Bioelectric impedance phase angle in breast carcinoma

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ABSTRACT

Context: Worldwide breast cancer is the most frequently diagnosed life threatening cancer and the leading cause of death in women. Bioelectric impedance analysis (BIA) affords an emerging opportunity to assess prognosis because of its ability to non invasively assess cell and plasma membrane structure and function by means of phase angle. **Aims:** To compare the phase angle between patients of breast cancer and their matched control with the help of BIA. **Settings and Design:** After taking clearance from ethical committee, a total of 34 female cases of histologically proven infiltrating ductal breast carcinoma were included from the surgery IPD, department of surgery. Equal numbers of the matched controls were recruited from the friends and relatives of cases. **Materials and Methods:** Bio Electrical Impedance Analyzer (BIA) BODY STAT QUAD SCAN 4000 was used to measure resistance (R) and reactance (Xc) by recording a voltage drop in applied current. Phase angle is the ratio of reactance to resistance and is a measure of cell vitality. Statistical analysis used: Unpaired "*t*" test was applied. **Results:** In control group, the phase angle showed a mean of 5.479 whereas in test group, it showed a mean value of 4.726. The *P* value showed a significant difference ($P < 0.0001$). The smaller the phase angle values were higher was the tumor, nodes, metastases (TNM) staging. The phase angles differed significantly from the healthy age matched control values. **Conclusions:** This study demonstrated that phase angle is a strong predictor of severity of breast cancer and differed significantly between the two groups.

Key words: Bio electrical impedance analyzer, breast cancer, phase angle

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INTRODUCTION

Worldwide breast cancer is the most frequently diagnosed life threatening cancer in women and the leading cause of death in females.[1] More than 1 million new cases of female breast cancer are diagnosed each year. Between one half and two thirds of American women diagnosed at Stage II and III, an annual figure estimated at 45,000-50,000, will develop metastatic breast disease within five years of diagnosis. In combination with the estimated 10,000-15,000 women who present with stage IV disease each year, and the 25 percent whose disease recurs after five years, this means that every year between 73,000 and 86,000 American women discover that they have metastatic breast cancer.[2] The inability to predict and prevent metastatic breast cancer is a major problem.

We know that breast cancer is now no longer seen as a single disease but a multifaceted disease comprised of distinct biological subtypes presenting a varied spectrum of clinical, pathological and molecular features with different prognostic and therapeutic implications. Malignant cells exhibit numerous anomalies in cell and its membrane which includes high aerobic lactate production, abnormal plasma membrane transport, altered cell to cell communication, appearance of new antigens, shift in ion ratios etc. All these changes lead to disturbed cell physiology and thus altered tissue electrical properties. Bioelectric impedance analysis (BIA) affords an emerging opportunity to improve prognosis because of its ability to non-invasively detect changes in tissue electrical properties. The altered tissue electrical properties documented in cancer patients occur even before the appearance of overt signs of cachexia.[3]

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BIA is simple, easy to use, objective, quick and easily reproducible technique to measure body composition. BIA works on the principle that a low voltage current is applied and the lean tissue which consists essentially of electrolytes containing water conduct the electrical current whereas fat acts as an insulator.[4] Impedance of the body is thus determined.[5] Impedance is a measure of how current is slowed or stopped as it passes through the body. It has two components -Resistance (R) and Reactance (Xc). Resistance is the restriction to the flow of an electric current whereas reactance is the resistive effect produced by tissue interfaces and cell membrane.[6] Reactance causes the current to lag behind the voltage creating a phase shift, which is quantified geometrically as the angular transformation of the ratio of resistance to reactance or the phase angle.[7] Phase angle is the marker of cell and cell membrane structure and functional status. Low phase angle suggests cell death or decreased cell integrity whereas higher phase angle suggests healthy cell and cell membrane.[8] A low phase angle has been associated with an impaired outcome in tumor diseases such as pancreatic cancer, colorectal cancer, and lung cancer as well as in HIV/AIDS, liver cirrhosis, dialysis, pulmonary disease, bacteremia and sepsis.[8-14]

The primary objective of this study was to evaluate the association of BIA derived phase angle with TNM staging of breast cancer.

MATERIALS AND METHODS

After taking clearance from ethical committee, 34 cases of histologically proven infiltrating ductal breast carcinoma from the Dept of Surgery were included in the study. A set of 34 healthy volunteers (friends and relatives of patients) matched by age and sex was the control group. All of them were subjected to under mentioned rigorous inclusion and exclusion criteria.

Inclusion criteria

1. Biopsy proven cases of infiltrating ductal carcinoma
2. Age >30 years and <60 years
3. Has given informed consent
4. Has not been treated prior for malignancy
5. Not suffering from diseases like diabetes, hypertension, electrolyte imbalance, cirrhosis, hepatitis, HIV etc.

Exclusion criteria

1. Any prior surgical, chemotherapy or radiotherapy
2. Over hydrated or dehydrated
3. Pregnancy
4. Heart disease with pacemakers
5. H/O alcohol or drug abuse
6. Patients on diuretics or any other drug known to cause water and electrolyte imbalance.

Height was measured on a parallel plane stadiometer without shoes with a correction of 0.5 cm. Weight was taken with minimal clothing on with correction of 0.1 kg respectively. Hip circumference was measured at maximum posterior extension of buttocks whereas waist circumference was measured at a plane across iliac crest in standing position at end expiration. Two measurements were made at each site in rotational order with a 3rd measurement if the first two differed by more than 1 cm. Subjects were instructed not to consume alcohol, coffee or do exercise 24 hours prior to test. They had to come with fasting of at least 4 hours. Following standard precautions were taken like subjects not wearing any metallic thing, no other electronic devices within 50 cm of BIA etc. Subject lied supine on a non-conducting couch with arms 30 degree apart from trunk and ankles at least 20 cm away from each other. The parts where electrodes were to be placed were cleaned with spirit swab. Bioelectric Impedance Analyzer BODY STAT QUAD SCAN 4000 was used. Red electrode was placed on the knuckles and black on the wrist next to ulna head in the right upper limb. In the right lower limb, red lead was placed behind the toes and black in between the medial and lateral malleoli. BIA was done at 50, 100 and 200 kHz. All the readings were taken within 5 minutes of lying down. The Impedance of the body was determined. Impedance has two components: Resistance (R) and Reactance (Xc). Resistance is the restriction to flow of an electric current whereas reactance causes current to lag behind the voltage creating a phase shift, which is quantified geometrically as the angular transformation of the ratio of resistance to reactance or the phase angle.[6] Phase Angle was calculated using following equation:

$$\text{Phase Angle} = (\text{Resistance})/(\text{reactance}) \times 180/\pi$$

All the patients proven to be cases of infiltrating ductal carcinoma breast were staged according to American Joint Cancer Committee recommendations on malignancy breast staging.

Phase angles of different stages were grouped accordingly. We analyzed the data with Graph pad prism software version 6.03 and Microsoft excel.

Phase angle of test group was compared with that of control group by applying unpaired *t* test. One way ANOVA was applied to compare the mean phase angle of different stages.

All breast cancer patients were assessed for phase angle preoperatively but the cases that were included in the

study were proven to suffer from infiltrating ductal breast carcinoma on biopsy postoperatively.

RESULTS

All the patients were staged according to American Joint Cancer Committee recommendations on malignancy breast staging [Table 1].

We had 7 patients of Stage IIa (T2NoM0) contributing to 20.58% whereas 11 patients were diagnosed to have Stage IIb (T2N1M0 and T3N0M0). Out of these patients, 7 patients belonged to T2N1M0 and 4 patients to T3N0M0. Stage IIIa (T2N2M0, T3N1M0, T3N2M0) had a total of 13 cases contributing to 38.2% of total. Stage IV (Any T, Any N, M1) had minimum number of cases amounting to just 3 cases thus contributing 8.8% of total cases [Figure 1].

Mean value of control and test group was calculated using unpaired t test. The mean value (±SEM) of control group was 5.479 (±0.0558) whereas that of test group was 4.726 (±0.0804). The two differed significantly from each other with a $P < 0.0001$, which showed the significance of ****. In Stage IIa, the range of phase angle varied from 5.4 to 4.7. The mean value ±SD was 5.071. (0.228) Stage IIb had a maximum value of phase angle 5.5 whereas the minimum value was 4.1 with a mean value ±SD of 4.891 (0.378). The values of phase angle in Stage IIIa varied from 5.1 to 4.1. The mean ±SD calculated was 4.631 (0.317) for this stage. Stage IV had highest value of 3.9 whereas least value of 3.5 with a mean value ±SD of 3.733 (0.208) [Table 2 and Figure 2].

One-way ANOVA was applied and the differences among means of all stages was statistically significant (****) with an f value of 13.85 and a $P < 0.0001$ [Table 3].

DISCUSSION

This prospective case control study included comparison of a control group (n = 34) and a test group (n = 34) diagnosed as cases of infiltrating ductal carcinoma breast based on triple assessment of breast and postoperative biopsy report.

In this study, we found that the phase angle differed significantly between the two groups and also showed a decreasing trend as the staging of infiltrating ductal carcinoma breast advances. When compared to stage IIa, the phase angle in groups related to Stage III and IV showed a significant decreasing trend. Hence phase angle could be a prognostic indicator in infiltrating ductal carcinoma breast.

Table 1: Clinical staging with TNM classification of patients

Stage	TNM	Number of patients
IIa	T2N0M0	7
IIb	T2N1M0	7
	T3N0M0	4
IIIa	T2N2M0	1
	T3N1M0	11
	T3N2M0	1
IV	T2N2M1	2
	T3N1M1	1

TNM: Tumor, nodes, metastases

Table 2: Mean phase angle of case and control

	Case (n=34)	Control (n=34)	P value	P summary
Phase angle	4.726±0.0803	5.479±0.0558	<0.0001	****

Values expressed are Mean±Standard error of mean. Unpaired t test was applied using Graph Pad Prism Software version 6.03. * (P<0.05), ** (P<0.01), *** (P<0.001), **** (P<0.0001)

Table 3: Mean phase angles in various stages of infiltrating ductal carcinoma breast

	Stage IIa	Stage IIb	Stage IIIa	Stage IV	F value	P value	P significance
Phase angle	5.071 (0.228)	4.891 (0.378)	4.631 (0.317)	3.733 (0.208)	13.85	<0.0001	****

Variables are expressed as Mean±SD. One-way ANOVA was applied using Graph Pad Prism Software Version 6.03. * (P<0.05), ** (P<0.01), *** (P<0.001), **** (P<0.0001)

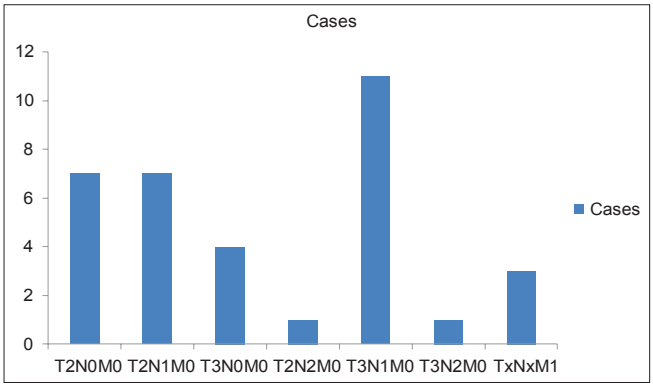

Figure 1: TNM staging and cases distribution

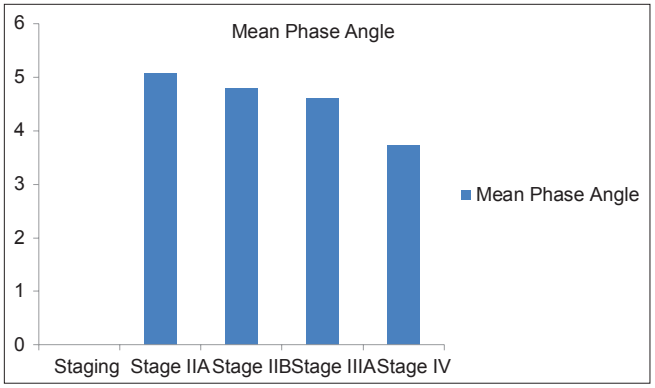

Figure 2: Staging and mean phase angle

The phase angle reflects the status of cell and cell membrane. It can be considered as a global marker of health.[6] The probable reason for the reduced phase angle in test group could be the altered and impaired cell structure and function. The neoplastic cells have impaired and reduced cell junctions, lost or new antigens, shift in ion ratios (Na, K, and Ca), abnormal plasma membrane transport, high aerobic lactate production and insertion of new proteins in cell membrane.[15] Any change in tissue physiology should produce changes in the tissue electrical properties. BIA-derived impedance and phase angle detect changes in electrical properties.[16] Reduced phase angle indicates a decreased ionic conduction with loss of dielectric mass. The observed impedance pattern, which is reflected in form of phase angle is determined by dielectric properties of the cancer cells which appear even before the appearance of overt signs of cachexia.[3] The standardized phase angle is an independent predictor for impaired functional and nutritional statuses and a better indicator of six month mortality than are malnutrition and disease severity in cancer.[14]

There are few studies which support the role of phase angle in malignancy e.g., Gupta D *et al.*, Implications for prognosis in advanced colorectal cancer and Davis MP *et al*. Phase angle changes during hydration and prognosis in advanced cancer.[17,18]

We conclude that if a lady presents with breast lump and reduced phase angle compared for her age strongly suggest breast malignancy after applying above mentioned exclusion criteria.

This study suggests that a reduced value of phase angle gives a clue for further investigation and could also be used as a prognostic indicator (for assessing staging) in patients of carcinoma breast.

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