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Cardiac and autonomic function in patients with Crohn's disease during remission

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ABSTRACT

Purpose: The aim of the study was to assess cardiac and autonomic function in patients with Crohn's disease and explore their relation to disease duration using cardiovascular reflex tests.

Materials and methods: Cardiovascular parameters, baroreflex sensitivity, spectral-indices of short-term heart rate variability and blood pressure variability were compared between patients with Crohn's disease in remission (n = 30) and a control group (n = 29). Cardiac autonomic function was assessed during response to standing (tilt) and deep breathing test (expiration/inspiration ratio-E/I). Aortic pulse wave velocity, aortic augmentation index and central systolic blood pressure were measured oscillometrically.

Results: At rest, Crohn's disease patients had significantly higher systolic ($p = 0.03$) and diastolic ($p = 0.03$) blood pressure, total peripheral resistance index ($p = 0.003$), sympathetic-parasympathetic ratio ($p = 0.033$) and lower baroreceptor effectiveness ($p = 0.047$), myocardial variables (stroke index; $p = 0.03$, cardiac index; $p = 0.025$, Heather index; $p = 0.039$, left ventricular ejection time; $p = 0.038$), as compared to controls. Orthostatic response to the tilt test in the Crohn's disease group and the control group was similar, no intergroup differences were observed for E/I ratio and autonomic parameters. In Crohn's disease patients, disease duration was negatively associated with baroreflex sensitivity and positively correlated with normalised high frequency heart rate variability, sympathetic-parasympathetic ratio at rest and post-tilt changes in Δsystolic blood pressure, $p < 0.05$. The control group had significantly lower central systolic blood pressure ($p = 0.043$) compared to Crohn's disease patients.

Conclusions: Crohn's disease patients in remission have preserved cardiac and autonomic function in response to cardiovascular reflex tests with a shift in cardiovascular autonomic regulation towards sympathetic predominate in the rest position.

1. Introduction

Both, Crohn's disease (CD) and ulcerative colitis (UC) belong to the group of inflammatory bowel diseases (IBD) that are characterised by their chronic nature and complex, multi-factor etiopathogenesis that is still not fully understood [1,2]. In CD the inflammatory process affects specific segments, involving all layers of the intestinal wall, and may affect any part of the gastrointestinal tract (GI), from the mouth to the anus [3]. However, it remains unknown whether the presence of the inflammation in the enteric nervous system (ENS) is a factor contributing to CD etiopathogenesis, or occurring as a consequence of the disease [4].

CD may be considered as a systemic disease, since extraintestinal manifestations may affect 21–41% of patients; however, many manifestations are present regardless of the disease activity [5,6]. Therefore, it is still not fully known whether the presence of autonomic dysfunction in IBD results from damage to the peripheral or central autonomic nervous system (ANS) [7]. Diagnostic criteria suggest that cardiovascular autonomic neuropathy may affect approximately 5% of IBD patients [8,9]. Inflammation in the ENS may alter cardiac function in CD patients. Results of studies using heart rate variability (HRV) to evaluate ANS dysfunction in CD and UC patients are inconsistent [10].

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Some studies indicate that the IBD course is associated with increased [11,12] or decreased [8,9] ANS activity. Conversely, other authors indicate that IBD patients do not differ from healthy subjects of similar age in terms of ANS function [13]. Studies suggest that subclinical autonomic neuropathy may be a factor in predicting an increased mortality rate in IBD [14]. Therefore, detecting cardiovascular autonomic dysfunction in IBD might help to properly direct the treatment at earlier stages of the disease.

The aim of the current study was to assess cardiac and autonomic function in CD patients and explore their relation to disease duration using standardized cardiovascular reflex tests

2. Materials and methods

2.1. Subjects

We included in the study 30 subjects with CD and 29 age-matched healthy controls. The CD group consisted of 10 women and 20 men, between 20 and 46 years of age, with disease duration of 0.5–17 years. The control group consisted of 25 women and 4 men, between 20 and 46 years of age. All the patients have been in clinical and endoscopic remission for the last 10–12 weeks (according to Crohn's Disease Activity Index – CDAI < 150 scores) [15] (Table 1). Exclusion criteria were: cardiac arrhythmias, ischaemic heart disease, hypertension, diabetes mellitus, cancer diseases and treatment with beta-blockers, anticholinergic, antiarrhythmic or depressants.

2.2. Ethics approval

The study protocol was approved by the Ethics Committee at Collegium Medicum in Bydgoszcz, Nicolaus Copernicus University in Torun (approval number: KB 251/2015). All subjects provided written informed consent.

Table 1
Subjects characteristics.

	CD	Control
Number of subjects [n]	n = 30	n = 29
Age [years]	30.8 ± 7.4	32.5 ± 6.2
Sex		
Female/Men	10/20	25/4
BMI [kg/m^2]	23.2 ± 3.8	21.8 ± 3.6
Disease duration [years]	8.6 ± 5.0	–
CDAI	93.6 ± 36.7	–
CRP [mg/l]	6.84 ± 9.72	–
RBC [mln/µl	4.80 ± 0.54	–
WBC [tys./µl]	7.63 ± 2.85	–
PLT [tys./µl]	275.63 ± 62.54	–
MPV [fl]	8.40 ± 1.60	–
HG [g/dl]	13.89 ± 1.40	–
MCH [pg]	29.05 ± 2.58	–
MCHC [g/dl]	33.59 ± 1.33	–
Location, n (%)		
Ileum	5 (17%)	–
Colon	6 (20%)	–
Ileocolic	19 (63%)	–
Behaviour		
Inflammatory	18 (64%)	–
Stenosing	4 (14%)	–
Penetrating	6 (21%)	–
Drug group		
Anti-inflammatory	22 (93%)	–
Immunosuppressives	14 (46.6%)	–
Steroids	3 (10%)	–
Ant-TNF/Adalimumab	22 (73.3%)	–

CDAI - Crohn's Disease Activity Index; BMI - body mass index, CRP - C-Reactive Protein; RBC - red blood cell count; WBC - white blood cell count; PLT - platelet count; MPV - mean platelet volume; HG - hemoglobin; MCHC - mean corpuscular hemoglobin concentration; MCH - mean corpuscular haemoglobin.

2.3. Cardiac haemodynamic and autonomic regulation

All measurements were conducted in conditions meeting criteria for functional testing of the ANS [16,17]. All cardiac and autonomic regulations were recorded using a Task Force Monitor (TFM, CNSystem, Medizintechnik, Graz, Austria). Beat-to-beat systolic (sBP) and diastolic blood pressure (dBP) were measured by a vascular unloading technique which was compared automatically to the oscillometric blood pressure measured on the contralateral arm [18].

The ECG was used to evaluate the heart rate (HR), while the impedance cardiography was used to evaluate stroke volume (SV), stroke index (SI = SV/body surface), cardiac output (CO = SV × heart rate), cardiac index (CI = CO/body surface), total arterial compliance (TAC = SV/PP), thoracic fluid content (TFC), left ventricular ejection time (LVET), left ventricular work index (LVWI), index of contractility (IC) and the Heather index (HI) representing positive cardiac inotropy. The total peripheral resistance index (TPRI) was calculated according to Ohm's law: total peripheral resistance index = mean BP/cardiac index [19]. The autonomic nervous system function was evaluated by baroreceptor sensitivity using sequence method and the spectral analysis of the short-term heart rate (HRV) and blood pressure variability (BPV) applying an autoregressive methodology. TFM calculates total power spectral density (PSD) and three frequency bands: very low frequency (VLF, 0–0.05 Hz), low frequency (LF, 0.05–0.17 Hz) and high frequency (HF, 0.17–0.40 Hz). LF band refers to sympathetic modulation of sinoatrial node (SA) and vasomotor function, while HF band to parasympathetic modulation of cardiovascular activity.

The power density of each spectral component was calculated both in absolute and normalised values (PSD-RRI, LFnu-RRI, HFnu-RRI for HRV and PSD-sBP, LFnu-sBP, HFnu-sBP, PSD-dBP, LFnu-dBP, HFnu-dBP for sBPV and dBPV). Ratio between LF and HF bands (LF/HF ratio) for heart rate and blood pressure variability represents the sympathetic -parasympathetic balance. Baroreceptor sensitivity (BRS) was calculated using sequence method as the slope of the linear regression between beat-to-beat sBP values (mmHg). Baroreceptor effectiveness index (BEI) was calculated as the ratio of baroreceptor to the number of BP ramps during 10 min of supine rest [20].

2.4. Clinical cardiovascular reflex tests

2.4.1. Deep breathing test (DBT)

The DBT test assesses parasympathetic vagal nerve function. During the test subjects were asked to breathe at the frequency of 6 breathings per minute in the supine position. The E/I ratio was calculated as the mean of the longest R-R interval during expiration divided by the mean of the shortest R-R interval during inspiration [21,22] E/I ratio of > 1.11 was considered normal.

2.4.2. Tilt test

The protocol included 20 min of baseline rest in the supine position followed by 5 min 20 s of tilt test at 70°. During tilting, the parameters were recorded at 1 min 20 s (phase I), 3 min 20 s (phase II), and 5 min 20 s (phase III). Changes in the body position were made using a tilt table with a foot support and fastening straps at the knee, hip and chest levels.

2.5. Arterial function assessment

Complex arterial function (stiffness) was performed using an Arteriograph (Tensiomed). Using the cuff for blood pressure measurements, the aortic pulse wave velocity (PWVao), the augmentation index (Aix) and the central systolic blood pressure (SBPao) were measured oscillometrically, and showed a strong correlation with the invasively

obtained values [23]. The aortic length is determined on the basis of the measured distance between patient's jugular notch and pubic symphysis, and used to establish the PWVao value.

2.6. Statistical analysis

Variable parameters were presented as mean values for each group together with their standard deviation (± SD). The statistical significance of differences between parameters in the two groups was verified with the Student's *t*-test or Mann-Whitney U test. The Pearson's $\chi 2$ test and the Fisher's exact test were used to evaluate dependence of variables measured in the ordinal scale. The power and significance of correlations between pairs of selected variables were calculated with the parametric Pearson's and or nonparametric Spearman's rank test. The level of significance for all tests was set at $p < 0.05$. All calculations were conducted with STATISTICA 10.0 PL statistical package (StatSoft).

3. Results

CD patients had significantly higher frequency of episodes of stomach ache ($p < 0.01$), post-meal symptoms ($p < 0.01$), diarrhoea ($p < 0.001$), and vertigo ($p < 0.05$) as compared to the control group (Table 2).

3.1. Baseline haemodynamic and autonomic data

No significant differences were observed between the CD and the control groups for HR, SV and CO, $p > 0.05$. At rest, CD patients were characterised by significantly higher systolic ($p = 0.03$), diastolic ($p = 0.03$), mean blood pressure (mBP) ($p = 0.037$), TPR ($p = 0.027$) and TPRI ($p = 0.003$) values and lower baroreceptor effectiveness ($p = 0.047$) values as compared to the control group. Despite similar heart rate values, LF/HF ($p = 0.033$) ratio was significantly higher in the CD group, and this indicates a dominance of the sympathetic activity in this group. CD patients were characterised by significantly lower values associated with myocardial contractility, i.e.: SI ($p = 0.03$), CI ($p = 0.025$), LVET ($p = 0.038$), HI ($p = 0.039$), TFC ($p = 0.044$) and TAC ($p = 0.039$) as well as higher index of contractility value. In contrast, no significant differences were observed between the groups in sBPV, dBPV and BRS parameters, $p > 0.05$ (Tables 3 and 4).

3.2. Clinical cardiovascular reflex tests

An orthostatic response to the tilt test in the CD group and the control group was similar and characterised by an HR increase and HI, SV, CO, CI, SI, LVET, IC, TFC, TAC, TPR decrease, but without statistical significance, $p > 0.05$. Furthermore, CD patients were characterised by significantly higher mBP, (phase 1, $p < 0.01$; phase 2, $p < 0.001$; phase 3, $p < 0.01$), sBP, dBP, and TPRI values during all phases of the tilt test, as compared to the control group (Fig. 1). In CD patients in phase I, a significant drop in LFnu-dBP ($p = 0.004$) and an increase in PSD-dBP ($p = 0.045$) were accompanied by a reduction in sympathetic activity reflected as a reduced LFnu-sBP value ($p > 0.05$), but no significant difference was obtained. In the CD group, significantly lower BRS values ($p = 0.036$) were observed during the tilt (Fig. 1). No differences were observed between the CD group and the control group for HRV, BPV and baroreceptor effectiveness parameters, $p > 0.05$. No intergroup differences were observed for post-tilt cardiac and ANS parameters, $p > 0.05$ (Table 4). CD patients did not differ significantly in terms of the E/I ratio (1.3 ± 0.2 *vs* 1.4 ± 0.2, $p = 0.16$) as compared to the control group.

Table 2
Distribution of autonomic dysfunction among the groups.

	CD (n = 30)	Control (n = 29)	p
Orthostatic disorders	6 (2%)	2 (6.9%)	> 0.05
Vertigo	9 (30%)	2 (6.9%)	0.04
Arrhythmia episodes	7 (23.3%)	4 (13.8%)	> 0.05
Vasomotor disorders	4 (13.3%)	3 (10.3)	> 0.05
Secretory disorders	6 (20%)	4 (13.8%)	> 0.05
Thermoregulatory disorders	9 (30%)	4 (13.8%)	> 0.05
Stomach ache	8 (26.6	0 (0%)	0.004
Constipation	3 (10%)	3 (10.3%)	> 0.05
Diarrhoea	13 (43%)	0 (0%)	< 0.001
Post-meal symptoms	12 (40%)	2 (6.9%)	0.005
Urinary bladder dysfunctions	4 (13.3%)	2 (6.9%)	> 0.05
Sexual dysfunction	3 (10%)	0 (0%)	> 0.05
Sleep disorders	6 (20%)	6 (20.7%)	> 0.05
Pupillary disorders	6 (20%)	1 (3.4%)	> 0.05

3.3. Arterial stiffness assessment

In the control group, significantly lower SBPao (118.3 ± 12.4 *vs* 124.9 ± 11.9; $p = 0.043$) and higher - although not statistically significant - Aix (30.0 ± 23.8 *vs* 20.70 ± 13.1, $p = 0.06$) and PWVao (14.20 ± 24.1 *vs* 7.81 ± 1.1; $p = 0.15$) values were observed as compared to CD patients.

3.4. Relationship between disease duration, CDAI index and cardiac and autonomic parameters

In CD patients the disease duration was positively correlated with normalised high frequency HRV and LF/HF ratio at rest and post-tilt changes in ΔsBP ($R = 0.40$, $p = 0.029$). Furthermore, the disease duration was also negatively associated with BRS parameter and high frequency normalized units blood pressure variability, ΔLF-sBP ($r = 0.40$, $p = 0.038$) (Fig.2). CDAI index was negatively correlated with systolic ($r = 0.039$, $p = 0.047$), diastolic ($R = = 0.45$, $p = 0.02$) and mean ($R = -0.41$, $p = 0.036$) blood pressure, left ventricular work index ($R = 0.41$, $p = 0.032$), baroreflex effectiveness ($R = -0.45$, $p = 0.02$), central systolic blood pressure ($R = -042$, $p = 0.028$) at rest and positively correlated with post-tilt changes in ΔsBP ($r = 0.46$, $p = 0.017$).

4. Discussion

The main findings of our study were that CD patients in remission had preserved cardiac and autonomic function in response to cardiovascular reflex tests. Furthermore, at rest, CD patients also had significantly higher sympathetic-parasympathetic ratio and lower baroreceptor effectiveness, myocardial variables (stroke index, cardiac index, Heather index, and left ventricular ejection time), as compared to the healthy controls, $p < 0.05$.

Our results indicate that although haemodynamic and autonomic parameters are within the normal range, CD patients had higher systolic and diastolic blood pressure at rest, as compared to the control group. This can be explained by an increase in sympathetic activity manifested as a significantly higher value of the sympathetic-parasympathetic ratio, and increased values of the peripheral vascular resistance. Based on previous studies we can presume that CD patients had a higher value of the sympathetic-parasympathetic balance when compared to the control group [11,24]. A shift in the ANS balance towards sympathetic dominance was demonstrated for UC [12] and CD patients [9]. On the contrary, Mouzas et al. [4] demonstrated that IBD subjects are characterized by a shift in the autonomic regulation towards the parasympathetic predomination. This discrepancy may also be explained by differences in the methods of assessing autonomic function, disease severity and patient selection criteria. Moreover, data for IBD patients were not reported separately, due to their small number [4].

In several chronic inflammatory diseases such as rheumatoid

Table 3
Resting and during tilt test central haemodynamic measures for patients with CD and controls. Values are presented as mean ± SD.

Variables	CD (n = 30) Control (n = 29)	Baseline	1.20 Phase I	3.20 min Phase II	5.20min Phase III	Δ delta
HR [1/min]	CD	68.8 ± 12.0	77.1 ± 10.8	82.9 ± 10.6	83.9 ± 10.5	15.1 ± 10.9
	Control	67.7 ± 8.5	75.4 ± 11.1	81.4 ± 9.5	83.24 ± 8.6	15.7 ± 17.2
sBP [mmHg]	CD	119.4 ± 12.2*	133.5 ± 11.4***	135.8 ± 11.7***	133.3 ± 10.7**	13.9 ± 7.4
	Control	110.5 ± 9.9	120.8 ± 13.9	123.6 ± 11.1	123.6 ± 9.9	12.04 ± 23.6
dBP [mmHg]	CD	78.3 ± 10.0*	97.7 ± 10.3**	100.8 ± 11.6***	97.3 ± 11.7**	19.0 ± 9.6
	Control	73.3 ± 6.9	87.5 ± 12.2	89.3 ± 11.3	87.8 ± 9.0	14.1 ± 16.9
mBP [mmHg]	CD	95.1 ± 11.1*	111.7 ± 10.6**	114.9 ± 11.3***	111.61 ± 10.9**	16.5 ± 7.8
	Control	89.8 ± 7.6	102.2 ± 11.6	104.3 ± 10.0	103.4 ± 8.6	13.4 ± 18.6
SV [ml]	CD	101.6 ± 26.7	83.2 ± 14.9	76.2 ± 14.3	75.42 ± 14.35	−26.2 ± 25.2
	Control	107.9 ± 18.3	83.0 ± 14.1	74.9 ± 11.1	73.6 ± 10.4	−28.7 ± 32.9
SI [ml/m^2]	CD	54.6 ± 16.2*	44.3 ± 8.4	40.5 ± 7.7	40.1 ± 7.6	−14.5 ± 14.0
	Control	61.8 ± 8.3	47.6 ± 6.8	43.1 ± 5.7	42.3 ± 5.7	−14.7 ± 16.7
CO [1/min]	CD	6.8 ± 1.4	6.3 ± 1.0	6.2 ± 1.1	6.2 ± 1.2	−0.5 ± 1.4
	Control	7.2 ± 1.2	6.1 ± 0.8	6.0 ± 0.7	6.1 ± 0.8	−0.7 ± 2.0
CI [1/(ml*m^2)]	CD	3.6 ± 1.0*	3.4 ± 0.6	3.3 ± 0.6	3.4 ± 0.7	−0,3 ± 0.8
	Control	4.2 ± 0.7	3.5 ± 0.5	3.5 ± 0.5	3.5 ± 0.6	−0.3 ± 1.2
TPR [dyn*s*cm^3]	CD	1147.8 ± 321.2*	1440.1 ± 311.2	1491.1 ± 313.4	1447.6 ± 324.0	299.8 ± 272.0
	Control	992.9 ± 178.9	1327.4 ± 199.1	1372.2 ± 211.4	1360.4 ± 235.8	260.7 ± 424.9
TPRI [dyn*s*m^2/cm^5]	CD	2192.4 ± 730.8*	2736.9 ± 722.3**	2830.0 ± 717.9*	2745.8 ± 728.1**	553.4 ± 505.2
	Control	1725.8 ± 316.8	2325.0 ± 476.4	2401.2 ± 486.4	2378.6 ± 496.3	395.0 ± 790.0
IC [1000/s]	CD	68.5 ± 28.1	55.4 ± 16.5	50.5 ± 15.4	49,8 ± 15.3	−18.7 ± 22.8
	Control	81.3 ± 15.8	62.3 ± 13.2	57.5 ± 12.4	57.2 ± 13.4	−15.1 ± 25.6
LVET [ms]	CD	308.0 ± 21.1*	281.8 ± 16.3	274.7 ± 16.4	273.9 ± 17.0	−34.1 ± 16.9
	Control	320.4 ± 11.1	287.3 ± 18.2	276.3 ± 16.1	275.9 ± 14.2	−42.3 ± 65.9
TAC [ml/mmHg]	CD	2.6 ± 0.7*	2.4 ± 0.6	2.3 ± 0.61	2.2 ± 0.58	−0.4 ± 0.7
	Control	3.0 ± 0.5	2.7 ± 0.5	2.3 ± 0.4	2.1 ± 0.3	−0.7 ± 1.0
TFC [1/Ω]	CD	29.7 ± 4.1*	27.9 ± 4.0	27.51 ± 4.0	27.5 ± 4.0	−2.2 ± 1.6
	Control	32.2 ± 4.8	29.8 ± 4.4	29.3 ± 4.3	29.2 ± 4.3	−5.1 ± 12.8
HI [1/s^2]	CD	0.4 ± 0.1*	0.3 ± 0.1	0.2 ± 0.1	0.2 ± 0.1	−0.1 ± 0.1
	Control	0.4 ± 0.1	0.3 ± 0.1	0.3 ± 0.1	0.3 ± 0.1	−0.1 ± 0.1

HR - heart rate; sBP - systolic blood pressure; dBP - diastolic blood pressure; mBP - mean blood pressure; SV - stroke volume; SI - stroke index; CO - cardiac output; CI - cardiac index; TPR - total peripheral resistance; TPRI - total peripheral index, TAC - total artery compliance IC - index cardiac; LVET - left ventricular ejection time; HI - Heather index; TFC - thoracic fluid content; Δdelta (change baseline - phase III); statistically significant differences are indicated with *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.

Table 4
Resting and during tilt test cardiac autonomic measures for patients with CD and controls.

Variables	CD (n = 30) Control (n = 29)	Baseline	1.20 Phase I	3.20 min Phase II	5.20min Phase III	Δdelta
LFnu-RRI [%]	CD	54.3 ± 15.4	60.4 ± 15.4	71.1 ± 14.7	75.2 ± 14.2	20.9 ± 15.8
	Control	48.9 ± 10.9	59.2 ± 11.4	79.9 ± 12.3	75.1 ± 11.7	22.0 ± 23.7
HFnu-RRI [%]	CD	52.1 ± 36.2	46.5 ± 38.1	37.6 ± 47.9	24.75 ± 14.2	−27.36 ± 38.5
	Control	51.12 ± 10.9	40.8 ± 11.4	28.8 ± 12.4	31.7 ± 39.99	−15.3 ± 44.5
PSD-RRI [ms^2]	CD	1677.8 ± 2294.5	2293.4 ± 1934.1	1459.2 ± 1063.1	1128.4 ± 869.3	−549.4 ± 2236.8
	Control	2008.7 ± 2040.1	1927.3 ± 1709.6	1425.2 ± 938.9	1270.2 ± 764.5	−692.5 ± 2190.7
LFnu-dBP [%]	CD	46.8 ± 14.9	37.46 ± 10.81**	44.1 ± 12.0	52.5 ± 12.5	5.7 ± 14.8
	Control	50.9 ± 14.4	44.1 ± 7.5	48.2 ± 9.5	53.2 ± 11.3	2.3 ± 20.3
HFnu-dBP [%]	CD	14.0 ± 10.4	9.2 ± 4.1	10.0 ± 3.8	10.3 ± 3.7	−3.7 ± 10.2
	Control	15.3 ± 8.1	11.3 ± 6.1	12.2 ± 6.8	12.3 ± 6.8	−1.8 ± 12.3
PSD-dBP [mmHg^2]	CD	21.8 ± 51.4	13.7 ± 20.5*	11.3 ± 15.4	10.20 ± 14.3	−11.6 ± 37.7
	Control	7.8 ± 6.2	7.6 ± 5.7	6.6 ± 4.4	5.9 ± 4.0	−5.8 ± 17.1
LFnu-sBP [%]	CD	41.2 ± 13.5	39.9 ± 9.4	46.9 ± 10.5	53.5 ± 11.4	12.2 ± 12.8
	Control	38.6 ± 11.2	39.1 ± 8.6	44.5 ± 9.5	49.1 ± 10.3	8.1 ± 17.4
HFnu-sBP [%]	CD	19.2 ± 9.4	14.2 ± 6.2	15.3 ± 5.8	15.9 ± 5.5	−3.3 ± 8.3
	Control	18.0 ± 9.57	12.3 ± 7.0	13.5 ± 7.5	14.6 ± 7.9	−1.7 ± 13.1
PSD-sBP [mmHg^2]	CD	31.2 ± 75.7	16.0 ± 19.8	12.9 ± 15.5	11.7 ± 13.6	−19.5 ± 63.0
	Control	12.6 ± 15.3	10.3 ± 9.1	8.4 ± 6.9	7.6 ± 5.8	−5.4 ± 14.9
LF/HF [1]	CD	1.1 ± 0.7*	1.3 ± 0.7	2.2 ± 1.3	2.9 ± 1.6	1.6 ± 1.7
	Control	0.8 ± 0.4	1.1 ± 0.5	2.2 ± 2.0	2.8 ± 1.6	1.3 ± 2.8
BRS [ms/mmHg]	CD	19.2 ± 9.8	12.7 ± 8.2	9.5 ± 3.8	9.2 ± 4.1*	−9.7 ± 10.6
	Control	23.9 ± 11.9	14.8 ± 9.2	10.6 ± 5.0	12.8 ± 9.5	−11.5 ± 16.0
Total BEI [%]	CD	70.2 ± 14.9*	72.5 ± 14.5	75.6 ± 14.8	70.0 ± 20.8	−0.1 ± 22.2
	Control	76.6 ± 8.5	75.1 ± 20.6	71.4 ± 14.9	70.4 ± 24.0	−6.2 ± 26.0

LF-RRI - low frequency R—R interval; HF-RRI - high-frequency R-R interval; PSD-RRI - power spectral density R-R interval; LF/HF - ratio between low and high band for heart rate and blood pressure variability; PSD-sBP - power spectral density of systolic blood pressure variability; LF-sBP - low frequency of systolic blood pressure variability; HF-sBP - high frequency of systolic blood pressure variability; PSD-dBP - power spectral density of diastolic blood pressure variability; LF-dBP - low frequency of diastolic blood pressure variability; HF-dBP - high frequency of diastolic blood pressure variability; BRS - baroreflex sensitivity; BEI - baroreflex effectiveness; nu - normalised values; statistically significant differences are indicated with *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.

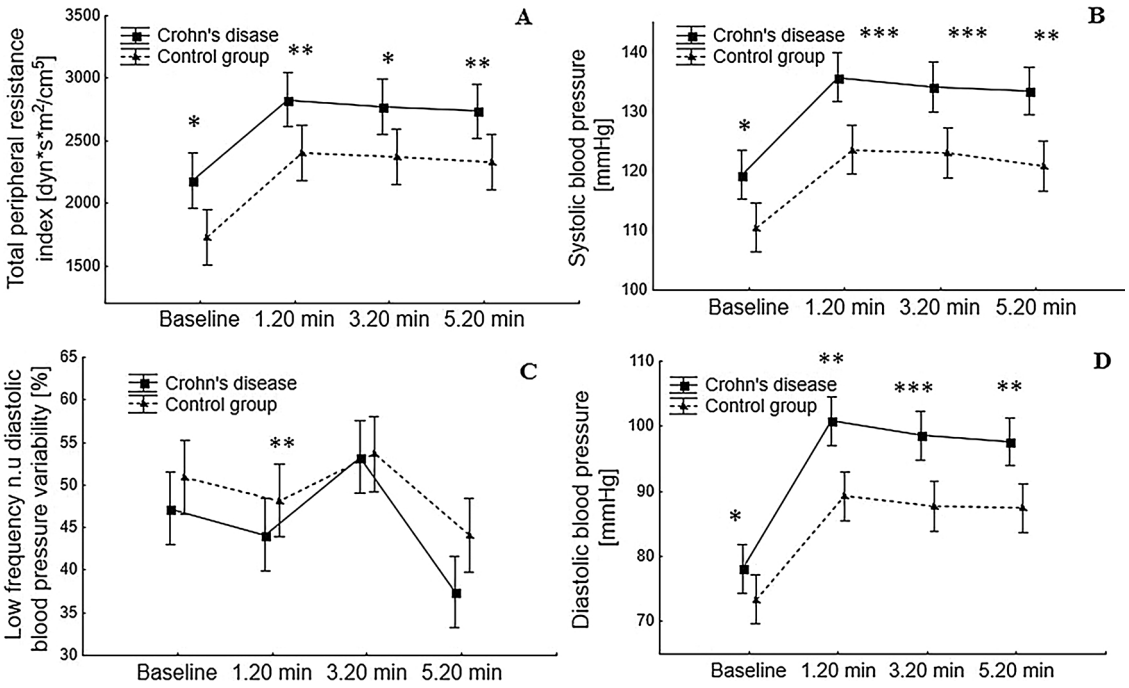

Fig. 1. Group mean values (± SD) at rest of total peripheral resistance [A], systolic blood pressure [B], low frequency normalized units blood pressure variability [C],diastolic blood pressure [D], compared to healthy controls. Statistically significant differences are indicated with *p < .05, **p < .01 and ***p < .001.

arthritis, systemic lupus erythematosus, irritable bowel syndrome, and IBD, the tone of the sympathetic nervous system (SNS) is also increased [25]. Therefore, it is likely that an autonomic imbalance with a sympathetic predomination and altered parasympathetic tone may have a key role in the pathogenesis of various immune related disorders including IBD [26]. Additionally, these syndromes are linked to chronic

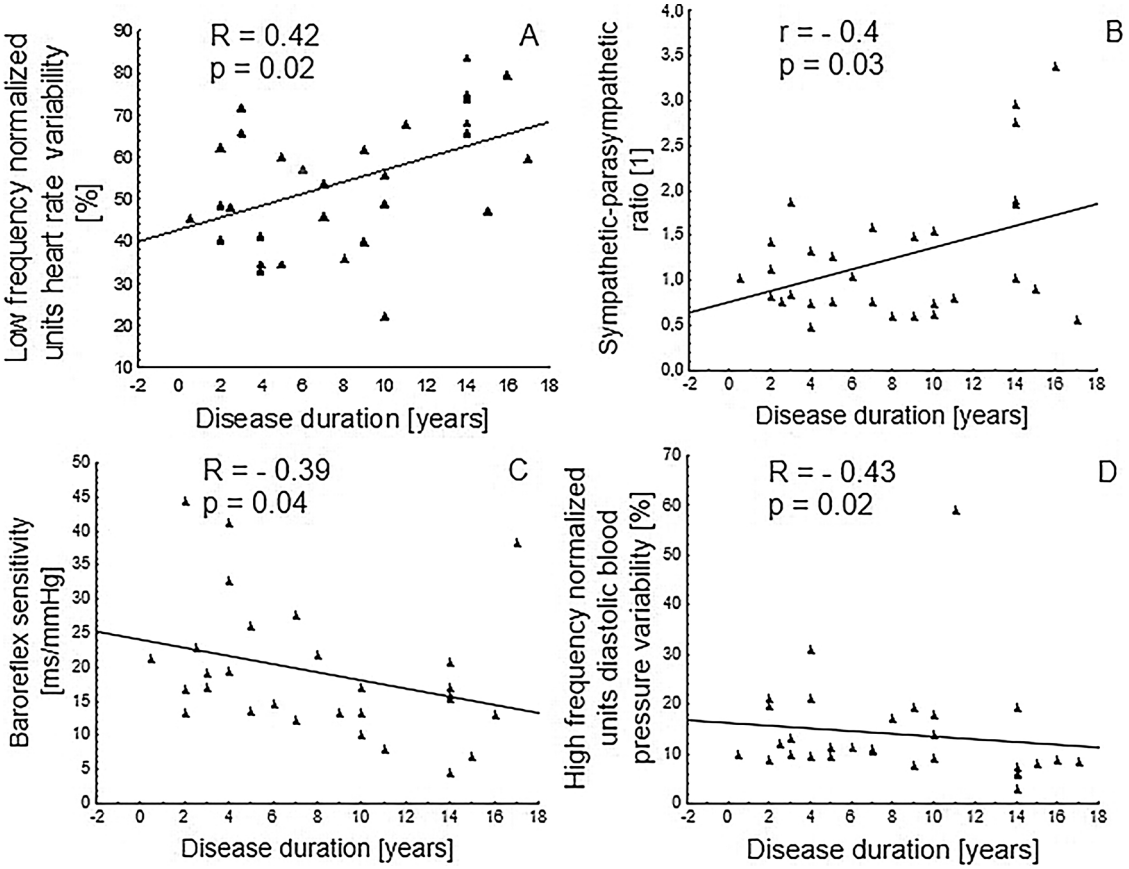

Fig. 2. Scatter plot of the association between change in haemodynamic parameters with disease duration and low frequency normalized units heart rate variability [A], sympathetic-parasympathetic ratio [B], baroreflex sensitivity [C], high frequency normalized units diastolic blood pressure variability [D] in CD group.

stress that might also lead to sympathetic predominance. Therefore, it is likely that sympathetic dysfunction could be a common underlying pathogenesis that brings on overlapping clinical features [27].

Involvement of the SNS in gut inflammation is also supported by the study of Dvorak and Silen [28], who showed axonal loss of autonomic nerves in the surgically resected ileum of CD patients. Recent studies confirm that CD and UC patients have structural abnormalities in the autonomic nerves of the gut including ganglia and neuronal hyperplasia, hypertrophy, and axonal degeneration [8,28,29].

Although subjects in the CD group were in remission, the CDAI index was associated with lower resting systolic and diastolic blood pressure, left ventricular work index, baroreflex effectiveness and central systolic blood pressure. This may be explained by the fact that the influence of the SNS on the immune response depends largely on the time point of sympathetic activation [8]. The active phase of inflammation is supported by the SNS which causes proinflammatory effects, whereas the chronic phase is regulated by the inhibition of the SNS [8,30]. In line with this hypothesis, substance P, vasoactive peptide, and cytokine 1, released during inflammation, may disrupt ANS function. In the latter case, ANS stimulation may result in secreting proinflammatory neurotransmitters and this in turn influences bowel motility and persistence of the inflammation [12]. Potential mechanisms underlying the sympathetic overactivity observed in CD patients may also be associated with excessive central stimulation, which may also contribute to a temporary reduced efficiency in the cardiovagal baroreflex control of the heart [31,32].

Based on previous studies we presume that CD patients have significantly lower baroreceptor effectiveness and slightly lower baroreflex sensitivity compared with healthy controls [32]. However, baroreflex effectiveness does not necessarily decrease the ability of the baroreflex to achieve an efficient blood pressure buffering probably due to unaffected peripheral vessels [33,34]. Cardiac autonomic dysfunction has been reported in IBD [24], however the link between the degree of autonomic dysfunction and the disease severity is ambiguous, with conflicting results [13,24,35]. The discrepancy may be explained by different number of UC and CD subjects included and poor information about clinical remission. For example, Coruzzi et al. [24] suggest that the remission phase of UC is associated with an impairment of cardiac vagal modulation as compared to both, the controls and CD patients while Topal et al. [13] concluded for an increased vagal modulation without making any distinction between UC and CD subgroups. As previously described in CD patients, the affected bowel segments are often localized within deeper layers than in UC, but with a normal lining between them. These differences might explain why UC is more evidently associated with autonomic alterations than CD [24].

The data in the present study demonstrate that CD patients have significantly lower myocardial variables, which indicates that myocardial inotropic function was slightly changed. Along these lines, we found a significant negative correlation between the CDAI index and LVET in the CD group. This assumption is also supported by echocardiographic studies which have demonstrated that CD is associated with an impairment in the left ventricle global longitudinal myocardial function [36]. Similarly, subclinical cardiac involvement among IBD patients was confirmed by Vizzardi et al. [37], who found a reduced left ventricular ejection fraction, diastolic dysfunction, myxomatous alterations of the atrioventricular valves and pericardial effusion as compared to controls. Diastolic dysfunction may also be a result of altered collagen metabolism seen in IBD patients [38]. Furthermore, Cruickshank et al. [39] also observed that a higher level of tumour necrosis factor-alpha may increase oxidative stress observed in cardiac diseases.

In our study, it was observed that CD patients had lower total arterial compliance compared to the controls, and this can be explained by significantly lower stroke volume values in this group. The data in the present study do not provide a clear answer whether CD patients are affected by accelerated arterial ageing. The central systolic blood pressure was significantly higher in CD patients, without changes in the pulse wave velocity and the augmentation index.

It cannot be excluded that GI can be modified by the frequency of acute episodes in relation to disease duration. Our results indicate a strong positive correlation between the disease duration and the SNS activity. Longer disease duration was associated with a reduction in arterial baroreflex sensitivity and an increase in the value of the sympathetic-parasympathetic ratio at rest. It is commonly accepted that a permanent shift in the sympathetic-parasympathetic balance results in numerous adverse changes, including the acceleration of atherosclerotic processes in the body and occurrence of acute coronary syndrome, as well as an increased risk of ventricular arrhythmias and sudden cardiac death [40].

Our results indicate that CD patients have normal short-term cardiac and autonomic function in response to cardiovascular reflex tests. Similar results were reported by other authors, who observed no differences in the autonomic function in IBD patients, as compared to the control group during head-up tilt [12] and deep breathing test [41]. Conversely, Ohlsson et al. reported that CD subjects with short duration of disease have lower systolic blood pressure after tilt which is consistent with early sympathetic neuropathy hypothesis [41]. Although autonomic nerve function tests were normal we cannot exclude autonomic neuropathy in CD patients due to subclinical nature of cardiovascular abnormalities. In our study we found that CD patients have similar increase in the heart rate and the sympathetic-parasympathetic balance ratio during the tilt test which indicate a similar modulating sympathetic activity of the sinoatrial node. No significant intergroup differences for post-tilt cardiac and autonomic function parameters indicate a similar reaction to the tilt in both groups. It is assumed that autonomic hyperreflexia was significantly related to more severe inflammation and systemic disease in IBD. Hyperreflexia may be a response to inflammation or a pathogenetic element that drives mucosal inflammation.

4.1. Study limitations

Significant limitations of this study include evaluation of cardiovascular ANS reflexes only during disease remission and no determination of plasma catecholamine levels.

Furthermore, patients and controls were not matched for gender, which could independently affect acquisition of autonomic dysfunction. Some of discrepancies between studies may be explained by lower mean age (30.8 ± 7.4) in CD patients which may be related to preserved compensatory mechanisms at the cardiac level. Our study did not evaluate the impact of the use of anti-inflammatory drugs for the management of cardiovascular risk in patients with IBD. However, recently, the use of tumour necrosis factor inhibitors in the treatment of resistant IBD suggests that the presence of anti-TNF-α antibodies may predispose to disorders within the nervous system, modifying its function [5].

5. Conclusions

CD patients in remission preserved cardiac and autonomic function as compared to healthy controls in response to cardiovascular reflex tests. Furthermore, longer disease duration and higher level of depression symptoms are associated with a shift in the cardiovascular autonomic regulation towards sympathetic activity. Although the ENS is a part of the ANS, the inflammatory process in ENS may not be the key determinant of cardiac impairment in CD patients. Further studies should focus on evaluating the relationship between cardiac and autonomic function during progression of the intestine bowel diseases. These findings would be helpful in clinical diagnosis and treatment for CD, that may also enlighten us as to the important role of neurohumoral regulation in CD.

Conflict of interests

The authors declare no conflict of interests.

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