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Cardiovagal regulation and transcutaneous pO_2 in breast cancer patients – a pilot study

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Vagal activity in patients with metastatic or recurrent breast cancer can predict their survival and it can be altered by behavioral, pharmacological and surgical interventions. Tumor oxygenation is important in defining the cellular metabolic microenvironment of human malignancies, O_2-depleted areas coincide with nutrient and energy deprivation and with a hostile metabolic microenvironment. In our work, we simultaneously measured two oxygen-sensitive parameters in breast cancer patients; blood oxygen saturation (SpO_2) and trans-cutaneous O_2 partial pressure ($tcpO_2$) in breast tissue. Concurrently, 5-minute beat-to-beat heart rate recording was carried out in order to get heart rate variability (HRV) data from time-domain analyses, frequency-domain analyses and entropy and symbolic dynamic non-linear methods. We compared these parameters in patients newly diagnosed with breast cancer, in patients after therapy and in healthy controls. We found lower $tcpO_2$ in patients with presence of malignant tumor compared to those post-treatment and/or without presence of malignancy. We also detected lower 2UV% (two unlike variations) and entropy in non-linear HRV analysis in all breast cancer patients and these parameters associated with parasympathetic activity did not return to the values comparable with healthy individuals after anti-cancer therapy, contrary to $tcpO_2$. Our findings show that breast tissue $tcpO_2$ can recover after the anti-cancer treatment, but complex heart rate control and cardio-vagal regulation remain impaired. This supports the idea that cancer patients and survivors might benefit from non-pharmacological interventions aimed at enhancing vagal activity, such as HRV biofeedback or Yoga.

Key words: tissue oxygenation, breast cancer, heart rate variability, cardiovagal regulation

Tumor hypoxia is associated with poor clinical outcome in a variety of tumors, including cervical, head/neck and breast cancer. It is relevant for tumor growth, metabolism, resistance to chemotherapy and metastasis. Despite the apparent importance of tumor oxygenation (O_2 partial pressure – pO_2) [1], data on pO_2 values in solid tumors originated mostly from rodent experiments [2, 3]. Early human investigations were sporadic [4, 5] or used in general anesthesia [6] or performed in selected patients with advanced disease [7] or burdened by artifacts from large electrodes [8]. In 1991, breast tissue oxygenation was measured using technique that minimized tissue compression encompassing a computerized electrode movement in the tissue, but this still required local anesthesia [9]. Contemporary techniques include: electron paramagnetic resonance imaging (small animals) [10], the MOBILE technique in the mouse (mapping oxygen by imaging lipid relaxation enhancement) [11], ultrasound (US)-guided diffuse optical tomography for mapping tumor deoxyhemoglobin (deoxyHb) and oxyhemoglobin (oxyHb) concentrations (*in vivo* patients) [12] and computerized Eppendorf pO_2 histography (patients) [13].

Herein, we employed the Medicap® company transcutaneous device to measure $tcpO_2$ with sensors using the photo-optical measuring principle extensively described elsewhere [14]. Trans-cutaneous oximetry ($tcpO_2$) is based on the measurement of the quantity of oxygen that diffuses through the tissue to the skin surface. The photo-optical sensors have recently been proven a promising alternative to the $tcpO_2$ sensors produced by the Radiometer® company,

and are now used in various commercially available devices based on electrochemical analysis of oxygen [15].

Heart rate variability (HRV) measuring "beat-to-beat" heart rate oscillations around its mean value is a result of dynamic relationships between sympathetic and parasympathetic nervous systems which indicate organism physiological adaptability and flexibility. HRV analysis has therefore attracted scientific community attention in different pathologies including cancer, becoming an important tool in both clinical and research setting and being a good predictor of cardiac events and mortality risk. Recent studies have revealed reduced HRV in breast cancer survivors using conventional HRV time and spectral analysis indicating cardiac-linked autonomic de-regulation associated with a higher risk of cardiovascular complications [16, 17].

However, the heart rate is controlled by a complex regulatory network including highly integrated neural system known as the central autonomic network (CAN) through which the brain controls visceromotor, neuroendocrine, and behavioral responses [18, 19]. Moreover, CAN is characterized by many nonlinear dynamic features such as reciprocally interconnected components through many feedback and feedforward mechanisms [20]. This perpetual control results in the complex oscillations of the heart rate, where more complex oscillations indicate more complex and healthier neuro-cardiac regulation and better organism adaptability. Thus, nonlinear methods applied in the HRV analysis can provide important information on potential abnormalities in the complex cardiac autonomic regulation associated with different diseases. In this context, symbolic dynamics as a nonlinear HRV method is suitable for assessment of cardiac time series complexity, independent of the HRV magnitude quantified by linear HRV analysis [21, 22].

Despite the fact that symbolic dynamics has been used in healthy probands and depressed patients [23], [24, 25], there are no studies related to malignant breast cancer. The aim of our pilot study was to determine $tcpO_2$ and balance autonomic nervous system (ANS) by linear and non-linear HRV analysis in patients with malignant breast tumor, in patients in remission after therapy and in healthy controls. We addressed the hypothesis that patients with newly diagnosed breast cancer have decreased breast tissue oxygenation assessed by trans-cutaneous oximetry and impaired cardiac vagal regulation, and these parameters are partially improved in patients after therapy. Moreover, we hypothesized that non-linear HRV analysis is more sensitive in detecting differences in autonomic cardiac regulation between patients with malignant breast tumor, patients in remission and healthy controls. To the best of our knowledge, this is the first study investigating breast cancer and non-linear HRV analysis.

Patients and methods

Patient characteristics. This study was cleared by The St. Elisabeth Cancer Institute (Slovakia) Ethics Review Board for human study, and the patients signed informed consent prior to participation. The study investigated 22 women. All subjects were divided into three groups; the first group (8 patients, age 34–74, mean 55.8) consisted of subjects newly diagnosed with breast cancer; the second group (7 patients, age 44–65, mean 54.1) included subjects minimally one year after anti-cancer therapy and the third group formed the control (7 subjects, age 40–74, mean 52.9) comprising healthy subjects (clinical examination, mammography and ultrasonography identified absence of breast cancer). These participants did not have previous cancer diseases and were selected randomly.

Participants with a history of cardiovascular disease, hypertension, diabetes mellitus (type I and II), acute or chronic infection were excluded from the study. Baseline personal history was taken and body weight, height, spO_2 and pulse rate were measured by Beurer pulsoximeter P030 (Ulm, Germany).

Methods for tcpO2 and SpO2 recordings. Patients were measured sitting in a 22±2 °C room. After a 5-minute period at rest, $tcpO_2$ and SpO_2 measurements were performed using a 2-modules Précise 8008 (Medicap®, Ulrichstein, Germany) and Beurer pulsoximeter P030 (Ulm, Germany), respectively. A one point calibration to air was performed before each experiment. The calibration values were set according to actual barometric pressure. The temperature of all probes was 43 °C, to allow maximal local vasodilatation, thereby decreasing the arterial to skin pressure gradient. $TcpO_2$ measurements were automatically temperature-corrected to 37 °C by the trans-cutaneous device. $TcpO_2$ data was recorded at a 1 Hz sampling rate in the breast tissue of all tested women, and arterial oxygen saturation (SpO_2) was measured by the second finger method.

HRV recordings. As a routine, patients were installed sitting in a 22±2 °C room. After a 5 minute period at rest, HRV measurements were performed using emWave Pro (HeartMath, LLC, Boulder, Colorado) with automatic pulse wave detection and calibration. HRV data was recorded at 370 Hz sampling rate and saved on a computer after each measurement. Data obtained from the plethysmograph have been shown to correlate highly and significantly with ECG-derived heart rate measurement during rest periods [26]. Beat-to-beat heart rate recordings were checked for the presence of artifacts, and artifact-free 5-minute sequences were analyzed using Kubios HRV 2.2 [27] and by custom software for symbolic dynamics analysis, as in Porta et al. [28].

Linear analysis – time-domain analysis. Time-domain analysis based on the calculation of beat-to-beat differences in heartbeat duration included calculation of mean heartbeat duration, the root mean square of successive differences (rMSSD) and the percentage of successive heartbeats differing more than 50 ms (pNN50). Parameters rMSSD and pNN50 are considered to reflect parasympathetic heart-rate regulation [29].

Table 1. Mean values of patient's characteristics, pulse rate, respiratory rate SpO_2 a $tcpO_2$ in test groups.

Variable	Breast cancer (n=8)	After therapy breast cancer (n=7)	Healthy subjects (n=7)	p-value
	mean (SD)	mean (SD)	mean (SD)	
Age / years	55.75 (14.58)	54.14 (6.91)	52.86 (13.25)	0.900
Height / m	167.38 (6.59)	163.43 (2.70)	165.57 (3.87)	0.305
Weight / kg	68.25 (15.08)	64.57 (5.03)	73.29 (16.10)	0.476
BMI / $kg{\cdot}m^{-2}$	24.35 (5.18)	24.18 (1.88)	26.65 (5.53)	0.530
Pulse rate / min^{-1}	71.00 (12.28)	65.43 (11.18)	68.57 (13.01)	0.682
Respiratory rate / min^{-1}	16.88 (5.89)	14.71 (3.73)	14.57 (3.51)	0.557
SpO_2 / %	96.63 (1.77)	97.79 (1.52)	97.57 (1.13)	0.304
$tcpO_2$ / mm Hg	60.99 (13.37)	76.35 (13.17)	76.14 (9.37)	0.036*

* significant differences between test groups ($p<0.05$)

Linear analysis – frequency-domain analysis. Spectral (frequency) analysis of HRV quantifies amplitude of oscillations in the distinct frequency bands. Firstly, the slow fluctuations were filtered using smoothness priors detrending [30]. Due to assumption of equidistant sampling, the time series of beat-to-beat heart rate recordings were converted by cubic spline interpolation with the 2 Hz sampling frequency. The power spectrum was assessed using Welch's periodogram based on Fast Fourier Transformation with 256 sample segment-length and 50% overlap. High-frequency band of HRV (0.15–0.40 Hz) reflecting respiratory sinus arrhythmia was evaluated as an index of cardiac vagal regulation.

Non-linear analysis – symbolic dynamics. Symbolic dynamics is based on the transformation of the time series into a series of symbols which reflect the range levels of RR-interval duration. Afterwards triplets of symbols (heartbeats) are classified in different patterns according to variations at the following levels: 0V% (zero variation), 1V% (one variation), 2LV% (two like variations) and 2UV% (two unlike variations). The occurrence rates of these patterns are then evaluated [31. 32]. Importantly, the 0V% (1V%) and 2LV% (2UV%) parameters can reflect cardiac-linked sympathetic and parasympathetic regulation, respectively [32, 24, 22].

Nonlinear analysis – entropy. Sample entropy (SampEn) measures complexity and irregularity of the biological signal. Compared to previous measures of entropy (e.g. Approximate entropy), SampEn is independent from the length of the analyzed time series and reduces calculation bias [33]. Healthy regulatory mechanisms are characterized by higher entropy values, thus indicating greater irregularity and complexity in the regulation of biological functions [28].

Statistical analysis. Data is presented as mean ± standard deviation (SD). The Shapiro-Wilk test was applied to test the normality of data distribution and Levene's test was used to test homogeneity variance. All intergroup comparisons were performed by analysis of variance (ANOVA) or the Kruskal-Wallis test as a non-parametric alternative to ANOVA when parametric conditions are violated (normality and/or homogeneity of variance). If the intergroup comparison showed a significant difference, a post hoc Tukey's test or Dwass-Steel-Chritchlow-Fligner test was used to identify pair-wise differences. Relationships between parameters were evaluated by Pearson's correlation coefficient analysis. The significance level was set at $p<0.05$.

Table 2. Entropy and symbolic dynamics analysis parameters.

Parameter	Breast cancer (n=8)	After therapy breast cancer (n=7)	Healthy subjects (n=7)	p-value
	mean (SD)	mean (SD)	mean (SD)	
0V%	26.44 (11.35)	27.81 (10.08)	16.00 (9.10)	0.086
1V%	45.40 (5.60)	44.14 (4.91)	43.48 (5.53)	0.782
2UV%	5.81 (5.49)	4.94 (2.83)	10.00 (6.09)	0.157
2LV%	22.35 (5.97)	23.10 (8.14)	30.52 (3.30)	0.038*
Entropy	1.68 (0.22)	1.73 (0.17)	1.98 (0.14)	0.011*

* significant differences between test groups ($p<0.05$)

Results

General and anthropometric characteristics of the study population are shown in Table 1 and entropy and symbolic dynamics analysis parameters in Table 2. There was a significant decrease in $tcpO_2$ in patients with malignant tumor compared to those after therapy and/or without malignancy (post hoc test $p=0.025$ and $p=0.027$, respectively; Figure 1).

There were no significant differences in HRV parameters of time-domain and frequency-domain analyses in the studied groups. However, we found a significantly lower pattern of 2UV% non-linear parameter in malignant patients and patients after breast cancer therapy compared to the controls ($p=0.018$, $p=0.035$, respectively; Figure 2). This suggests that breast cancer disease may be associated with changes in cardio-vagal regulation. In contrast to $tcpO_2$, parameters in post-therapy patients associated with parasympathetic activity did not return to values comparable with healthy individuals.

Entropy was significantly lower in both malignant groups in comparison with healthy women ($p=0.0042$ for

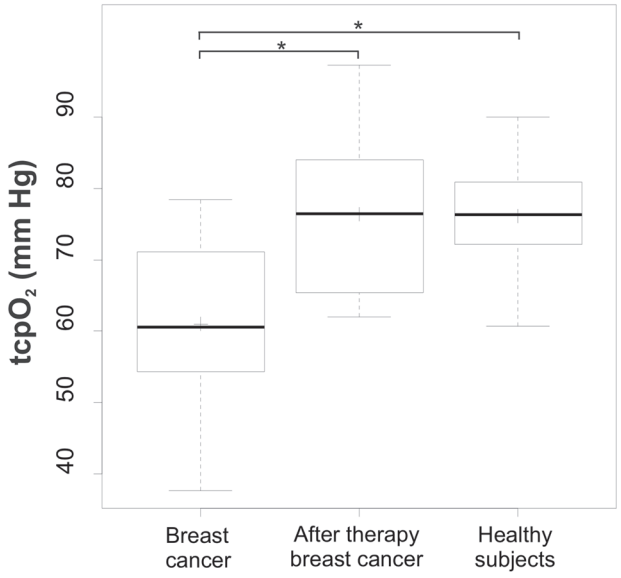

Figure 1. Trans-cutaneous O_2 partial pressure ($tcpO_2$) for all patient groups. The asterisk denotes significant difference between groups ($p<0.05$).

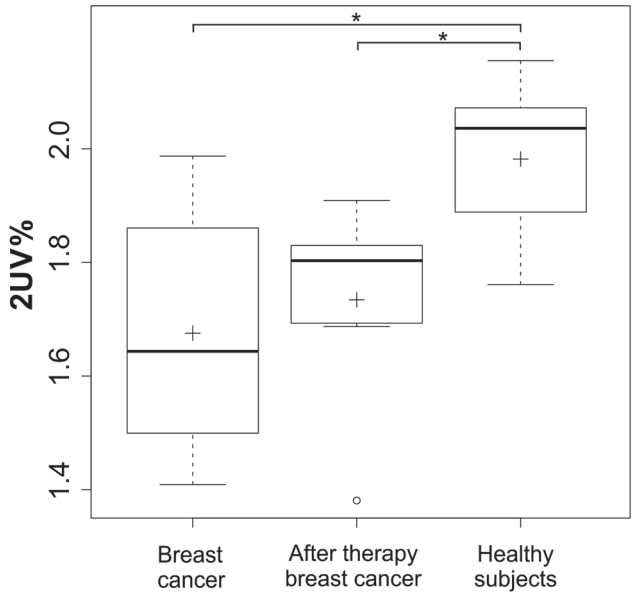

Figure 2. Two unlike variations (2UV%) parameter in non-linear analysis of HRV for all patient groups. The asterisk denotes significant difference between groups ($p<0.05$).

Table 3. Correlation between BMI, pulse rate, $tcpO_2$ and SpO_2.

Correlations pairs	Correlation coefficient (r)	p-value
BMI / Pulse rate	0.441	0.040*
BMI / SpO_2	–0.637	0.001*
BMI / $tcpO_2$	–0.371	0.089
SpO_2 / $tcpO_2$	0.583	0,004*

* significant correlation ($p<0.05$)

malignant patients and p=0.0198 for patients in remission; Figure 3). This implies that breast cancer patients may have impaired parasympathetic activity because short-term HRV predominantly reflects the ANS parasympathetic branch. This impairment also remains in patients in remission, thus indicating that improved cardio-vagal regulation does not occur spontaneously along with the anti-cancer treatment and could potentially require additional intervention. We found positive correlation in our groups of women between pulse rate and body mass index (BMI), a negative correlation between BMI and SpO_2 and weak correlation between BMI and $tcpO_2$. These results reveal the suspected positive relationship between SpO2 and tcpO2 (Table 3).

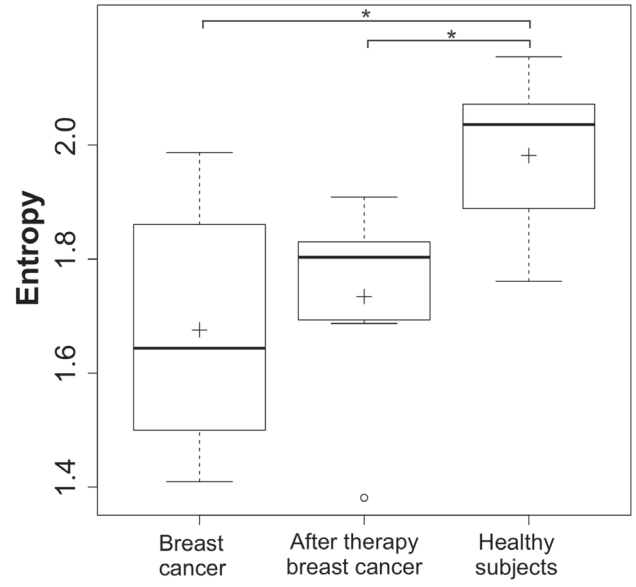

Figure 3. Entropy values for all patient groups. The asterisk denotes significant difference between groups ($p<0.05$).

Discussion

Herein, we simultaneously measured two oxygen-sensitive parameters in breast cancer patients, SpO_2 in blood and $tcpO_2$ in breast tissue, as well as basic anthropometric parameters. Concurrently, short-term (5 minute) HRV was measured to assess cardiac autonomic balance. It is accepted that $tcpO_2$ and HRV decline with increasing age, and both are gender-dependent, therefore we tried to eliminate possible bias by creating age and gender-matched groups. We found a positive correlation between pulse rate and BMI, negative correlation between BMI and SpO_2, weak negative corre-

lation between BMI and $tcpO_2$ and positive correlation between SpO_2 and $tcpO_2$.

This suggests that both hemoglobin saturation and tissue oxygenation might be life-style sensitive, while $tcpO_2$ in breast tissue could be influenced by malignant tumor, which could result in the weakened correlation with BMI. This is also supported by our data showing lower $tcpO_2$ in malignant breast tissue compared to healthy women and post-therapy breast cancer patients. Lower $tcpO_2$ in breast tissue with malignant tumor may reflect changed tumor environment and hypoxic activity of the active tumor mass because the SpO_2 values did not differ in the tested groups. The observation that $tcpO_2$ values in breast cancer survivors are comparable to values in healthy women without prior cancer history can therefore be a result of surgical removal of the tumor.

There is a scattering of the tissue pO_2 values between 1 mm Hg and values typical for arterial blood (80–100 mm Hg). Whereas in the normal tissues the medians range from 24 to 66 mm Hg, the respective values in all malignancies analyzed thus far are <20 mm Hg [34]. Since we used a trans-cutaneous system detecting the oxygen that diffuses through the tissue to the skin surface, we should take in consideration that a trans-cutaneous gradient exists that results in the surface $tcpO_2$ being lower than the arterial underlying oxygen pressure [15]. Thus, also our mean values for patients with breast malignancy (60.99±13.37) reflect the oxygen compromised breast cancer tissue, ranging from values higher that were described directly in tumor tissue to values lower than are typical for arterial blood. In both healthy controls (76.14±9.37) and women in remission (76.35±13.17), the mean values of $tcpO_2$ are higher than mentioned above, but as expected, still below the values typical for arterial blood. The observed lower oxygenation in tumorous breast tissue may result from inadequate perfusion and diffusion in the tumors and from reduced O_2 transport capacity in some cancer patients [13]. It is interesting that our $tcpO_2$ values in malignant breast tissue are comparable to values in the arms of women with lymphedema (60.1±8.8) due to breast cancer treatment [35], and these did not change following therapy which improved edema and fibrosis.

Our HRV analysis results revealed reduced complexity in heart rate control indexed by lower entropy associated with decreased cardio-vagal regulation in the symbolic 2UV% dynamics index in both newly diagnosed breast cancer patients and those in remission compared to the healthy controls. We suggest that diminished cardiac regulatory network complexity could indicate insufficient heart rate adaptation to different challenges associated with the higher cardiovascular risk in breast cancer patients and survivors. This altered adaptability may result from impaired function of the complex interactions of viscero-motor, neuro-endocrine, and behavioral regulatory circuits in CAN [18, 19]. Since CAN includes numerous feedback and feedforward mechanisms of the reciprocally interconnected components, non-linear HRV analysis could represent a more suitable tool for evaluating complex dynamic heart-rate regulation [20–22].

Importantly, it appears that cardiac-linked vagal regulation is predominantly disturbed in cancer patients, and it remains disturbed after anti-cancer treatment. Recent studies have shown that vagal nerve activity may predict cancer prognosis [36, 37]. Based on these data, we should consider using non-pharmacological interventions that improve cardiac vagal control in breast cancer patients and survivors, e.g. HRV biofeedback [38, 39] and Yoga [40]. It is note-worthy that cardiac vagal control is associated with emotion and social cognitive regulation. Specifically, higher resting cardiac vagal modulation provides better cognitive control and, in contrast, reduced cardiovagal regulation can be associated with maladaptive cognitive and emotional regulation [19, 41–44]. Our previous studies have demonstrated lower cardio-vagal regulation in different diseases associated with emotional and cognitive dysregulation such as depression [23, 45] or attention deficit/hyperactivity disorder – ADHD [46, 47, 22]. In accordance with the neuro-visceral theory describing the connection between mental and somatic functioning [41, 48], we suggest that modification of the cancer-linked life quality connected with potential affective dysregulation and perseverative cognition (e.g. worry, stress-related rumination) could lead to deficient cognitive-emotional regulatory circuitry which results in the impaired complex cardio-vagal integrity found in our study.

In contrast to recent studies which found reduced HRV indices in the traditional time and frequency domains in breast cancer survivors [16, 17], our traditional linear HRV analysis found no significant differences between patients suffering from breast cancer and controls in this study. However, above mentioned studies measured HRV in the supine position and the latter one from 30 min recordings. Our data suggests that non-linear HRV analysis is more sensitive in detecting discrete abnormalities in complex neurocardiac integrity in breast cancer patients.

In conclusion, we found lower $tcpO_2$ in the breast tissue of women with malignant tumor than in healthy women and breast cancer survivors. Our HRV analysis results revealed reduced complexity of the heart rate control associated with decreased cardio-vagal regulation in both breast cancer groups. Therefore, although breast tissue $tcpO_2$ can recover after anti-cancer treatment, the non-linear HRV parameters associated with parasympathetic activity remain impaired. However, interpretation of our results for different age and gender groups should be made with highest caution as further research regarding various age or gender is required. Our findings are important for the potential application of non-pharmacological therapeutic interventions that improve cardiac vagal control in breast cancer patients and they underline consideration of new perspectives in cancer survivor care.

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