Research Article

Bioelectric impedance phase angle in carcinoma prostate - a hospital-based study

Ruchi Tyagi[1], Shashank Mishra[2], Naveen Gaur[1], Archana Panwar[1], Dhanesh Saini[2], Kiran Singh[1], Deepak Kumar[2], Ghulam Jeelani[2]

[1]Department of Physiology, Subharti Medical College, Swami Vivekanand Subharti University, Meerut, Uttar Pradesh, India.
[2]Department of Surgery, Subharti Medical College, Swami Vivekanand Subharti University, Meerut, Uttar Pradesh, India.
Correspondence to: Ruchi Tyagi, E-mail: drruchityagi268@gmail.com

Received December 30, 2015. Accepted January 16, 2016

Abstract

Background: Prostate cancer is the leading cause of cancer death in men worldwide. A common problem faced by both clinicians and patients is that prostate malignancy does not cause symptoms until it metastasizes or become locally advanced. Prostate specific antigen (PSA) one of the important screening tools is controversial as its low predictive value results in high number of unnecessary prostate biopsies.

Objective: To explore bioelectric impedance analysis (BIA) derived phase angle as a screening and prognostic tool in histologically proven prostate cancer.

Material and Methods: This prospective case control study included the measuring of phase angles, PSA, and Gleason scoring in patients of prostate cancer and comparing it with their matched controls using unpaired *t*-test. All the patients of carcinoma prostate were grouped into various stages and one-way ANOVA was applied followed by post hoc Tukey Krammer test.

Result: Controls showed a mean ± SEM value of 4.790 (0.0424) and cases had a mean ±SEM 3.0048 (0.069). The *p*-value was <0.0001. Phase angles decreased significantly as the staging advanced showing a *p*-value of <0.0001.

Conclusion: This study demonstrated that phase angle is a strong predictor of presence and severity of carcinoma prostate patients. Further studies are required to validate its role as a screening and prognostic tool.

KEY WORDS: Bioelectric impedance analysis, prostate cancer, phase angle

Introduction

Prostate cancer is the second most frequently diagnosed cancer in men worldwide, accounting for approximately 240,000 deaths annually.[1] Each year 189,000 prostate cancer cases are diagnosed, representing approximately 30% of all cancers diagnosed in men.[2] Until prostate cancer metastasizes or becomes locally advanced, it does not generally cause symptoms. Most prostate cancers are diagnosed based on elevated PSA or an abnormal digital rectal examination. Several issues contribute to the controversy regarding annual screening. PSA testing has a relatively low predictive value which results in a high number of unnecessary prostate biopsies.[3] Little is certain about what causes prostate cancer, or the best prevention approach.[4] Established risk factors such as age, African-American race, family history, or genetic variants identified from genome wide association studies have not yet advanced the development of individualized screening and prevention studies.[4] As a matter of fact high prevalence and mortality as well as the long period of time to tumor development make prostate cancer an attractive target for prevention.

Bioelectrical impedance analyzer derived phase angle is a cheap, noninvasive, easy, and reproducible method with minimal intra- and inter-observer variability[5] to assess malignancy by measuring altered tissue electrical properties.[6] BIA works on the principle that electric current flows at different rates through the body depending upon its composition. A low-voltage current is applied and the lean tissue which

Access this article online	
Website: http://www.ijmsph.com	Quick Response Code:
DOI: 10.5455/ijmsph.2016.30122015335	

consists essentially of electrolytes containing water conducts 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). Resistance is the restriction to the flow of an electric current whereas reactance 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, whereas 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 HIV/AIDS, liver cirrhosis, dialysis, pulmonary disease, bacteremia, and sepsis.[11-17]

We know that 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, and reduced number of cell junctions and appearance of new antigens. Shifts in ion ratios (Na/K/Ca) occur within neoplastic cells resulting in abnormality in cell shape, cell movement, and cell-to-cell communication. Alteration in cell membrane proteins play a major role in malignant behavior.[18] All these changes lead to disturbed cell physiology and thus altered tissue electrical properties. The altered tissue electrical properties documented in cancer patients occur even before the appearance of overt signs of cachexia.[19] Can we establish BIA as a prognostic/diagnostic marker in malignancy was the aim of this study. This study is an attempt to assess BIA-derived phase angle as a marker for early diagnosis or assessment of staging noninvasively which can lead to early diagnosis and treatment (secondary prevention).

Methods

After taking clearance from ethical committee, all the patients with raised prostate specific antigen (PSA) and abnormal digital rectal examination were assessed for phase angle preoperatively. But only those patients (n=41) who were histologically proven cases of adenocarcinoma prostate and fulfilled the inclusion and exclusion criteria were included in the study. Gleason scoring was done for all cases. A set of 41 healthy volunteers (friends and relatives of patients) matched by age was the control group. Informed consent was taken from both the groups. Only those cases were included who were biopsy proven cases of adenocarcinoma prostate with age >30 years and <60 years. These patients has not been treated prior for malignancy and were not suffering from diseases such as diabetes, hypertension, electrolyte imbalance, cirrhosis, hepatitis, and HIV. Exclusion criteria included any prior surgical, chemotherapy, or radiotherapy; over hydration or dehydration; heart disease with pacemakers and history of alcohol or drug abuse; and 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 third measurement if the first two differed by more than 1 cm. Subjects were instructed not to consume alcohol, coffee, or do exercise 24 h prior to test. They had to come with fasting of at least 4 h. 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 at least 20 cm away from each other. The parts where electrodes were to be placed were cleaned with spirit swab. 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: 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.[15] 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 prostate cancer were staged according to American Joint Cancer Committee recommendations. Phase angles and Gleason scoring of different stages were grouped accordingly. We analyzed the data with Graph pad In stat version 3.10 and Microsoft excel. Phase angle of test group was compared with that of control group by applying unpaired *t*-test. Unpaired *t*-test was also applied to PSA levels of case and control. One-way ANOVA was applied to compare the phase angle, Gleason scoring, and PSA levels of different stages. Post hoc test Tukey Kramer Multiple Comparison was also applied.

Result

We had 3 patients in Stage I, 11 patients in stage IIa, and 13 cases were diagnosed to have stage IIb. Stage III had a total of 10 patients whereas 4 cases contributed to stage IV. Stage IIb had a maximum number of cases whereas stage I

had minimum number. Mean (SEM) PSA of control was 3.0463(0.1030) whereas in cases of prostate carcinoma it was 22.0634 (1.546). Both the groups were compared using unpaired *t*-test. The two differed significantly with a two-tailed *p*-value of <0.0001 [Table 1].

Mean (SEM) phase angle of control was 4.7902(0.04246) and that of patients of prostate cancer was 3.0048 (0.06922). Both means differed significantly from each other when compared with unpaired *t*-test. The two tailed *p*-value was <0.0001with a *t*-value of 21.985 with 80 degrees of freedom [Table 1].

PSA, Gleason scoring, and phase angle mean values for all stages were calculated and compared using one- way ANOVA [Table 2] followed by post hoc Tukey Krammer test [Table 3]. PSA and Gleason scoring increased as the staging advanced. The differences among the means for PSA as well as for Gleason scoring were significantly different. The phase angle values showed a reduction in their mean values as the staging advanced [Table 2]. All the values exhibited a significant difference when compared using one-way ANOVA showing a *p*-value of $p < 0.0001$.

Discussion

In this study, we found that the phase angle was significantly lower in cases of carcinoma prostate and differed from

Table 1: PSA and phase angle in controls and cases of prostate cancer

	control	case	*t*-value with degree of freedom	*p*-value	*p*-value summary
PSA	3.0463 (0.103)	22.063 (1.546)	12.275 80 degree	< 0.0001	****
Phase angle	4.7902 (0.042)	3.0048 (0.069)	21.985 80 degree	<0.0001	****

All values are expressed as mean (SEM). Unpaired *t*-test was applied using Graph Pad Instat version 3.10. **p*-value < 0.05, ***p*-value < 0.01, ****p*-value < 0.001, *****p*-value < 0.0001.
PSA: Prostate specific antigen.

Table 2: PSA Gleason scoring and phase angle in various stages of prostate cancer

Stages	I *n* = 3	IIa *n* = 11	IIb *n* = 13	III *n* = 10	IV *N* = 4	*F*-value	*p*-value	*p*-value summary
PSA	8.6 (0.115)	14.781 (0.9314)	25.607 (1.867)	24.77 (3.463)	33.9 (4.801)	8.680	<0.0001	****
Gleason scoring	5.666 (0.333)	6.454 (0.2073)	7.538 (0.1831)	8.1 (0.279)	8.75 (0.250)	15.384	<0.0001	****
Phase angle	3.8 (0.0)	3.409 (0.938)	2.953 (0.0268)	2.64 (0.0371)	2.375 (0.025)	49.316	<0.0001	****

PSA: Prostate specific antigen.

Table 3: Post hoc Tukey Kramer Test showing significance levels among the stages for PSA, Gleason scoring, and phase angle

Stages	PSA	Gleason scoring	Phase angle
I vs IIa	*p*>0.05, ns	*p*>0.05, ns	p<0.05, *
I vs IIb	*p*<0.01, **	*p*<0.01, **	p<0.001,***
I vs III	*p*<0.05, *	p<0.001, ***	p<0.001, ***
I vs IV	*p*< 0.001, ***	*p*< 0.001, ***	*p*< 0.001, ***
IIa vs IIb	*p*<0.01, **	*p*<0.01, **	*p*<0.001, ***
IIa vs III	*p*<0.05, *	*p*<0.001, ***	*p*<0.001, ***
IIa vs IV	*p*<0.001, ***	*p*<0.001, ***	*p*<0.001, ***
IIb vs III	*p*>0.05, ns	*p*>0.05, ns	*p*<0.01, **
IIb vs IV	*p*>0.05, ns	*p*<0.05, *	*p*<0.001, ***
III vs IV	*p*>0.05, ns	*p*>0.05, ns	*p*>0.05, ns

Table showing the comparison between mean differences of PSA, Gleason scoring and phase angles of various stages by posthoc Tukey Kramer Multiple comparison test. If *q*>4.064 then *p*<0.05. *p*>0.05 ns, *p*<0.05*, *p*<0.01**, *p*<0.001***. PSA: Prostate specific antigen.

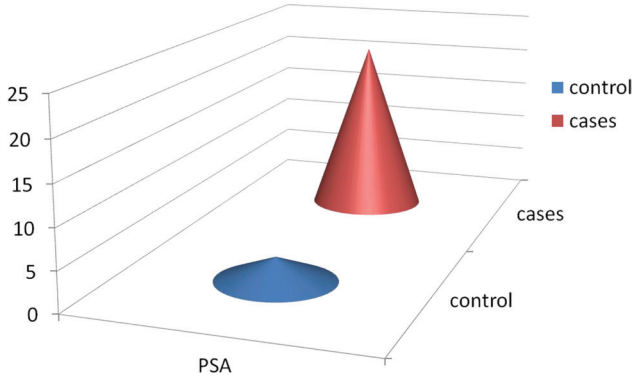

Figure 1: Compared mean serum PSA in control and cases.

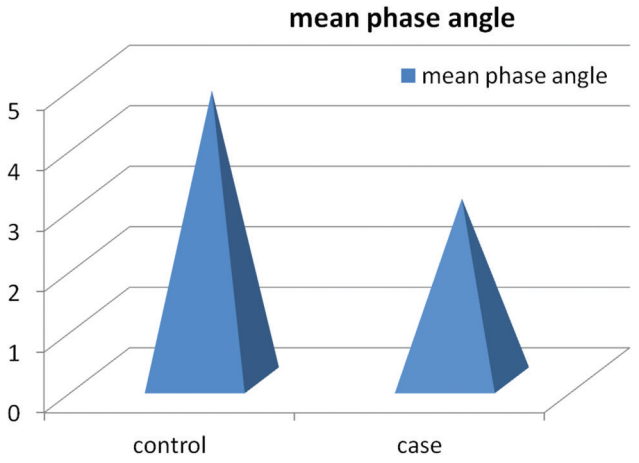

Figure 2: Mean phase angles compared in control and case of Ca prostate.

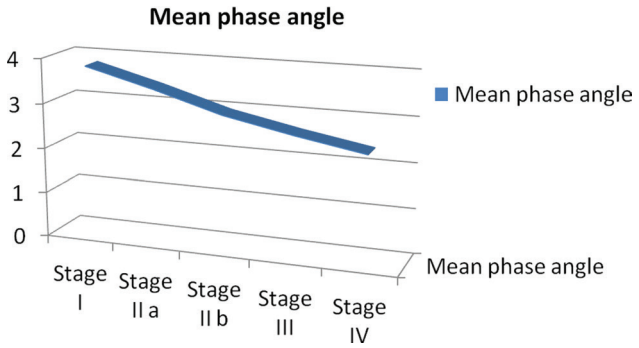

Figure 3: Mean phase angle in various stages of Ca prostate.

their matched controls. So any patient who presents with abnormal digital examination with a reduced phase angle (after applying exclusion criteria mentioned in this study) should be investigated histopathologically on priority. One-way ANOVA was applied and mean phase angles of all the stages were compared. Phase angle showed a decreasing trend as the staging of carcinoma prostate advances and also differed from each other significantly. When compared to stage I, the phase angle in groups related to stages IIa, IIb, III, and IV showed a significant decreasing trend. So as the disease got worsened the phase angle also reduced. If two patients of carcinoma prostate comes to us and one shows a much reduction in phase angle, it has been seen that this patient presented with higher staging and it indicates that disease is more advanced in this patient thus telling the prognosis. Further longitudinal studies are required to consolidate its role as a prognostic tool.

The phase angle reflects the status of cell and cell membrane. It can be considered as a global marker of health.[20] 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.[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.[6] 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. The standardized 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 that support the role of phase angle in malignancy (eg. study by Gupta on implications for prognosis in advanced colorectal cancer and study by Davis on phase angle changes during hydration and prognosis in advanced cancer.[21, 22]

Conclusion

In a country like India, where we have limited resources and a large number of population to diagnose and investigate, we can use phase angle as a screening tool in patients presenting with abnormal digital rectal examination or symptoms pertaining to malignancy. 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 prostate cancer.

References

1. Ferlay J, Shin HR, Bray F, Forman D, Mathers C, Parkin DM. Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. Int J Cancer 2010;127:2893-917.
2. Jemal A, Murray T, Samuels A. Cancer statistics. CA Cancer J Clin 2003;53:5.

3. Charles Brunicardi F. *Schartzs Principles of Surgery, 8th edn*. New York: Mc Graw Hill Medical Publishing Division.
4. Fowke JH, Motley SS, Concepcion RS, Penson DF, Barocas DA. Obesity, body composition and prostate cancer. BMC Cancer 2012;12:23.
5. Diaz EO, Villar J, Immink M, Gonzales T. Bioimpedance or anthropometry? European J Clin Nutr 1989;43:129-37.
6. Malecka-Massalka T, Smolen A, Zubrzycki J, Lupa-Zatwarnicka K, Morshed K. J Physiol Pharmacol 2012;63:101-4.
7. Simons JP, Schols AM, Westerterp KR, Velde GP, Wouters EF. The use of bioelectrical impedance analysis to predict total body water in patients with cancer cachexia. Am J Clin Nutr 1995;61:741–5.
8. Zarowitz BJ, Pilla AM. Bioelectrical impedance in clinical practice. DICP 1989;23:548–55.
9. Barbosa Silva MC, Barros AJ. Bioelectrical impedance analysis in clinical practice: a new perspective on its use beyond body composition equations. Curr Opin Clin Nutr Metab Care 2000; 8:311-7.
10. Baumgartner RN, Chumlea WC, Roche AF. Bioelectric impedance phase angle and body composition. Am J Clin Nutr 1988; 48:16-23.
11. Selberg O, Selberg D. Norms and correlates of bioimpedance phase angle in healthy human subjects, hospitalized patients and patients with liver cirrhosis. Eur J Appl Physiol 2002;86:509-16.
12. Faisy C, Rabbat A, Kouchakji B, Laaban JP. Bioelectrical impedance analysis in estimating nutritional status and outcome of patients with chronic obstructive pulmonary disease and acute respiratory failure. Intensive Care Med 2000;26:518-25.
13. Maggiore Q, Nigrelli S, Ciccarelli C, Grimaldi C, Rossi GA, Michelassi C. Nutritional and prognostic correlates of bioimpedance indexes in hemodialysis patients. Kidney Int 1996;50:2103-08.
14. Ott M, Fischer H, Polat H, Helm EB, Frenz M, Caspary WF, et al. Bioelectrical impedance analysis as a predictor of survival in patients with human immunodeficiency virus infection. J Acquir Immune Defic Syndr Hum Retrovirol 1995;9:20-5.
15. Schwenk A, Ward LC, Elia M, Scott GM. Bioelectrical impedance analysis predicts outcome in patients with suspected bacteraemia. Infection 1998;26:277-82.
16. Schwenk A, Beisenherz A, Romer K, Kremer G, Salzberger B, Elia M. Phase angle from bioelectrical impedance analysis remains an independent predictive marker in HIV-infected patients in the era of highly active antiretroviral treatment. Am J Clin Nutr 2000;72:496-501.
17. Norman, K. Cut off percentiles of bioelectrical phase angle predict functionality, quality of life and mortality in patients with cancer. Am J Clin Nutr 2010;92:612-19.
18. Trump BF, Heatfield BM, Phelps. PC, Sanefuji H, Shamsuddin AK. Europe Pub Med Central 1980;3:43-60.
19. Toso S, Piccoli A. Bioimpedance vector pattern in cancer patients without disease versus locally advanced or disseminated disease. Nutrition 2003;19:510-14.
20. Barbosa-Silva MC, Barros AJ. Curr Opin Clin Nutr Metab Care. 2005;8:311-17.
21. Gupta D. BIPA in clinical practice. Implications for prognosis in advanced colorectal cancer. American J Clin Nutr 2004; 80: 1634-8.
22. Davis MP. Bioelectric impedance phase angle changes during hydration and prognosis in advanced cancer. Am J Hosp Palliat Care 2009;26:180-7.

How to cite this article: Tyagi R, Mishra S, Gaur N, Panwar A, Saini D, Singh K, Kumar D, Jeelani G. Bioelectric impedance phase angle in carcinoma prostate - a hospital-based study. Int J Med Sci Public Health 2016;5:1826-1830

Source of Support: Nil, **Conflict of Interest:** None declared.