

Role of bioelectric impedance phase angle in ovarian malignancy: A hospital-based study

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ABSTRACT

Background: A woman's risk at birth of having ovarian cancer at some point in her lifetime is 1–1.5% and mortality due to the disease is almost 0.5%. It accounts for 3% of all cancers in females. Despite a low contributory percentage, it remains the fifth leading cause of cancer related death. This is because most ovarian cancers are detected when they have spread beyond the ovary. **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 Ovarian Cancer and their matched control with the help of BIA. **Settings and Design:** After taking clearance from ethical committee a total of 33 female cases of histological proven serous cyst adenocarcinoma were included from the surgery in Patient Department, Department of surgery. Equal numbers of matched controls were recruited from the friends and relatives of cases. **Subjects and Methods:** 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 and One Way ANOVA were applied. **Results:** In control group Phase angle showed a mean $\pm$ SEM 5.073 (0.0698) while in test group it showed a mean value $\pm$ SEM 3.536 (0.0616). Mean of stage I was 3.800 (0.1154) while that of stage II was 3.620 (0.2588). Means of stage III and IV are 3.275 (0.158) and 2.90 (0.141) respectively. One Way ANOVA was applied to see any significant differences among the phase angle values of all stages. The results were statistically significant. The smaller the phase angle values higher was the Malignant Tumours (TNM) staging. **Conclusions:** The phase angles differed significantly from the healthy age matched control values and also among the stages. This study demonstrated that phase angle is a strong predictor of severity and prognosis of ovarian cancer and differed significantly between the groups. Further studies are required to validate its role as a screening and prognostic tool.

Key words: Bio-electrical impedance analyzer, ovarian cancer, phase angle

INTRODUCTION

Worldwide each year, more than 225,000 women are diagnosed ovarian cancer and 140,000 women die from this diseases.^[1] A woman's risk at birth of having ovarian cancer at some point in her lifetime is 1–1.5% and that of dying from it is almost 0.5%.^[2] It accounts for 3% of all cancers in females. Despite a low contributory percentage, it remains the fifth leading cause of cancer related death.^[3] This is because most ovarian cancers are detected when they have spread beyond the ovary. In addition to genetic testing, other screening

strategies for ovarian cancer have also been evaluated. However despite enormous efforts, there is no proof that routine screening with serum markers, sonography or pelvic examination decrease mortality.^[4,5] This study is an attempt to find out a non invasive predictor for presence and severity of malignancy. Malignant cells exhibit numerous anomalies in cell and its membrane which include 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 at early stage. The altered tissue electrical properties documented in cancer patients occur even before the appearance of overt signs of cachexia.^[6]

BIA is simple, easy to use, objective, quick and easily reproducible technique to measure body composition.

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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.^[7] Impedance of the body is thus determined.^[8] 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). R is the restriction to the flow of an electric current while Xc is the resistive effect produced by tissue interfaces and cell membrane.^[9] 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.^[10] Phase angle is the marker of cell and cell membrane structure and functional status. Low phase angle suggests cell death or decreased cell integrity while higher phase angle suggests healthy cell and cell membrane.^[11] A low phase angle has been associated with an impaired outcome in tumor diseases such as pancreatic cancer, colorectal cancer, lung cancer as well as in Human Immunodeficiency Virus (HIV)/Acquired Immunodeficiency Syndrome (AIDS), liver cirrhosis, dialysis, pulmonary disease, bacteraemia and sepsis.^[12-17] This study aims to find out a non invasive and cheap alternative predictor for early diagnosis of carcinoma ovary as it is asymptomatic till late stages and can also give an insight about the advancement of disease.

SUBJECTS AND METHODS

After taking clearance from ethical committee 33 cases of histologically proven serous cyst adeno carcinoma ovary were included from the Dept of Surgery and Obstetrics and Gynaecology, Subharti Medical College Meerut. Thirty-three 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

- Biopsy proven cases of serous cyst adeno carcinoma
- Aged 30–60 years
- Has given informed consent
- Has not been treated prior for malignancy
- Not suffering from diseases like Diabetes, hypertension, cirrhosis, hepatitis, HIV, electrolyte imbalance etc.

Exclusion criteria

- Any prior surgical, chemotherapy or radiotherapy
- Overhydrated or dehydrated
- Pregnancy
- Heart disease with pacemakers
- H/O alcohol or drug abuse
- Patients on drugs like diuretics etc.

Height was measured on a parallel plane stadiometer without shoes with a correction of 0.5 cm. Weight was taken with minimal clothings on with correction of 0.1 kg

respectively. Hip circumference was measured at maximum posterior extension of buttocks while 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 third 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 atleast 4 hours. Following 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° apart from trunk and ankles atleast 20 cm away. The parts where electrodes were to be placed were cleaned with alcohol. BIA 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 min of lying down. The Impedance of the body was determined. Impedance has two components: R and Xc. R is the restriction to flow of an electric current while Xc 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.^[13] Phase angle was calculated using following equation:

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

All ovarian cancer patients were assessed for phase angle preoperatively but only those cases were included in the study which were proven to suffer from **serous cyst adeno carcinoma on biopsy postoperatively.**

All the patients proven to be cases of serous cyst adenocarcinoma ovary were staged according to International Federation of Gynaecology and Obstetrics (FIGO) recommendations on ovarian malignancy staging and phase angles of different stages were grouped accordingly. We analysed 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. Mean phase angles of all the stages were analyzed by using One Way ANOVA.

RESULTS

All the patients were staged according to TNM and FIGO classification for staging ovarian carcinoma [Figure 1 and Table 1]. We had 16 patients of Stage I (T1aN0M0, T1bN0M0, T1cN0M0) contributing to 48.48% while five patients were diagnosed to have Stage II (T2aN0M0, T2bN0M0 and T2cN0M0). Out of this, three patients belonged to T2aN0M0 and two patients to T2bN0M0. Stage III (T3aN0M0, T3bN0M0, T3cN0M0 and TN1M0) had a total of eight cases contributing to 24.24% of total.

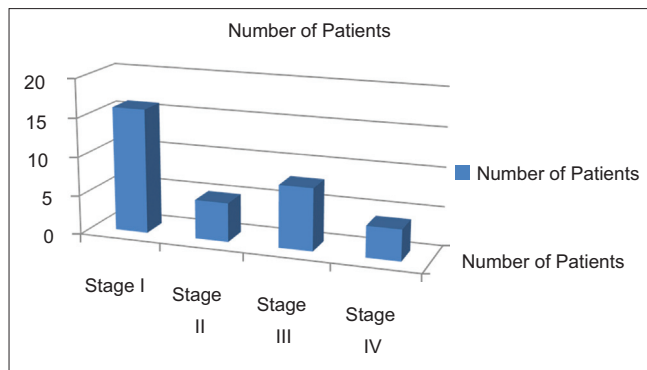


Figure 1: Patients distribution according to TNM Staging

Stage IV (Any T, Any N, M1) had minimum number of cases amounting only four cases contributing 12.12% of total cases. In Stage I, the range of phase angle varied from 4–3.6. The mean value $\pm$ SD was 3.800 (0.1154). Stage II had a maximum value of phase angle 3.9 while minimum value was 3.3 with a mean value $\pm$ SD of 3.620 (0.2588). The values of phase angle varied from 3.5–3.1 for Stage III. The mean $\pm$ SD calculated was 3.275 (0.1581) for this stage. Stage IV had highest value of 3.1 while least value of 2.8 with a mean value $\pm$ SD of 2.90 (0.141). The mean value of test group $\pm$ SEM was 3.536 (0.0616) while that of control group Mean $\pm$ SEM was 5.073 (0.0698). The two differed significantly from each other with a $P < 0.0001$ and showed a significance level of ****. One way ANOVA was applied and the differences among means of all stages was statistically significant (****) with an F value of 45.56 and a $P < 0.0001$.

DISCUSSION

The current study was undertaken to investigate if BIA derived phase angle differed significantly from the control group and whether phase angle of test group showed any pattern with staging of carcinoma ovary. This prospective case control study included comparison of a control group ($N = 33$) and a test group ($N = 33$) diagnosed as cases of serous cyst adenocarcinoma. All ovarian cancer patients were assessed for phase angle preoperatively but only those cases were included in the study which was proven to suffer from serous cystadenocarcinoma on biopsy postoperatively. All the patients were staged according to TNM and FIGO classification for staging ovarian carcinoma. The phase angle in test group Mean $\pm$ SEM was 3.536 (0.0616) while that of control group Mean $\pm$ SEM was 5.073 (0.0698). The two differed significantly from each other with a $P < 0.0001$ and showed a significance level of ****. From these observations we found that the phase angle differed significantly between the two groups [Table 2]. The phase angle also showed a decreasing trend as the staging of serous cystadenoma ovary advances [Table 3]. The differences between the mean were statistically significant in various stages and showed a significance level of **** [Table 4 and Figure 2].

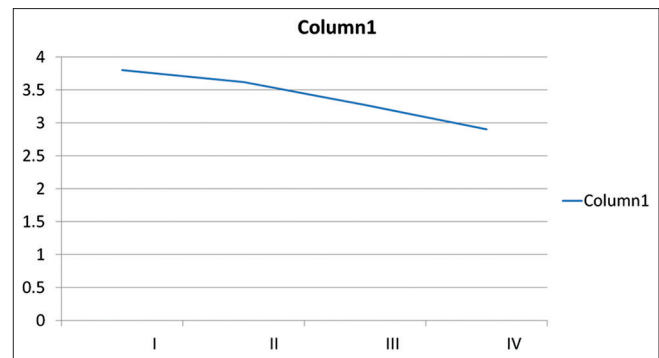


Figure 2: Mean Phase Angles in various stages of Carcinoma Ovary

Table 1: Distribution of Patients according to TNM and FIGO staging for carcinoma ovary

FIGO staging	TNM	No. of patients
I	T1aNO0	4
	T1bNO0	4
	T1cNO0	8
II	T2aNO0	3
	T2bNO0	2
III	T2cN1M0	3
	T3bN1M0	4
	T3cN1M0	1
IV	T3bNO0	2
	T3cNO0	2

TNM: Tumor Node Metastasis, FIGO: International Federation of Gynecology and Obstetrics. Values are expressed as numbers. Total number of patients ($n=33$)

Table 2: Phase angle in control and patients of carcinoma ovary

	Control ($n=33$)	Case ($n=33$)	P value	P summary
Phase angle	5.073 (0.0698)	3.536 (0.0616)	<0.0001	****

Values are expressed as mean $\pm$ standard error of mean. Analysis of data was done by unpaired t test using graph pad prism software version 6.03. $t=16.494$ with 64 degree of freedom. The 95% confidence interval of the differences: -1.722 to -1.350 . * ($P<0.05$), ** ($P<0.01$), *** ($P<0.001$), **** ($P<0.0001$)

Table 3: Mean phase angle in various stages of carcinoma ovary

FIGO staging	Phase angle
I	3.800 (0.1154)
II	3.620 (0.2588)
III	3.275 (0.1581)
IV	2.900 (0.141)

Variables presented are mean $\pm$ standard deviation

Table 4: Mean in different stages of carcinoma ovary

	I	II	III	IV	F P
Phase angle	3.800 (0.1154)	3.620 (0.2588)	3.275 (0.1581)	2.900 (0.141)	$F=45.56$ $P<0.0001$

Variables are expressed as mean $\pm$ SD. One way ANOVA applied using graph pad prism version 6.03. * ($P<0.05$), ** ($P<0.01$), *** ($P<0.001$), **** ($P<0.0001$)

The phase angle reflects the status of cell and cell membrane. It can be considered as a global marker of health.^[9] The probable reason for the reduced phase angle in test group could be the altered and impaired cell structure and function as a result of neoplasia. 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.^[18] Any change in tissue physiology should produce changes in the tissue electrical properties. BIA derived Impedance and phase angle detect changes in electrical properties.^[19] 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 patients which appear even before the appearance of overt signs of cachexia.^[6] The standardised phase angle is an independent predictor for impaired functional and nutritional status and a better indicator of 6 month mortality than are malnutrition and disease severity in cancer.^[17]

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, Davis MP, *et al.*; Phase angle changes during hydration and prognosis in advanced cancer.^[20,21]

This study concludes that a reduced value of phase angle gives a clue for further investigation and could also be used as a prognostic indicator in patients of carcinoma ovary.

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