AUTONOMIC DYSFUNCTION IN EXTREME OBESITY

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Abstract: Heart rate variability (HRV) provides valuable information in various clinical settings. Limited information exists on changes in cardiac autonomic modulation in extremely obese patients (BMI>40). The aim of this study was to investigate the influence of extreme (morbid) obesity and concomitant diseases on cardiovascular autonomic function. Participants of this study are 40 women and 40 men with a mean age of 47.9 diagnosed with morbid obesity (mean BMI 47.49) and hospitalized to further bariatric treatment. In 42 patients diagnosed with hypertension (treated with beta blockers and ACE inhibitors along with well controlled blood pressure), type 2 diabetes (treatment with oral drugs) also occurred. Furthermore, 46 patients were diagnosed with depression. None of the participants used antidepressants or sedative agents. A total of 80 healthy people (40 women and 40 men) with a mean age of 42.7 and with a mean BMI of 24.6 formed the control group. All patients had 24-hour ECG monitoring using the Holter method in order to evaluate the autonomic activity with time and frequency domain analysis (heart rate variability – HRV).

Results: The obese group showed a significant reduction of parasympathetic activity and a significant increase in sympathetic activity. No significant differences in cardiac autonomic modulation were noted between the Hypertensive-Diabetic patients and those with morbid obesity only. However, the in studied group, obese patients with depression had lower time and frequency domain parameters ($p<0.05$) except Standard deviation of NN intervals (SDNN), and the ratio of Low frequency (LF)) / High frequency (HF) power (LF/HF) in contrast to obese non-depressive individuals. The additional burden of diabetes and hypertension in depressed patients did not affect the cardiac autonomic modulation differences.

Further prospective study can be undertaken within the same subjects to evaluate the effect of weight loss on the cardiac autonomic activity.

Conclusions:

1. Extreme obesity altered cardiac autonomic activity independently of hypertension and diabetes.
2. Depression associated with morbid obesity intensified HRV reduction.

Keywords: heart rate variability, obesity, concomitant diseases

INTRODUCTION

Proper cardiovascular function is essential in maintaining homeostasis of the body as a whole [31]. The autonomic nervous system (ANS) plays an essential role in the regulation of cardiovascular homeostasis, in which the sympathetic and parasympathetic nervous systems should remain in balance [13,36]. One of the most advanced and widely used methods of assessing ANS activity is Heart Rate Variability (HRV), which is the evaluation of cyclic, temporal differences between successive heartbeats, corresponding to the R-R intervals of an electrocardiogram (ECG). Changes in the length of the R-R intervals depend on the activity of the sinus node and reflect the influence of the functional state of the autonomic system on the heart. A normal HRV confirms a healthy status, whereas a low HRV may be a predictor of various disease states [49]. Several studies have shown that ANS dysfunction occurs in obesity and imbalance between components of the autonomic nervous system may be one of the most important predictors of cardiovascular death [8,16].

The prevalence of obesity worldwide is reaching epidemic proportions [43]. Obesity, especially severe – morbid obesity (body mass index – BMI ≥40 kg/m2) and its metabolic consequences are associated with increased risk of morbidity and mortality and reduced life expectancy [28]. It should be emphasized that adipose tissue is not only a fat storage, but also an endocrine organ, which is both a place of formation of many biologically active substances and integration of signals sent from others. It should also be noted that a significant percentage of obese people also have other diseases that are most often complications of obesity. These include, among others: hypertension, diabetes, dyslipidemias, heart failure, ischemic heart disease and depression [5]. Both depression and obesity are significant public health problems [3] with high prevalence worldwide and an associated increased cardiovascular risk [17]. Studies have shown an association between depression and obesity, with the prevalence of depression in obese individuals being twice as high as in normal weight individuals [5]. The relationship between depression and obesity, while established

and confirmed in numerous epidemiological studies and meta-analyses, has yet to be fully elucidated. The relationship has been studied repeatedly, with some authors arguing that depression causes weight gain and obesity, and others that obesity leads to depression, suggesting bidirectional causality [48]. It has been suggested that both depression and obesity result from dysregulation of the stress response, primarily involving the hypothalamic-pituitary-adrenal (HPA) axis [26]. Further mechanisms linking these two conditions include inflammation, oxidative stress, and other endocrine dysfunctions [27] as well as psychological mechanisms such as ruminations, stigma, and ostracism, which contribute to and maintain a bidirectional relationship [27].

It is known that obesity, hypertension, diabetes mellitus and depression are associated with dysregulation of autonomic functions independently [14,40]. Unfortunately, there is limited information on changes in cardiac autonomic modulation in extremely obese patients (BMI ≥40 kg/m2), especially those burdened with comorbidities.

The aim of this study was to investigate the influence of extreme obesity and concomitant diseases on cardiovascular autonomic function.

MATERIALS AND METHODS

PARTICIPANTS

Participants of this study are 40 women and 40 men with a mean age of 47.9, diagnosed with morbid obesity (mean BMI 47.49) and hospitalized to further bariatric treatment. In 42 patients diagnosed with hypertension (treated with beta blockers and ACE inhibitors along with well controlled blood pressure), type 2 diabetes (treatment with oral drugs) also occurred. Furthermore, 46 patients were diagnosed with depression based on the results of the Beck Depression Inventory II (mean 15.6). None of the participants used antidepressants or sedative agents. A total of 80 healthy people (40 women and 40 men) with a mean age of 42.7 and with a mean BMI of 24.6 formed the control group. The participants were informed about the procedures and objectives of this study and signed informed consent forms.

HRV ANALYSIS

All subjects had 24-hour ECG monitoring using the Holter method in order to evaluate the autonomic activity with time and frequency domain analysis (heart rate variability – HRV). After manual correction for artifacts and ectopic beats, HRV analysis was performed. The recordings were evaluated temporally, including 24-hour recording, separately for the

hours of daytime activity (6:00-22:00) and nighttime rest (22:00-6:00), and a 15-minute period from day and night. A spectral analysis was performed on the same 15-minute intervals of ECG recordings from the daytime and nighttime hours.

Time-domain indices were calculated as follows:

1) Standard deviation of NN intervals (SDNN) expressed in ms, which reflects the cyclic components responsible for the variability of heart rate.
2) Root mean square successive difference of NN intervals (rMSSD) expressed in ms, which reflects estimates of short-term variability of heart rate. rMSSD is highly sensitive to the fluctuation of high frequency of HRV and is an index of vagal control of the heart.
3) Number of interval differences of successive NN intervals greater than 50 ms in the entire recording (NN50), which reflects estimates of short-term variability of heart rate and is an index of vagal control of the heart.

Frequency-domain indices were obtained through autoregressive (AR) spectral analysis. The frequency-domain indices were calculated as follows:

1) Low frequency (LF) power (0.04 to 0.15 Hz) in ms2, which reflects both sympathetic and parasympathetic cardiac activity and is strongly related to blood pressure regulation [12,38].
2) High frequency (HF) power (0.15 to 0.40 Hz) in ms2, which primarily reflects cardiac parasympathetic tone [12,38].

In addition, the LF/HF ratio was computed as the ratio of LF(ms2)/HF(ms2) as it is thought to be a measure of sympathovagal balance [25].

DEPRESSION MEASUREMENT

The previously validated Beck Depression Inventory-II (BDI-II) was used to measure depressive symptoms. BDI-II is composed of 21 multiple-choice questions (scores range between 0 and 63) and takes approximately 5 min to complete. According to the original data, 14 points were taken as the cut-off point.

STATISTICAL DATA ANALYSIS

Data were expressed as mean values ± standard deviation (SD). The normal distribution of data was tested using Shapiro–Wilk tests. Unpaired t – tests were used to compare the differences between the two groups. $P < 0.05$ was considered to be statistically significant.

RESULTS

Obesity effects on 24-h Heart Rate Variability in time and frequency domain analysis and statistical differences between groups were shown in Table 1.

Tab. 1. Age, BMI, and cardiac-autonomic markers in obese and healthy subjects.

Mean	Obese	Healthy	P value
Age	47.5	45.9	0.3
SD	2.32	3.41	
BMI	47.3	24.6	0.001
SD	3.26	2.81	
SDNN	41.21	83.45	0.0001
SD	15.88	27.31	
rMSSD	33.75	54.69	0.0001
SD	32.11	45.43	
pNN50	7.4	11.3	0.001
SD	2.3	3.45	
HF ms^2	324.5	764.1	0.001
SD	231.2	268.7	
LF ms^2	1245.8	947.6	0.01
SD	561.23	248.61	
LF/HF	3.7	2.1	0.01
SD	1.22	2.67	
TP	2876.9	3798.6	0.01
SD	582.55	834.21	

Results are reported as *Mean and Standard deviation SD*. SDNN = standard deviation of all NN intervals in ms; rMSSD = square root of the mean of the sum of the squares of differences between adjacent NN intervals in ms; NN50 = number of pairs of adjacent NN intervals differing by more than 50 ms in the entire recording; LF = low frequency power; HF = high frequency power; LF/HF = the ratio LF(ms^2)/HF(ms^2).

Analysis of time domain parameters, SDNN, pNN50 and RMSSD of obese subjects were significantly lower, compared to volunteers with normal BMI. The frequency domain parameters, the LF and LF/HF ratio in both groups was also statistically different. The obese subjects had an HF and TP values lower then healthy, and the LF values and LF/HF ratio was higher than in the control group.

The spectral components changes of HRV in a healthy person and a obese patient is shown in figure 1 and 2.

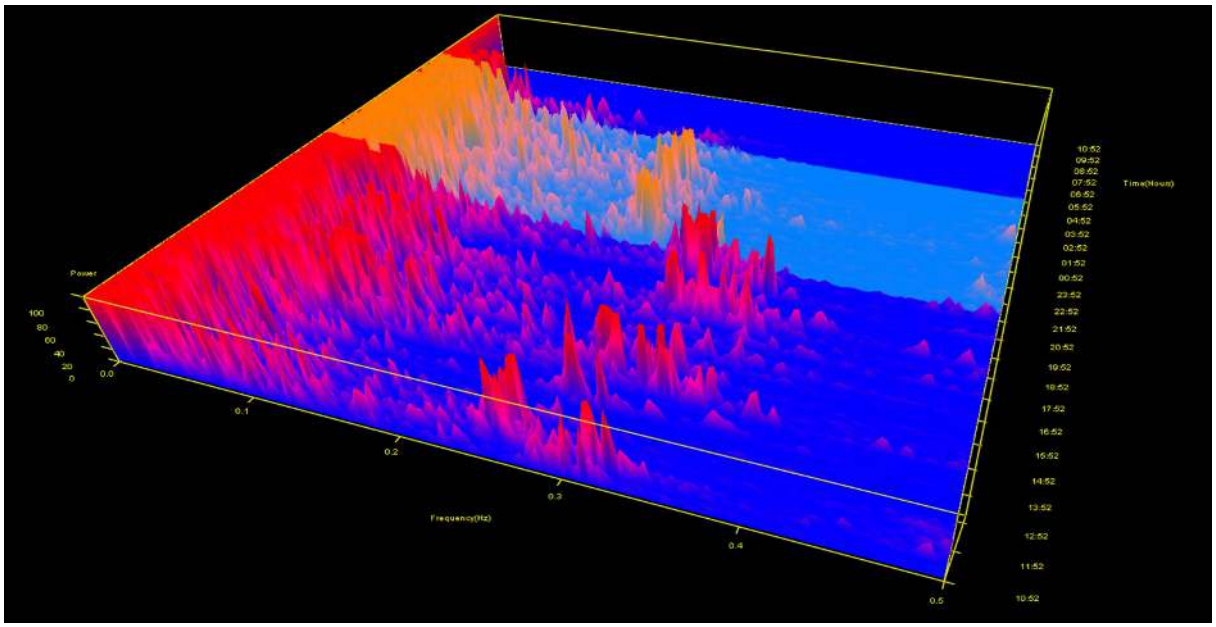

Fig. 1. The spectral components changes of HRV in a healthy person.

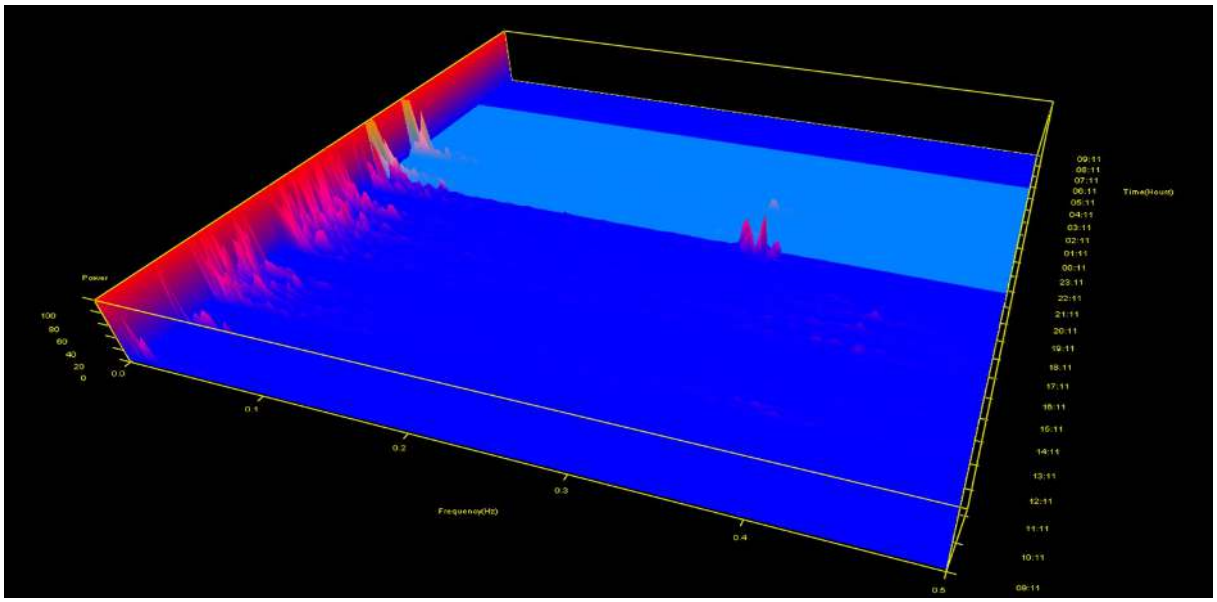

Fig. 2. The spectral components changes of HRV in an obese patient.

Concomitant disease effects on 24-h Heart Rate Variability in time and frequency domain analysis and statistical differences between groups were shown in Table 2.

Tab. 2. Age, BMI, and cardiac-autonomic markers in obese and obese with concomitant disease subjects.

Parameter	OO	O&HD	P value
Age	47.5	49.2	0,3
SD	3,3	5,4	
BMI	48.3	49.6	0.7
SD	5.2	1.8	
SDNN	46.2	44.7	0.21
SD	16.8	12.3	
rMSSD	36.7	34.6	0.65
SD	32,1	30,7	
pNN50	12.5	12.6	0.9
SD	1.3	2.4	
HF ms^2	365.9	341.5	0.2
SD	261.2	208.7	
LF ms^2	1285.8	1311.9	0.6
SD	666.3	578.2	
LF/HF	3.5	4.2	0.09
SD	1.2	2.6	
TP	3111.3	2982.7	0.08
SD	502.5	689.2	

Results are reported as *Mean and Standard deviation SD and* . SDNN = standard deviation of all NN intervals in ms; rMSSD = square root of the mean of the sum of the squares of differences between adjacent NN intervals in ms; NN50 = number of pairs of adjacent NN intervals differing by more than 50 ms in the entire recording; LF = low frequency power; HF = high frequency power; LF/HF = the ratio LF(ms^2)/HF(ms^2). OO - Only Obese patients; O&HD - Obese with Hypertension and Diabetes.

No significant differences in cardiac autonomic modulation were noted between the Hypertensive-Diabetic patients and those only with morbid obesity.

Impact of depression on 24-h Heart Rate Variability in time and frequency domain analysis was shown in Table 3.

Tab. 3. Age, cardiac-autonomic markers in obese depressive and non-depressive patients.

	Depressive N=46		**Non-Depressive N=34**	
	Mean	**SD**	**Mean**	**SD**
Age	47.2	2.5	46.9	3.6
SDNN	33.5	10.2	44.1	15.8
rMSSD	23.8	11.3	34.8*	18.2
pNN50	4.9	2.5	11.4*	7.5
HF ms^2	187	115.6	341.1*	221.4
LF ms^2	882.5	154.7	1259.2*	321.2
LF/HF	4.1	2.5	3.9	2.5
TP	2534	2.5	4250.9*	2.5

SDNN = standard deviation of all NN intervals in ms; rMSSD = square root of the mean of the sum of the squares of differences between adjacent NN intervals in ms; NN50 = number of pairs of adjacent NN intervals differing by more than 50 ms in the entire recording; LF = low frequency power; HF = high frequency power; LF/HF = the ratio LF(ms^2) /HF(ms^2).

In the studied group, obese patients with depression had lower time and frequency domain parameters ($p<0.05$) except SDNN, and LF/HF ratio in contrast to obese non-depressive individuals.

DISCUSSION

Over the past few decades, the prevalence of obesity in the world has been increasing at a rapid rate [11]. Overall, obesity can be considered a chronic relapsing and progressive disease and a leading risk factor for global deaths [3]. According to the severity and duration of weight gain, obesity can progressively cause and/or exacerbate a broad spectrum of comorbidities, including type 2 diabetes, hypertension, dyslipidemia, cardiovascular disease, liver dysfunction, respiratory and musculoskeletal disorders, infertility, psychosocial problems, and certain types of cancer [19]. Another important manifestation of obesity is impairment in the autonomic nervous system (ANS), present in all age groups [35]. Numerous studies have shown that obesity is characterized by a dysfunction of the sympathetic and parasympathetic nervous systems, and that an imbalance between the

components of the AUN may be one of the most important predictors of cardiovascular death [29,39].

In epidemiological studies, obesity has been proven to be associated with AUN dysfunction regardless of coexisting diabetes or hypertension [14,40]. However, the impact of other diseases that could potentially intensify ANS dysfunction in obese individuals has so far been the subject of few studies.

Our study was carried out to find out the HRV response in obese patients with hypertension and type 2 diabetes and obese patients with depression to find out the presence of additive effects of HRV changes in obese patients with comorbidities. If obesity can alter the HRV response as much as hypertension, diabetes, or depression solely, then obese patients burdened with these diseases should have more severe HRV changes.

In this study, the obese patients had significantly lower parameters of time domain analysis (SDNN, pNN50 and RMSSD) compared to volunteers with normal BMI. The frequency domain parameters, the LF and LF/HF ratio in both groups was also statistically different. The obese subjects had HF and TP values lower then healthy people, and LF values and LF/HF ratio was higher than in the control group. These results are in accordance with reports from other authors [20,46,47].

The pathophysiology of obesity and its comorbidities is complex and involves many different pathways. Many studies highlight the role of inflammatory adipokines. These comorbidities include type 2 diabetes, in which insulin resistance is exacerbated by TNF-α and other inflammatory secretagogues in adipocytes; endothelial dysfunction and hypertension, which result from the activity of renin angiotensin system -secreting adipokines; and dyslipidemia, which is caused by hypercholesterolemia and hypertriglyceridemia. These comorbidities and the effects of fatty acid lipotoxicity promote atherogenesis, including coronary artery disease. The presence of insulin resistance, sympathetic nervous system activation and sodium retention in obesity are overlapping mechanisms [32]. Insulin resistance activates the sympathetic nervous system, upregulates angiotensin II receptors and reduces the synthesis of nitric oxide, leading to increases in heart rate and blood pressure [1,17,23,24]. Furthermore, increased effects of leptin, the activation of hypothalamic-pituitary-adrenal axis, the presence of obstructive sleep apnea and baroreflex dysfunction in obesity further contribute to the activation of the sympathetic nervous system [18,37]. Finally, in obese patients there is an increase in renal tubular reabsorption with a consequent sodium retention, further contributing to the development of hypertension [33].

In the aspect of ANS activity in subjects with obesity and comorbidities, our results were surprising. In the groups of subjects with obesity alone and with obesity combined with hypertension and diabetes, no statistical differences in the values of the parameters of both time and frequency analysis of HRV were found. These results are in contrast to reports by other authors who showed an increase in the autonomic imbalance in patients with diabetes and hypertension compared to the non-diabetes group [2], and multiple studies which have shown that diabetes (hyperglycemia) may lead to neuronal damage and subsequent autonomic dysfunction measured by high heart rate or low HRV [4,7,9,45]. Moreover, also reduced HRV in patients with hypertension alone [41] and in persons with obesity alone [30,44] were found. Study of Mamatha S. D et al. revealed that significant reduced HRV indicating alteration in both parasympathetic and sympathetic outflow, which is manifested by the more positive correlation of HRV with obese hypertensives, compared to non-obese hypertensives [22].

Discrepancies in our results in relation to those obtained by other authors may be due to the severity and time of duration of obesity in the studied group (morbid obesity), as a positive correlation between anthropometric indices and ANS imbalance was shown [34], and /or from the fact that both hypertension and diabetes were, in this group, very well treated with oral medicines (beta blockers, ACE and Metformin), which offsets, to some extent, the increased sympathetic stimulation.

Our study has shown that obese depressed patients had lower HRV parameters in the time and frequency domain ($p<0.05$), except SDNN and LF/HF ratio, compared to obese non-depressed subjects. The results obtained in our study are consistent with the reports of others. Yadav and colleagues have shown that obese patients have lower HRV parameters except LF/HF parameter [46]. Depression and obesity are interrelated health burdens. Both conditions are associated with AUN deregulation. Typically, they are associated with overactivity of the sympathetic nervous system; however, researchers emphasize that the patterns of activation may be different and result from either a direct predominance of the sympathetic component or a decrease in parasympathetic activity. It should be emphasized here that decreased autonomic system activity in obesity may be an independent cause of the development of depression, in which decreased parasympathetic component activity is a major factor in the development of the disorder [31,46]. Additionally, it has been shown that lower HRV in depressed individuals reflects impaired integration of brain mechanisms underlying effective autonomic and behavioral control (underlying obesity) [11]. Multiple studies indicate that some reduced parameters in HRV analysis values are characteristic of depressed individuals [10,15,21,42]. It has also been shown that lower HRV parameters

positively correlate with the severity of the depression symptoms [19]. These reports explain little specificity of the reduction in HRV in the studied group, in which depression was detected during screening tests and the patients had not been treated because of it before. It has also been shown that HRV analysis is a better predictor of the development of full-blown depression than it is a marker of current depressive state [6]. It has also been shown that obese individuals are twice as likely to develop depression [39-41] and that depression may be not only the effect but also the cause of obesity [9]. Reported decreased mood has been associated with an increase in food intake, also among college students [2].

The bidirectional relationship between depression and obesity is associated with dysfunction of the psycho-immune neuroendocrine (PINE) network. Disturbances within the network, common to both metabolic disorders and depression, explain the development of depression among obese patients as well as obesity among depressed patients [31]. Studies also highlight changes in autonomic system activity among the mentioned groups [31]. The dependence of emotional regulation on autonomic processes and its relationship with regulatory metabolic processes is also described in the polyvagal theory [34].

To summarize, despite the limited number of cross-sectional studies, there is a series of reports that associate various HRV indices with obesity and comorbidities. Because HRV is a measure of the body's ability to maintain homeostasis, therefore, HRV analysis is an easy marker of worsening health, especially in patients with chronic diseases. Therefore, clinicians should include the assessment of ANS activity in the diagnostic and therapeutic process because it depends on many psychophysiological parameters and provides good feedback for the success of complex therapy.

CONCLUSIONS

1. Extreme obesity altered cardiac autonomic activity independently of hypertension and diabetes.
2. Depression associated with morbid obesity intensified HRV reduction.

AUTHORS' DECLARATION

Study Design: Ewelina Zawadzka-Bartczak, Dagmara Bartczak-Szermer. **Data Collection:** Ewelina Zawadzka-Bartczak, Dagmara Bartczak-Szermer. **Manuscript Preparation:** Ewelina Zawadzka-Bartczak, Dagmara Bartczak-Szermer. The Authors declare that there is no conflict of interest.

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