Original Article

Association of Heart Rate Variability and Baroreceptor Sensitivity with Biochemical Markers in Breast Cancer Patients

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Abstract

Background and Aim: The global burden of breast cancer is on the rise, not sparing countries undergoing rapid urbanization. India is one among the top emerging countries to be affected by this disease. Breast cancer survivors are at increased risk of developing cardiovascular complications due to autonomic dysfunction and oxidative stress. Changes in autonomic balance can be assessed by measuring resting heart rate variability (HRV) and baroreceptor sensitivity (BRS). Serum levels of malondialdehyde and inflammatory markers give an estimate of ongoing oxidative stress. **Methods:** A study was conducted in two groups: (i) study group consisted of women with breast cancer who have undergone modified radical mastectomy and awaiting radiotherapy and (ii) control group consisted of normal healthy age-matched volunteers. Resting HRV and BRS were measured for participants of both the groups. Estimation of serum oxidative stress markers and inflammatory markers was also done. **Results:** Decrease in HRV and BRS accompanied by increase in oxidative stress markers and inflammatory markers in circulation was observed in cancer patients when compared to control group. **Conclusion:** Autonomic dysfunction, high oxidative stress, and decreased BRS were prominent in breast cancer patients, which could expose them to future cardiovascular events.

Keywords: Baroreceptor sensitivity, breast cancer, heart rate variability, inflammatory markers, oxidative stress

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Introduction

The incidence of breast cancer is on the rise in the past few decades due to urbanization and alteration in lifestyle. India is one among the three countries contributing to about one-third of the global disease burden due to dramatic lifestyle modifications and socioeconomic inflation.[1] Breast cancer along with cervical cancer contributes to 41.6% of all cancers among Indian women,[2] with the sole contribution by breast cancer being 23% of the total. Conventional management of nonmetastatic breast cancer includes an integrated treatment plan involving surgery, chemotherapy, and radiotherapy. The stress that cancer survivors undergo due to diagnosis of cancer is further aggravated by stress due to the tedious treatment protocols that patients are subjected to. Stress contributes to disturbance in autonomic balance due to alterations in the hypothalamic–pituitary–adrenal (HPA) axis and increases free radical damage due to oxidative stress. Chemotherapeutic drugs also have considerable ill effects on the cardiovascular functioning due to their side effect profile.[3] Studies have shown chest wall radiation to affect the underlying mediastinum consisting of the lungs and heart. It carries an increased risk of cardiovascular diseases, despite the availability of improved radiation techniques.[4] There is considerable evidence that autonomic dysfunction is accompanied by sympathetic overactivity and vagal impairment in cancer patients.[3,4] Cancer pathogenesis is accompanied by sympathovagal imbalance that causes a substantial increase in morbidity and mortality due to cardiovascular diseases. Hence, assessment of sympathovagal balance would

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Table 1: Comparison of age and anthropometric and basal cardiovascular parameters between participants in control and study groups

Parameters	Control group ($n=62$)	Study group ($n=68$)	*P*
Age (years)	45.98±6.82	47.36±6.44	0.2376
Weight (kg)	57.90±3.89	59.67±7.94	0.8367
BMI (kg/m^2)	23.30±3.34	26.49±4.7	0.0001
BHR (/min)	70.50±6.90	83.37±4.36	0.0001
SV (ml/min)	70.85±6.90	66.63±11.15	0.0115
SBP (mmHg)	106.50±6.40	114.35±16.2	0.0005
DBP (mmHg)	68.14±5.10	70.84±10.77	0.0745
RPP (mmHg/min)	75.07±5.54	98.15±15.28	0.0001
TPR (bpm.mmHg)	0.75±0.54	0.96±0.23	0.0040
BRS (ms/mmHg)	17.86±5.58	6.81±4.26	0.0001

Data presented are mean±SD. The $P<0.05$ was considered statistically significant. BMI: Basal metabolic rate, BHR: Basal heart rate, SV: Stroke volume, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, RPP: Rate pressure product, TPR: Total peripheral resistance, BRS: Baroreceptor sensitivity, SD: Standard deviation

Table 2: Comparison of frequency- and time-domain indices of heart rate variability recorded in supine position between participants in control and study groups

Parameters	Control group ($n=62$)	Study group ($n=68$)	*P*
FDI			
TP (m^2)	975.40±418.20	613.21±473.47	0.0001
LF_{nu}	40.90±17.85	59.02±19.52	0.0001
HF_{nu}	56.42±25.18	34.72±20.25	0.0001
LF:HF ratio	1.20±0.64	2.26±2.31	0.0007
TDI			
Mean RR (s)	0.850±0.149	0.727±0.475	0.0500
RMSSD (ms)	30.15±14.42	19.29±12.47	0.0001
NN50	24.60±11.40	9.65±18.46	0.0001
pNN50	7.22±3.07	5.11±2.48	0.0001

Data presented are mean±SD. The $P<0.05$ was considered statistically significant. TP: Total power, LF: Low frequency, HF: High frequency, nu: Normalized units, Mean RR: Mean RR interval, RMSSD: Square root of the mean squared differences of successive NN intervals, NN50: Number of pairs of adjacent NN intervals differing by more than 50 ms, pNN50: Percentage of NN50, SD: Standard deviation, FDI: Frequency-domain indices, TDI: Time-domain indices

provide a clue for early detection of risk for developing cardiovascular diseases.

Heart rate variability (HRV), a simple and noninvasive tool for the measurement of vagal activity and sympathovagal balance, is considered as a potential marker of stress.[5] Decreased HRV is implicated as an important marker of worsening cardiovascular health when compared with age- and sex-matched healthy individuals.[6] Literature search reveals a sparse availability of studies to establish sympathovagal imbalance among breast cancer patients undergoing oncologic treatment.

The vagus nerve exerts a neurally mediated control over the baroreceptors that function as pressure sensors for blood pressure (BP) regulation. The change in interbeat interval (IBI, in milliseconds) observed for every unit change in systolic BP (in mmHg) is measured as baroreceptor sensitivity (BRS).

Table 3: Comparison of inflammatory markers and oxidative stress parameters between participants in control and study groups

Parameters	Control group ($n=62$)	Study group ($n=68$)	*P*
hs-CRP (mg/dl)	3.90±0.80	6.07±2.13	0.0001
IL-6 (pg/ml)	19.94±3.71	60.55±5.15	0.0001
TNF-α (pg/ml)	20.32±4.62	27.31±6.31	0.0001
IFN-γ (pg/ml)	9.50±2.33	20.40±3.29	0.0001
MDA (mMol/l)	15.25±6.78	47.77±4.66	0.0001

Data presented are mean±SD. The $P<0.05$ was considered statistically significant. hs-CRP: High-sensitive C-reactive protein, IL-6: Interleukin-6, TNF-α: Tumor necrosis factor-alpha, IFN-γ: Interferon-gamma, MDA: Malondialdehyde, SD: Standard deviation

Table 4: Correlation of baroreceptor sensitivity with cardiovascular and biochemical parameters

BRS	Correlation constant (*r*)	*P*
BHR	0.429	0.000
SV	−0.396	0.001
SBP	−0.442	0.000
DBP	−0.485	0.000
RPP	−0.309	0.010
TPR	−0.074	0.549
LF:HF ratio	−0.288	0.017
hs-CRP	0.069	0.579
IL-6	−0.010	0.933
TNF-α	0.019	0.880
IFN-γ	−0.091	0.461
MDA	−0.153	0.214

$P<0.05$ were considered statistically significant. BRS: Baroreceptor sensitivity, BHR: Basal heart rate, SV: Stroke volume, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, RPP: Rate pressure product, TPR: Total peripheral resistance, LF: Low frequency, HF: High frequency, hs-CRP: High-sensitive C-reactive protein, IL-6: Interleukin-6, TNF-α: Tumor necrosis factor-alpha, IFN-γ: Interferon-gamma, MDA: Malondialdehyde

It is well known that oxidative stress and inflammatory markers are involved in the pathogenesis and progression of cancer. Plasma thiobarbituric acid reactive substance provides an estimation of oxidative stress, and levels of circulating inflammatory markers indicate the immune status. With increase in oxidative stress, levels of products of lipid peroxidation increase leading to an increase in plasma levels of malondialdehyde (MDA). Chronic inflammation in the background of tumorigenesis results due to release of inflammatory cytokines such as interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), and interferon-gamma (IFN-γ) into the circulation. These metabolic changes enhance systemic injury and worsen cancer prognosis.[7,8]

Although a few investigators have established reduced HRV in cancer patients, to the best of our knowledge, there are no studies that estimate the status of autonomic nervous system functioning in relation to the levels of inflammatory markers and oxidative stress in breast cancer patients undergoing postmastectomy chest wall radiation. Hence, we chose to study the same.

Materials and Methods

Participants

The study was done in two groups: (i) control group consisted of healthy volunteers and (ii) study group consisted of female breast cancer patients recruited from Outpatient Unit of the Department of Radiotherapy, Regional Cancer Center, JIPMER, Puducherry, India.

Inclusion criteria

The study group included 68 female breast cancer patients between 30 and 60 years' age group diagnosed with Stage II breast cancer, who had completed chemotherapy and modified radical mastectomy and awaiting locoregional radiotherapy. Control group included healthy age-matched female volunteers.

Exclusion criteria

Patients with recurrent malignancies or other coexisting malignancies were excluded from the study. Those who had received prior radiation to the chest wall were also excluded from the study. We also excluded patients with confounding factors such as diabetes mellitus and hypertension and those on drugs that modulate the autonomic nervous system.

Methods

Study participants were asked to report to the Department of Physiology, at around 9:00 A.M. at least 2 h following a light breakfast. They were instructed to avoid coffee, tea, and any drug that influence the autonomic nervous system for 12 h before the test.

Measurement of heart rate variability

Resting HRV was obtained from the 5 min electrocardiography (ECG) recording in supine posture. The ECG signals were digitalized using ML870 PowerLab 8/30 ADInstruments Data Acquisition Systems and stored for offline analysis by computer software – Kubios HRV, version 2.1, Kuopio, Finland. The software detected R-wave and computed all the RR intervals from the ECG recording. IBIs were plotted on a time scale to obtain the oscillatory curve[9,10] and analyzed by two methods: time-domain analysis and frequency-domain analysis.

Measurement of baroreceptor sensitivity

Finapres is a noninvasive method of continuous finger arterial pressure monitoring. Finapres Medical Systems, The Netherlands, was used in the current study. Sequence method was adopted in the time-domain technique to obtain the sensitivity of baroreceptors by computing slope of systolic pressure changes against RR interval changes. The average of the IBI-BP slopes gives a measure of the BRS.[11,12] Systolic, diastolic, and mean arterial pressures are derived values obtained from reconstructed brachial artery pressure. Cardiac output, stroke volume, and total peripheral resistance are obtained by statistical analysis by model flow method with the help of computer software program (Beatscope) that analyzes the finger arterial pressure and the reconstructed brachial artery pressure. Rate pressure product (RPP) is obtained as the product of heart rate and systolic BP that gives an idea about the myocardial oxygen consumption.

Measurement of biochemical markers

Five-milliliter venous blood was collected to assess serum levels of high-sensitive C-reactive protein (hs-CRP), IL-6, TNF-α, IFN-γ, and MDA by ELISA kit method.

Statistical analysis of data

The data obtained were analyzed using GraphPad Prism 7 statistical software, San Diego, USA. Variables were normally distributed and represented as mean and standard deviation. Correlation between variables was done using Pearson's correlation test.

Results

Table 1 shows participants in the study group to have significantly higher basal heart rate, systolic BP, RPP, and total peripheral resistance among breast cancer patients. BRS and stroke volume were significantly lower when compared to controls ($P < 0.05$). As seen in Table 2 total power, normalized units of high frequency (HF_{nu}), mean RR, square root of the mean squared differences of successive NN intervals (RMSSD), number of pairs of adjacent NN intervals differing by more than 50 ms (NN50), and percentage of NN50 (pNN50) of resting HRV that represent the vagal tone were significantly decreased among cancer patients when compared to their controls. HF_{nu} that represents the sympathetic tone and low frequency-HF ratio that represents sympathovagal imbalance were found to be significantly increased in breast cancer ($P < 0.05$). Table 3 shows that inflammatory markers such as hs-CRP, IL-6, TNF-α, IFN-γ, and MDA were significantly higher in breast cancer patients when compared to controls ($P < 0.05$). Pearson's correlation of BRS with cardiovascular parameters in Table 4 showed a significant correlation ($P < 0.05$) but not with serum inflammatory and oxidative stress markers.

Discussion

HRV was found to be decreased in individuals with sympathovagal imbalance. The alterations in resting HRV often precede the clinical changes in heart rate and serve as a clue to impending cardiovascular morbidity and mortality due to dysautonomia. In our study, the time-domain parameters, i.e. RMSSD, NN50, and pNN50 are found to be low in breast cancer patients when compared with their age-matched controls. Our findings were comparable to earlier studies conducted by Caro-Morán *et al*. and Crosswell *et al*.[13,14] The ability to cope with stress is decreased in those with

sympathetic predominance and vagal impairment. HRV indicates the effective modulation of sympathetic and parasympathetic systems on the cardiovascular system in cardiac and noncardiac diseases.[15] It depicts the adaptive capacity in situations of stress to maintain health. The higher the HRV the better is the adaptability and lower is the risk for developing cardiovascular events leading to survival longevity. The short-term HRV indices in breast cancer patients obtained by both time- and frequency-domain analysis in the current study are in accordance with the HRV values available from the study conducted by Vigo *et al*. in 2015[16] and Fagundes *et al*. in 2011.[17] The analysis of Finapres recording in our study suggests low BRS in cardiovascular regulation. Previous studies have demonstrated BRS in normal and healthy volunteers to be in a wide range of 15–50 ms/mmHg.[18] Markedly low values of BRS (<3 ms/mmHg) have a positive association with the risk of occurrence of sudden cardiac death.[19] BRS of the breast cancer patients in the current study was noticed to fall in a wide range with the median of 5.41 ms/mmHg. The low value of BRS is due to the vagal impairment and alteration in the autonomic balance that underlies the BP regulatory mechanisms to maintain the cardiovascular homeostasis. Impaired cardiac autonomic control is an indicator of risk for the development of cardiac electrical instability and arrhythmias.[18] Autonomic dysfunction leading to oxidative stress and chronic inflammation may lead to accelerated decline in cardiovascular health due to accelerated.[20]

The serum levels of IL-6 in breast cancer patients are higher when compared to normal controls. The increase in inflammatory cytokines such as IL-6, TNF-α, IFN-γ, and CRP is probably due to disturbance in the HPA axis that causes an increase in the cortisol levels.[21,22] The levels of inflammatory markers in breast cancer patients matched with those in previous studies.[23,24] The scavenging action against the excessive free radicals is responsible for the decrease in the antioxidant levels. Excessive lipid peroxidation contributes to oxidative stress, leading to the accumulation of its products in the serum. Levels of serum MDA, one of the products of lipid peroxidation, increase in the background of oxidative stress. We observed higher levels of serum MDA among breast cancer patients when compared to controls. This was in line with an earlier study conducted by Panis *et al*.[7]

The association of BRS with other cardiovascular parameters showed a significant correlation, suggesting that BRS can be used as an indicator of cardiovascular status. Although autonomic dysfunction and oxidative stress are significantly higher in breast cancer patients when compared to controls, we failed to demonstrate significant association of BRS with inflammatory markers and oxidative stress marker.

Breast cancer patients have decreased HRV and BRS. Serum levels of inflammatory markers in the background of oxidative stress are higher in breast cancer patients. Significant correlation was present between BRS and other cardiovascular parameters, while its association with inflammatory markers could not be established in other study.

Conclusion

Autonomic dysfunction, high oxidative stress and decreased BRS were prominent among breast cancer patients, which could expose them to future cardiovascular risks.

Limitations of the study

Although significant correlation was present between BRS with cardiometabolic markers, the cause–effect relationship could not be established in the present study. This could probably be achieved by studying a larger population of breast cancer survivors.

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Conflicts of interest

There are no conflicts of interest.

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