the diagnostic phase in many cases is completed only when a biopsy specimen is subjected to histopathological analysis.

Despite advances made in detecting and diagnosing breast disease, there is still a 10–30% false negative rate resulting in interval cancers [4,5] and an excessive amount of expense, physician concern and patient anxiety over false positives resulting from the screening and diagnostic process.

A new approach, termed the Biofield test, may have the potential to augment the process of diagnosing breast cancer. This technique is based on the analysis of skin surface electrical potentials measured by an array of specially designed sensors which are placed on the breasts. The unit of measurement is in millivolts (mV), a readily quantifiable biophysical unit of potential energy which can be recorded noninvasively and then algorithmically processed to produce an immediate and objective assessment of breast tissue in vivo. The information from the test can then be used as an index of abnormal proliferation which could aid in the detection and diagnosis of neoplastic activity.

### 2. Underlying mechanisms of the technique

Normal epithelial cells, including those that line breast ducts, are electrically polarized by an ionic gradient across the cell membrane [6]. The charge gradient is asymmetric between the apical and basolateral cell membranes and is known as the transepithelial electrical potential [7,8]. This concept is illustrated in Fig. 2, which shows the electrical gradients across normal epithelium which lines the terminal ductal lobular units of the breast. The electrical gradient across the membrane is maintained by the different permeabilities to ions (predominantly K⁺ and Na⁺) and water at the luminal aspect of the duct as compared to the abluminal side and results in a transepithelial potential difference of about 30 mV, i.e. the net difference of the apical potential (—70 mV) and the basolateral potential (—100 mV). The vectorial transport of ions which maintain the transepithelial potential difference is facilitated by the tight junctions which divide the cell membrane into distinct apical and basolateral domains. As epithelial cells divide, the charge gradient across the epithelial layer is dissipated, resulting in electrical depolarization.

When epithelial cells in certain areas of the breast divide more rapidly than those in other areas of the breast, as when a cancer develops, it results in a pocket of relative depolarization which can produce a differential in electrical potential at the skin surface. These differentials have been measured using a specially designed sensor array and measurement device [9–11].

### 3. Field carcinogenesis

One question which arises when a new technology for breast cancer detection is introduced is whether it can provide useful information for small lesions as well as large ones. It is generally accepted that the effectiveness of most diagnostic tests decreases as lesion size decreases. How then is it possible that electropotential measurements made at the skin surface can detect abnormal proliferation associated with a nonpalpable malignant lesion within the breast? The available evidence suggests that cancer develops within a background of dysregulated proliferation encompassing a field which contains and extends beyond the tumor itself [12–14]. Preliminary studies which employ invasive needle electrodes indicate that the region of electrical depolarization extends to the skin surface in quadrants of the breast which harbor a malignancy (Davies R.J., personal communication).
4. Noninvasive measurement of breast electropotentials

Accurate measurement of skin surface electropotentials requires use of a specialized device and sensor system [10]. The sensors which have been developed for this application are extremely accurate transducers, low in noise and electrical impedance. Each single-use sensor is pre-loaded with a specially designed conductive gel. The device utilizes microprocessor technology for control of signal sampling, filtering, and data processing. The device also contains a functional test unit which allows the technician or service personnel to verify signal integrity inclusive of the device and cable system.

A key aspect of this technology is the ability to sample electrical potentials concurrently from an array of many sensors placed on the breast. This allows multiple comparisons between sensor sites for the detection of abnormal proliferation which reveal regions or pockets of relative depolarization on the surface of the breast, analogous to pockets of low and high pressure systems seen on weather maps. In both cases, it is the relative difference in energy over a curved surface which is informative.

The technology in its present form confers a number of inherent advantages. These include:
(1) The test is completely noninvasive and there is no pain associated with the procedure.
(2) There is no exposure to ionizing radiation or other energy.
(3) The test is simple to implement and can be performed by a technician.
(4) Conducting the test takes about 15 min and the result is available immediately.
(5) The test can be repeated as often as needed.
(6) The test result is objective and does not require an expert for interpretation.
(7) The test, when widely available, should be cost effective.

Because the test is noninvasive, simple to use, and is expected to be cost effective, it eventually could be integrated into a variety of health care settings where breast evaluation occurs and may provide adjunctive information for assisting in the resolution of screen detected abnormalities or suspicious palpable lesions. In Europe, there may be up to 8 million women each year who would benefit from a more accurate and convenient method of diagnosis of suspicious breast lesions, the majority of which (over 7 million) present with palpable findings.

5. Test procedure

The test procedure superficially resembles that of an electrocardiogram. However, the informative signal is a result of selective filtering of skin surface potentials to identify the electrical characteristics associated with dysregulated proliferation. The patient lies supine and the location of the lesion is identified either by palpation or, if the lesion is nonpalpable, by estimation based on the mammogram. Each of the 16 measurement sensors is labeled with a visual code to aid in proper positioning relative to the location of the lesion. The technician first places the appropriate sensor on the skin over the center of the suspicious lesion. Four other designated sensors are then placed in medial, lateral, superior, and inferior positions relative to the sensor placed over the center of the lesion. Two sensors are then placed in the center of the two quadrants adjacent to that which contains the suspicious lesion and an additional sensor is placed in the axilla.

The pattern of sensor placement is then reproduced in a mirror-image pattern on the opposite breast. In this way, the opposite breast serves as a control for evaluation of asymmetry between the two breasts. Lastly, reference sensors are placed on each of the two palms. All electropotential measurements are made relative to the two reference sensors.

Once the sensors are positioned, a period of time is allowed for the conductive gel to equilibrate with the skin. In the early studies, a period of 10 min was allowed for equilibration, but more recent data suggest that this could be reduced without affecting performance. After equilibration, signal acquisition occurs and takes approximately 1 min. The device is programmed to alert the technician should spurious measurements occur, requiring a re-test.

6. Initial observations from early clinical trials

Clinical trials conducted in Europe, the US, and Japan have focused primarily on the differential diagnosis of previously localized breast lesions. For this application, a standard array of eight sensors per breast has been studied (Fig. 3). In addition, the effectiveness
of larger arrays for breast cancer screening have been explored in preliminary studies which are discussed later in this paper.

The initial diagnostic studies conducted in Europe and the US indicated that breast cancers produced significantly greater electropotential differentials, both within the symptomatic breast and between the two breasts as compared to benign lesions [9,11,15]. Because more than one electropotential differential provides discriminative information, diagnosis may be enhanced by combining the most informative differentials into pattern recognition algorithms [16,17].

7. Clinical trials approach

In the most recently analyzed study, conducted at eight centres in five European countries, the comparison between the Biofield result and histopathology was evaluated for 661 patients using a prospective algorithm under double-blinded conditions. The participating centers are listed in Table 1. One advantage of this study was the utilization of a blinded pathology review, which produced a relatively consistent evaluation of tissue proliferation for each tested lesion. A manuscript describing the results of this study is currently in preparation. A similar study conducted at six centres in the US is currently undergoing analysis.

In the study protocols, patients undergo the Biofield test prior to open biopsy. The result of the Biofield test is then compared with that of histopathology to determine accuracy of the test. Analysis of the clinical studies to date indicates that the Biofield test can achieve a sensitivity of about 90%, and that this sensitivity is maintained for small and nonpalpable cancers. In addition, the test identifies about 90% of atypical and in situ lesions as positive. It cannot as yet be determined whether the test is capable of discriminating invasive cancers from noninvasive cancers or atypical lesions. Specificity of the test approaches 50% for nonproliferative benign lesions and is somewhat lower for proliferative benign lesions. As in previous studies, cancers in the European multicenter study produced significantly greater electropotential differentials than benign lesions (Fig. 4). Borderline (atypical and in situ) lesions tend to produce differentials intermediate between benign lesions and invasive cancers.

One important measure of the clinical utility of a diagnostic test is the negative predictive value, or the probability that a negative test result indicates that the patient is free of disease. This measure is calculated using the sensitivity and specificity of the test along with the prevalence of disease in the population for which the test is intended.

A test which can achieve a sensitivity of 90% and a specificity of 40–50% has a negative predictive value of about 96% in a population with a cancer prevalence of 15%. Negative predictive value increases as prevalence decreases (Table 2). With sufficient confidence that a negative test indicates that the patient is free of disease, the specificity comes to represent the percentage of other diagnostic tests which may be avoided. Of course, as with any new diagnostic test, the Biofield result

Table 1
Sites participating in European multicentre study

<table>
<thead>
<tr>
<th>Institution</th>
<th>Principal Investigator(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Institut Gustave-Roussy, Paris (Villejuif), France</td>
<td>Dr. Daniel Vanel</td>
</tr>
<tr>
<td>Institut Montpellierain D’Imagerie Medico-Biologique (IMIM), Montpellier, France</td>
<td>Prof. J.L. Lamarque</td>
</tr>
<tr>
<td>National Expert and Training center for Breast cancer Screening, Nijmegen, The Netherlands</td>
<td>Dr. Roland Holland</td>
</tr>
<tr>
<td>University of Hamburg, Hamburg, Germany</td>
<td>Prof. H.J. Frischbier</td>
</tr>
<tr>
<td>Esglingen Hospital, Esglingen, Germany</td>
<td>Prof. Volker Barth</td>
</tr>
<tr>
<td>Guy’s Hospital, London, UK</td>
<td>Prof. Ian Fentiman</td>
</tr>
<tr>
<td>Istituto Europeo Di Oncologia, Milan, Italy</td>
<td>Dr. Virgilio Sacchini</td>
</tr>
<tr>
<td>Istituto Nazionale per lo Studio e la cura dei Tumori, Milan, Italy</td>
<td>Dr. Mirella Merson</td>
</tr>
</tbody>
</table>

Fig. 4. European multicentre study. Electropotential differentials of benign, borderline and malignant lesions. Mean values with standard error bars.

Table 2
Negative predictive value as a function of prevalence

<table>
<thead>
<tr>
<th>Cancer risk (prevalence)</th>
<th>NPV with negative Biofield*</th>
</tr>
</thead>
<tbody>
<tr>
<td>10%</td>
<td>97.3%</td>
</tr>
<tr>
<td>15%</td>
<td>95.8%</td>
</tr>
<tr>
<td>20%</td>
<td>94.1%</td>
</tr>
</tbody>
</table>

* Based on 90% sensitivity and 40% specificity.
8. Future applications of the technology

As previously described, most of the clinical research has focused on evaluating effectiveness of the test for the differential diagnosis of localized suspicious breast lesions.

A next step would be further development and clinical assessment of the technology as a new modality for breast cancer screening. For this application, additional sensors would be utilized to allow measurement of electropotentials independent of lesion location and for asymptomatic women (Fig. 5). The objective would be identification of high risk patients by detecting abnormal levels of relative depolarization in the breasts, as reflected by higher electropotential differentials. These patients could then be referred for imaging or other tests. Initial pilot studies using a nondirected, or screening type array indicate that cancers produce higher differentials than benign lesions or unbiopsied, ostensibly normal tissue [18].

Another potential application of the technology may be for the diagnosis of recurrent cancer. In the irradiated breast for example, mammography has been shown to have a sensitivity of only 64% for recurrent carcinoma in patients who previously had undergone conservative surgery [19]. The Biofield diagnostic array could be utilized for these cases because the region of suspicion, i.e. the site of the previous cancer, is identifiable. Pilot studies are currently under way in Europe to determine the potential effectiveness of the Biofield test for this application.

Monitoring the effectiveness of therapy may be another potentially useful application of the technology. Currently, it is difficult to assess the effectiveness of therapy prior to mortality reduction endpoints in randomized trials. An alternative approach might be to evaluate tissue proliferation before, during, and after cycles of therapy. There are two indirect lines of evidence that support the used of the Biofield technology for the assessment of tissue proliferation. The first line of evidence comes from the multicenter trials, in which it was found that proliferative and atypical benign lesions produced greater electropotential differentials than nonproliferative benign lesions. The second line of evidence is from studies in which higher electropotential differentials were found to correlate with the thymidine labeling index of excised malignant tumors, an in vitro measure of cell proliferation sometimes used for prognosis [15].

Although the technology described in this paper is still in its early stages, a potential positive impact has been demonstrated under rigorous clinical trial protocols. Improvements and new applications would be expected to occur as additional research and validation in actual clinical settings is performed.

References


