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Original Research Article

Cardiac Autonomic Modulation in Cancer Patients as Assessed by Time Domain Measures of Heart Rate Variability

Shilpa N. Bijoor[1], Subbalakshmi NK[2], Sourjya Banerjee[3]

[1]Ph.D. Research Scholar, Department of Physiology,
[2]Associate Professor, Department of Physiology,
[3]Assistant Professor, Department of Radiation Oncology,
Kasturba Medical College, Mangalore, Manipal University, Mangalore, Karnataka, India

Corresponding Author: Subbalakshmi NK

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ABSTRACT

Introduction: Cancer is a leading cause of mortality. Recent research is probing into association between autonomic control and cancer.
Aim & Objective: To find out the cardiac autonomic control in cancer patients compared to healthy subjects employing SDNN and E: I ratio.
Method: 48 cancer patients and 48 healthy subjects (control) were studied. In them E: I ratio, SDNN, Heart rate (HR), Body mass index (BMI), Blood pressure were measured. E: I ratio, SDNN and HR was measured from one minute lead II electrocardiogram in supine position. Data was analyzed by Mann-Whitney test and unpaired t test. p value less than 0.05 was considered significant.
Results: E: I ratio and HR was lower in cancer patients compared to control ($p = 0.0001$, 0.0003 respectively). SDNN did not differ significantly between cancer patients and control ($p = 0.059$). BMI, age, blood pressure did not differ significantly between cancer patients and control.
Conclusion: As E:I ratio is a measure of fluctuation in parasympathetic activity and resting HR is mainly under vagal tone, it could be concluded that in cancer patients cardiovascular parasympathetic control is impaired compared to healthy subjects.

Keywords: E: I ratio, SDNN, heart rate, vagal activity, cancer.

INTRODUCTION

Cancer is one of the leading causes of death inspite of medical developments. [1] In India it was found that 6-7 lakhs of people die alone of cancer in a year. [2] Prevention of cancer remains one of the most important goals. The major challenge faced in science is that this disease manifests differently which makes screening and prevention of this disease difficult. Recent research is probing into association between autonomic control and cancer. [3] The experimental studies in animals have observed that cancer induces cardio-myocyte remodeling and hypo-innervations of the heart. [4] Vagotomy is reported to enhance metastasis of breast cancer cells. [5] Signs and symptoms of autonomic dysfunction such as irregular pattern of sweating, orthostatic hypotension, bladder

control and bowel disorder is seen in late stage of cancer. [6] Moreover visceral control is mainly achieved by autonomic nervous system. [7] Thus we hypothesize that pathogenesis of cancer and autonomic dysfunction is interlinked.

Indices of heart rate variability (HRV) provide insight into cardiac autonomic control. [8] Time domain measures of HRV are simple to perform and have been extensively used in cardiology and diabetes and now extending to cancer. [9] Maximum - minimum heart beats/minute (E:I ratio), Standard deviation of R to R interval (SDNN) are the commonly used time domain measures of HRV. [10] E:I ratio gives information regarding efferent parasympathetic nerve damage. [11] SDNN gives the information regarding both sympathetic and parasympathetic activity. [12] Thus assessing these two HRV parameters simultaneously may provide better insight into the role of vagus in relation to cancer. So, present study was designed to find out the cardiac autonomic control in cancer patients compared to healthy subjects employing SDNN and E:I ratio.

MATERIALS AND METHODS

This was a hospital based case control study. The study was conducted in Oncology Department, Kasturba Medical College Hospital, Mangalore, Karnataka, India. The study was approved by the Institutional Ethics Committee. Each patient was explained the purpose of the study, procedures and written informed consent was taken from the subjects.

Subjects: 48 cancer patients aged between 46-70 years. Controls: 48 healthy subjects matched for age and sex of study subjects.

Inclusion criteria: This study included patients with Head & Neck, Cervical, Gastrointestinal Cancer.

Exclusion criteria: Patients who were on antihypertensive drugs, sedatives, or anti-arrhythmic drugs, history of cardiovascular diseases and diabetics were excluded from the study or any other known factor influencing heart rate variability.

Parameters assessed: SDNN and E: I ratio

Parameters measured: Body mass index, blood pressure, heart rate, SDNN and E: I ratio.

Study protocol

All the subjects in the study and control groups were subjected to clinical examination. In addition to routine general examination, the height and weight of all the subjects were measured. The body mass index (BMI) was calculated using the formula: weight in kilograms (kg) divided by height in meters (m) squared. Blood pressure was measured in sitting position in all the subjects. The mean of the two was recorded as blood pressure.

Assessment of Expiratory: Inspiratory ratio (E: I ratio) in response to deep breathing

This test was performed in the morning after subjects were completely relaxed. Before beginning the test, subjects were taught to breathe, at six breaths per minute: five seconds for each inhalation and five seconds for each exhalation. The examiner raised his hand to signal the start of each inhalation and lowered to signal the start of each exhalation Lead II electrocardiogram was then recorded continuously at a speed of 25 mm/s for 60 s while the subject breathed as instructed (Cardiart 108T/MKVII, BPL Ltd. Bangalore, Karnataka, India). The R–R intervals were measured accurately. The longest interval during expiration and the shortest R–R interval during inspiration was expressed as Expiratory: Inspiratory ratio (E: I ratio). [13,14]

Assessment of standard deviation of R to R interval (SDNN)

SDNN were estimated from one minute resting lead II electrocardiogram tracing in supine position in completely relaxed state. All the R–R intervals were measured accurately and fed into a computer. SDNN was then estimated with appropriate statistical functions using Microsoft Windows XP Professional (Microsoft Corporation, Redmond, WA, USA).

Steps followed in computing SDNN: Step #1: Mean of entire set of R–R intervals was calculated, Step #2: from each of the duration of R–R interval mean R–R interval was subtracted, Step #3: Each R–R interval was squared. Step #4: all the squared R–R interval were summed up, Step #5: Squared R–R intervals were divided by one-minus sample size. Step #6: square root of the number obtained in step 5 was estimated. [12]

Assessment of resting heart rate (HR)

The HR was obtained from counting total number of R–R intervals in one minute electrocardiogram recorded in lead II in supine position in completely relaxed state.

Statistical Analysis:

Unpaired 't' test was applied to unpaired data of independent observations made in two separate groups. Whenever the standard deviation between the groups was not comparable non-parametric equivalent, Mann-Whitney 'U' test was applied. Level of significance was measured using two tailed test. P value less than 0.05 was considered significant.

RESULTS

Data is presented as mean ± SD. Data on comparison of baseline characteristics between control and study subjects is presented in table 1. Data on comparison of HRV analysis is presented in table 2.

Comparison of baseline characteristics between control and study groups

Resting heart rate was significantly lower in cancer patients compared to control ($p<0.0003$). Age, body mass index, blood pressure of study subjects did not differ significantly compared to control (table 1).

Comparison of HRV parameters between control and study groups

E: I ratio was significantly lower in study group compared to control group ($p<0.0001$, table 2). There was no statistically significant difference in SDNN between study and control groups ($p = 0.059$, table 2).

Table1. Comparison of baseline characteristics between control and study group (values are mean ± SD)

Variables	Control (n=48)	Study group (n=48)	t/u statistics	p value
Age(years)	56.87±7.46	56.73±7.31	0.09	0.92
BMI (kg/m^2)	21.89±2.906	21.96±3.50	0.105	0.91
SBP (mmHg)	123.71±11.34	121.80±6.90	11025	0.48
DBP (mmHg)	81.40±4.17	80.00±4.58	1.59	0.11
HR (beats/minute)	80.49±9.46	74.02±7.23	3.75	0.0003

n = sample size, t = unpaired t test value, u = Mann-Whitney u test value.

Table 2. E: I ratio and SDNN in control and study group (values are mean ± SD)

Parameters	Control (n=48)	Study group (n=48)	t/u statistics	p value
E: I	1.39±0.16	1.113±0.061	11.29	0.0001
SDNN (milliseconds)	27.57±10.87	23.78±8.58	1.910	0.059

n = sample size, t = unpaired t test value, u = Mann-Whitney u test value.

DISCUSSION

The result of this study showed that cancer patients had decreased E: I ratio but SDNN did not show much of a difference in cancer patients when compared to healthy subjects. E: I ratio and SDNN are the two commonly used indices of cardiovascular autonomic functions. [15] E: I ratio measured during deep breathing at 6 respiratory cycles per minute is an index of cardiac

parasympathetic activity. [16] On the other hand SDNN measures both parasympathetic and sympathetic activity. [17] Thus it could be said that in cancer patients mainly vagally mediated parasympathetic activity is reduced.

In the present study, among the baseline characteristics heart rate was significantly lower in cancer patients compared to the healthy controls. The previous studies have documented tachycardia in cancer patients. [18] The discrepancy observed between our study and their study could be due to inclusion and exclusion criteria of the study participants. In their study subjects were unselected with regard to comorbid conditions such as diabetes and cardiovascular disease. [3,19] In our study cancer patients with these comorbid conditions were excluded. Heart rate is a measure of mean level of autonomic input rather than fluctuation in autonomic input. Resting heart rate is under vagal tone. [20] Thus lower heart rate observed in cancer patients suggests that cancer patients may have enhanced vagal tone. However further studies are required to confirm our findings.

CONCLUSION

As E:I ratio is a measure of fluctuation in parasympathetic activity and resting HR is mainly under vagal tone, it could be concluded that in cancer patients cardiovascular parasympathetic control is impaired compared to healthy subjects.

Conflict of interest statement

No potential conflicts of interest relevant to this article were reported

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