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Original article

"Sympathetic Overactivity Estimated by Heart Rate and Blood Pressure Variability in Rectal Cancer Patients".

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ABSTRACT

AIMS: The relationship between heart rate variability (HRV) and blood pressure variability (BPV) with respect to cardiovascular parameters and baroreceptor sensitivity has not previously been analyzed in rectal cancer patients. Spectral domain analysis of heart rate and blood pressure variability appears to be an effective tool for assessing parameters of autonomic nervous system function. METHODS: Therefore, 30 rectal cancer patients and 30 healthy volunteers were enrolled in this study. Autonomic nervous system (ANS) activities were evaluated by HRV and BPV. Electrocardiograms and blood pressure were recorded with linear and nonlinear analysis of HRV and spectral domain analysis of BPV at rest. RESULTS: The low frequency (LF) and high frequency (HF) resting HRV parameters of cancer patients were lower than those of control patients (LF, 195.4 vs. 316.5, p=0.002; HF, 115.2 vs. 398.6, p=0.002, respectively). The time domain (pNN50) and nonlinear analysis of HRV parameters (Poicare plot – SD2, SampleEnthrophy, DFAα1, DFAα2) were significantly lower in cancer patients than in the healthy controls. These results correlated with sympathetic overactivity. CONCLUSION: rectal cancer affects the sympathetic-parasympathetic balance by mediating sympathetic overactivity. These ANS abnormalities could be responsible for poor prognosis in rectal cancer and may cause motility dysfunction in the gastrointestinal tract.

INTRODUCTION

The presence of neoplastic disease may cause dysfunction in various organs and systems, including the regulatory activities of the autonomic nervous system (ANS). Disturbances in the sympathetic and parasympathetic components of the ANS have not been investigated in this context. The status of vagal nerve activity and its effect on the regulation of multiple organs could be a prognostic factor in malignant disease because ANS abnormalities have been reported in cancer patients, particularly in advanced cases [1-4]. Time, spectral domain analysis of heart rate variability (HRV), and spectral domain analysis of blood pressure variability (BPV) are methods that are used to evaluate the ANS. Compared to the early stages of the neoplasic process, advanced cancers exhibit decreased parameters of HRV analysis, such as standard deviation of all normal beat to beat intervals (SDNN) and root mean square successive difference between adjacent normal beat to beat intervals (RMSSD) [5]. Recent studies have revealed that sympathetic nerves contribute to perineural invasion of cancer cells and stimulate tumor growth. β-adrenergic signaling regulates tumor progression through immune cells, such as macrophages [6]. Parasympathetic nerves can also influence cancer cell expansion and progression [6,7]. Moreover, the vagus nerve, which is a primary component of the parasympathetic nervous system, inhibits inflammation and oxidative stress and increases sympathetic activity [5,8,9].

Frequency domain analysis of HRV and BPV provides information on autonomic homeostasis. Furthermore, this method is suitable for the quantification of sympathetic and parasympathetic activity [10,11]. Monitoring HRV is a noninvasive procedure that is used to examine the autonomic innervation of the heart and the vegetative modulation of the sinus node. As such, HRV is frequently used in research on various autonomic disorders. BPV monitoring is a functional test for the sympathetic innervation of blood vessels. Both HRV and BPV monitoring appear to be useful tools for examining cancer-induced changes in autonomic activity.

Nonlinear methods of analysis have been applied to distinguish autonomic contributions with respect to HRV modulation. HRV is the result of a complex regulatory system that is related to the electrical depolarization of cardiac cells, which is primarily

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regulated by the autonomic nervous system, the mechanical and functional properties of cardiac cells, and the action of electrolytes during the refractory period of the action potential in cardiac cells. Nonlinear methods are useful tools for quantitatively characterizing the properties of the cardiac regulatory system using one of its measures, the heart rate [12]. Certain pathological conditions, such as myocardial infarction, diabetes mellitus and aging, are defined by the loss of complexity in dynamics of the heart rate regulatory system [13]. The most important role of nonlinear HRV indices is to improve the ability to identify patients at high risk of cardiovascular death [13-15]. Nonlinear HRV indices provide unique information about cardiological status, which is a diagnostic advantage of this method. Comparisons of nonlinear HRV measures between cancer and healthy subjects have so far focused on their prognostic value [16-19].

To our knowledge, this is the first study to analyze ANS activity based on a relationship between HRV and BPV parameters, cardiovascular parameters, and baroreceptor sensitivity (BRS) in patients with rectal cancer. This knowledge is pivotal for better understanding of correlations between changes in autonomic nervous system activity and cardiovascular associated disorders. These abnormalities accompany and/or result from neoplastic processes, which may be significant for rectal cancer patients, particularly for prognosis. The purpose of the study was the evaluation of disturbances in autonomic system activity as measured by HRV, BPV, and BRS as well as parameters of "cardiovascular hemodynamics" in rectal cancer patients.

MATERIAL AND METHODS

Thirty patients with histologically confirmed adenocarcinoma of the rectum (14 men, 16 women; mean age 61.2 ± 9.7 years) and 30 healthy persons (14 men, 16 women; mean age 60.2 ± 12.3 years) were enrolled in this study. Healthy controls were recruited from University Hospital's employees using advertisements (online and on bulletin boards). Every volunteer filled out a health questionnaire and was examined by a physician.

All rectal cancer patients received surgical resection. Radical resection of rectal tumors was achieved in 25 of 30 cases (83.3%). The median patient age was 61.82 years (range, 43-76 years). Patient characteristics are shown in Table 1. Body mass index (BMI) and body surface area (BSA) were not significantly different between cancer patients and controls. BMI and BSA were 27.1 ± 5.6 vs 27.9 ± 4.6 [kg/m2] and 1.84 ± 0.2 vs 1.80 ± 0.2 [m2] in cancer patients and controls, respectively.

This study was conducted in the Department of Oncology, University Hospital and Department of Pathophysiology Medical College of Jagiellonian University in Krakow, Poland from September 2014 to December 2015.

Inclusion criteria for this study were as follows: histological confirmation of rectal cancer; minimum age of 18 years; Eastern Cooperative Oncology Group (ECOG) performance status of 1 or 0; lack of systemic disorders; and adequate bone marrow, renal and hepatic functions. Exclusion criteria were defined as follows: pregnancy, presence of a chronic disease, chronic cardiovascular disorders (arterial hypertension, ischemic heart disease, cardiac defects and cardiomyopathies), uncompensated insulin-dependent diabetes, obesity, cachexia, liver diseases, peptic ulcer disease, use of medications that modulate autonomic or central activity (antidepressants, antiepileptic agents), and implantation of a cardiac pacemaker.

Ethical issues

The study protocol was approved by the Local Bioethics Committee (opinion no. KBET/98/B/2014). All enrolled subjects were provided with information on study objectives before providing their written informed consent for participation.

Assessment of autonomic system activity

The examination protocol included 20-min ECG recordings from 6 conventional leads, continuous beat-to-beat blood pressure monitoring by plethysmography, cardioimpedance, HRV and BPV analysis, determination of BRS, and measurement of cardiovascular hemodynamics using a Task Force Monitor 3040i (CNSystems, Austria). Measurements were taken between 8.00 and 10.00 AM after an overnight (12-h) fast with the subject in a supine position after achieving a respiratory rate of 14 breaths/min. Seventy-two hours before testing, subjects were in a stable clinical status, refrained from drinking coffee or performing strenuous physical exercise, and refrained from taking any medication that modulates autonomic activity.

The frequency domain analysis of R-R intervals (HRV) and arterial blood pressure was based on the Aggregating Algorithm Regression (AAR). The following parameters were considered for analysis: power spectral density (PSD) defined as total power (TP) of the spectrum at 0.0033-0.4 Hz, very low frequency (0.0033-0.4 Hz) component (VLF) reflecting HRV modulated by chemoreceptors of the renin-angiotensin-aldosterone system (RAA), low frequency (0.04-0.15 Hz) component (LF) reflecting HRV modulated by the sympathetic system associated with cyclic changes in arterial blood pressure and depending on BRS, high frequency (0.15-0.4 Hz) component (HF) reflecting HRV controlled by the parasympathetic system associated with breathing, low frequency to high frequency component ratio (LF/HF) measuring the relationship between the two components of vegetative modulation, and normalized components LFnu [LF/(TP-VLF)*100] and HFnu [HF/(TP-VLF)*100] [11].

The time domain (SDNN, standard deviation of all RR intervals; RMSSD, root mean square of the RR intervals successive differences; and pNN50, percentage of pairs of adjacent RR intervals differing by more than 50 ms) and nonlinear analysis of HRV parameters were also measured, including recurrence (%REC), determinism (%DET), DFAα1 (short-term fractal exponent of Detrended Fluctuation Analysis that corresponds to a period of 4 – 16 RRi), DFAα2 (long-term fractal exponent of DFA that correspond to a period of 16 – 64 RRi), sample entropy (SampEn), approximate entropy (ApEn), and Poincaré plot (SD1 and SD2 were assessed using KubiosPro 2.0 software) (Kuopio, Finland) [19].

The following parameters were used to determine cardiovascular status of subjects: heart rate (HR), systolic blood pressure (sBP), diastolic blood pressure (dBP), mean blood pressure (mBP), cardiac index (CI), total peripheral resistance index (TPRI), left ventricular ejection time (LVET), left ventricular work index (LVWI), total arterial compliance (TAC), baroreceptor reflex sensitivity (BRS), and baroreceptor effectiveness index (BEI). Protocols and methods of the present trial were conducted according to our previous study [20,21].

Statistical analysis

All calculations were performed using TIBCO Statistica for Windows, version 13.3 PL (TIBCO Software Inc., Palo Alto, CA USA, Jagiellonian University license) with the threshold of statistical significance set at $p<0.05$. Normality of quantitative variable distribution was verified using the Shapiro-Wilk test. Statistical characteristics of quantitative variables are presented as the means and standard deviations (for normally distributed data) or as the median, minimum and maximum values (for data that are not normally distributed). The significance of intergroup differences was verified using the Mann-Whitney U-test to assess difference in analyzed parameters in both groups. Associations between pairs of analyzed variables were determined using Spearman's correlation coefficient.

RESULTS

HRV analysis

The resting HRV parameters LF and HF were lower in the cancer patients than in the controls (LF 195.4 vs. 316.5, p=0.002; HF 115.2 vs. 398.6, p=0.002). The LF/HF ratio was higher in the cancer group than in the healthy control group, but this difference was not statistically significant (LF/HF ratio 1.9 vs. 1.7). We stratified rectal cancer patients according to LF/HF-HRV ratio values to obtain a frequency domain measure of parasympathetic-sympathetic balance. Cut-off values for LF/HF ratio were defined as the mean value of this parameter in the controls ± 1 SD (De Couck et al. 2014). As a result, we identified 6 rectal cancer patients with LF/HF ratio < 0.6 (evidence of parasympathetic overactivity) and 10 patients with LF/HF ratio > 1.5 (evidence of sympathetic predominance).

In the time domain HRV analysis, only pNN50 was significant lower in cancer patients compared to healthy controls. These results are presented in Table 2.

Nonlinear analysis of HRV indicated lower values for some parameters such as Poincaré plot – SD2, SampleEnthrophy, ApEn, DFAα1, DFAα2 in cancer patients. The mean DFAα1 and DFAα2 values were lower in cancer patients than in healthy controls (mean value). Exact values for these indices are shown in Table 3.

BPV analysis

Generally,the parameters of systolic BPV as determined by spectral analysis were lower in rectal cancer patients than in healthy controls. Only LFnu-sBP and LF/HF-sBP were higher in patients with rectal cancer. Unfortunately, none of these changes reached statistical significance. Similar changes were noted in diastolic BPV indices. All the data that were collected are shown in Tables 4 and 5. The abovementioned differences corresponded to disturbances in the parasympathetic-sympathetic balance due to sympathetic overactivity in the patient group.

Analysis of cardiovascular hemodynamic parameters

No significant differences were observed in HR between the patients and the controls, but systolic and diastolic BP parameters were significantly higher in cancer patients. BRS and BEI indicators of baroreceptor sensitivity were significant lower in rectal cancer patients than in controls. These results as well as the significantly higher TPRI in the patient group, correlated with sympathetic overactivity, while CI, LVMI and TAC were all significantly reduced in patients with rectal cancer. These results are shown in Table 6.

Table 1
Rectal cancer patients' characteristics.

Rectal cancer patients' characteristics	n=30
sex	M : F = 14 (46.7%) : 16 (53.3%)
median age (range)	61.2 years (43-76)
kind of surgical treatment	anterior resection of rectum – 17 (56.7%) abdominoperineal amputation of rectum - 10 (33.3%) proctocolectomy and partial resection of ileum - 1 (3.3%) TEM (transendoscopic microsurgery) and metastasectomy – 1 (3.3%) anterior resection of rectum and metastasectomy – 1 (3.3%)
surgical treatment	radical – 25 (83.3%); paliative – 5 (16.7%)
radiotherapy	YES – 21 (70%) NO – 9 (30%)
chemotherapy	YES – 22 (73.3%); NO – 7 (23.3%) transcatheter arterial chemoembolization (TACE) – 1 (3.3%)
symptoms before surgical treatment (first symptom/-s)	hemorrhagia – 11 (36.7%) hemorrhagia and changing in bowel habits – 9 (30%) changing in bowel habits – 4 (13.3%) hemorrhagia and pain – 3 (10%) none (accidental diagnosis) – 2 (6.7%) abdominal pain – 1 (3.3%)
present symptoms	any symptoms – 27 (90%) abdominal pain – 1 (3.3%) flatulence – 1 (3.3%) fatigue and abdominal pain – 1 (3.3%)
CEA level after surgical treatment	normal – 27 (90%) abnormal – 3 (10%) mean: 9.3±33.8 ng/ml

Table 2

The differences in linear time and spectral domain analysis HRV indices between the rectal cancer patients group and the control group.

PARAMETERS	PATIENTS [Mean±SD] Me[min-max]	CONTROLS [Mean±SD] Me[min-max]	P
LFnu-RRI [%]	54.2±15.9	50.6±16.9	0.382*
HFnu-RRI [%]	45.8±15.9	49.3±16.9	0.382*
VLF-RRI [ms²]	192.5[27-8575]	309.1[36-4406]	**0.058**
LF-RRI [ms²]	195.4[20-2495]	316.5[43-3951]	**0.002**
HF-RRI [ms²]	115.2[9-6262]	398.6[36-5112]	**0.002**
PSD-RRI [ms²]	607.3[67-8982]	1255.9[195-9693]	**0.02**
LF/HF-RRI	1.9±1.0	1.7±1.5	0.242*
SDNN [ms]	59.6±39.0	68.1±31.7	**0.067***
pNN50 [%]	9.9±16.9	24,2±24.5	**0.005**
RMSSD [ms]	55.3±69,6	52.1±37.8	0.118*

p - statistically significant difference - value – U Mann-Whitney; p* - statistically significant difference - value – unpaired Student T test;

Table 3

The differences in nonlinear analysis HRV indices between the rectal cancer patients group and the control group.

PARAMETERS	PATIENTS [Mean±SD]	CONTROLS [Mean±SD]	P
DFAα1	0.61±0.4	1.00±0.2	**0.001**
DFAα2	0.99±0.1	1.11±0.1	**0.034**
ShanEn	3.6±0.5	3.3±0.4	**0.001**
SampleEn	1.2±0.4	1.5±0.3	**0.000**
ApEn	1.2±0.2	1.9±0.2	**0.000**
%REC	44.9±11.7	34.4±9.6	**0.0003**
%DET	98.9±1.7	98.1±1.2	**0.0001**
Poicare plot SD1	39.1±49.3	36.9±26.7	0.114
Poicare plot SD2	70.8±34.7	88.0±38.5	**0.031**

p - value – unpaired Student T test, p - statistically significant difference, SD – standard deviation

Table 4

The differences in spectral analysis systolic BPV indices between the rectal cancer patients group and the control group.

PARAMETERS	PATIENTS [Mean±SD] Me[min-max]	CONTROLS [Mean±SD] Me[min-max]	P
LFnu-sBP [%]	42.2±12.0	41.6±9.9	0.855*
HFnu-sBP [%]	16.6±10.0	12.5±4.7	0.436*
VLF-sBP [ms²]	3.9[1-12]	5.7[0.9-994]	0.223
LF-sBP [ms²]	4.2[0.84-17]	5.3[1-111]	0.344
HF-sBP[ms²]	1.4[0.50-32]	1.4[0.3-68]	0.867
PSD-sBP [ms²]	11.0[3.44-61]	12.3[2.6-1173]	0.423
LF/HF-sBP	3.5±2.0	4.4±3.1	0.573*

p- statistically significant difference - value – U Mann-Whitney, p* - statistically significant difference - value – unpaired Student T test;

Table 5

The differences in spectral analysis diastolic BPV indices between the rectal cancer patient group and the control group.

PARAMETERS	PATIENTS [Mean±SD] Me[min-max]	CONTROLS [Mean±SD] Me[min-max]	P
LFnu-dBP [%]	46.2±14	45.6±12.7	0.855*
Hfnu-dBP [%]	15.8±14	13.5±8.9	0.880*
VLF-dBP [ms²]	1.8 [0.4-5]	2.8 [0.3-827]	0.062
LF-dBP [ms²]	2.3 [0.6-6]	3.1 [0.6-96]	0.173
HF-dBP[ms²]	0.6 [0.08-5]	0.7 [0.1-42]	0.395
PSD-dBP [ms²]	4.9 [2.4-11]	7.4 [1.3-966]	0.132
LF/HF-dBP	6.0±5.0	5.9±5.8	0.757*

p- statistically significant difference - value – U Mann-Whitney; p* - statistically significant difference – value – unpaired Student's T test; sBP – systolic blood pressure; dBP – diastolic blood pressure; mBP – mean blood pressure

Table 6

Differences in hemodynamic indices between the patients with rectal cancer and the control group.

Parameter	PATIENTS [Mean±SD]	CONTROLS [Mean±SD]	p
HR [bpm]	68.9±10.0	65.3±8.2	0.118
sBP[mm Hg]	120.1±14.0	108.4±13.0	**0.001**
dBP [mm Hg]	78.5±10.0	70.5±11.3	**0.004**
mBP [mm Hg]	95.9±11.0	86.3±12.3	**0.001**
BRS [ms/mmHg]	13.3±13.0	23.3±16.5	**0.001**
BEI	52.0±17.0	70.9±12.9	**0.000**
TPRI [dyne*s*m²/cm⁵]	3986.1±1138.0	2373.4±873.9	**0.000**
CI [	2.1±1.0	3.3±1.2	**0.000**
LVET [ms]	293.7±14.0	305.7±15.2	**0.004**
LVMI [mmHg*l/min/m²]	2.8±1.0	3.8±1.4	**0.002**
TAC [ml/mmHg]	1.4±0.0	2.4±0.9	**0.000**

p - value – unpaired Student T test, p - statistically significant difference

Table 7

The correlation between HRV indices and cardiovascular hemodynamics parameters in the rectal cancer patients.

Parameters	R (Spearman)	P
LFnu-RRI & BRS	-0.39	**0.03**
HFnu-RRI & BRS	0.39	**0.03**
LF/HF –RRI & BRS	-0.43	**0.02**
PSD-RRI & LVWI	-0.44	**0.03**

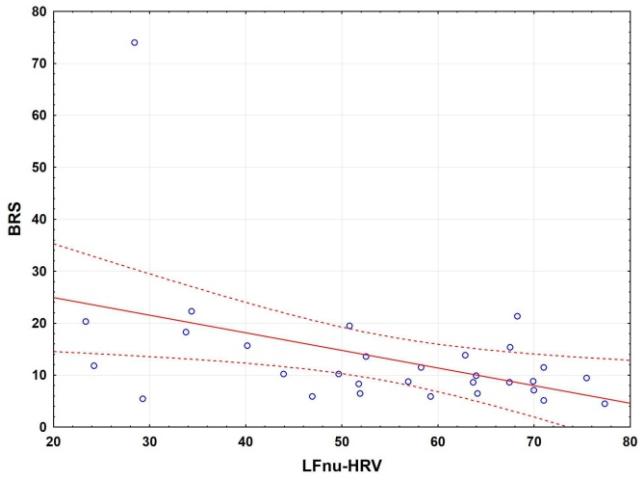

Figure 1. Correlation between LFnu-HRVand BRS in rectal cancer patients.

Spearman correlation ratio R=-0.39, p=0.03; BRS – baroreceptor sensitivity, LFnu-HRV- low frequency component of HRV analysis (normalized unit) – indicator of sympathetic component of autonomic nervous system.

CONCLUSION

Dysfunction of the autonomic nervous system in cancer patients, especially disturbances in the sympathetic-vagal balance, result in changes to cardiovascular system regulation. Despite a lack of differences in heart rate, other hemodynamic parameters, such as blood pressure, CI, LVWI, and TPRI, were altered. Dynamic parameters of HRV are helpful indicators of poor prognosis in cancer patients independent of clinical condition after radical and/or palliative therapy. Our analysis of nonlinear HRV indices supports an association with worsening of the heart rate regulatory system. These changes could be additional factors that determine patient clinical condition and may convey poor prognosis.

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