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Obesity is independently associated with changes in cardiac function in young healthy males

Powiązanie otyłości ze zmianami w funkcjonowaniu mięśnia sercowego u zdrowych, młodych mężczyzn

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Abstract

Introduction. Obesity among young people has increased dramatically worldwide, and the prevalence continues to increase. Studies performed in both adults and children have confirmed that abnormalities of cardiac function and autonomic nervous system are present in those with obesity and might explain at least in part the increased mortality seen in those with obesity.

Materials and methods. The present study explores hemodynamic, autonomic and cardiovascular function in a cohort of well-characterized young men with obesity and compared these measures to those from a cohort of men of comparable age without obesity. Subjects underwent examination using Task Force® Monitor non-invasive assessment of the cardiovascular functions.

Results. The obesity group had a significantly higher resting heart rate (74.3 ± 11.8 vs. 56.0 ± 8.9 n/min, $p < 0.0001$), systolic (128.1 ± 9.4 vs. 114.3 ± 7.0 mm Hg, $p < 0.0001$) and diastolic (85.1 ± 8.2 vs. 70.7 ± 6.2 mm Hg, $p < 0.0001$) blood pressure compared to the age- and sex-matched, non-obesity group. This was coupled with significantly reduced stroke volume (81.3 ± 22.7 vs. 112.8 ± 20.3 ml, $p < 0.0001$), cardiac output (5.9 ± 1.5 vs. 6.2 ± 1.4 l/min; $p < 0.0001$) thoracic fluid content (28.5 ± 3.3 vs. 36.0 ± 3.3 1/Ohm, $p < 0.0001$) and contractility parameters, index of contractility (31.7 ± 12.9 vs. 68.8 ± 16.1 1000/s, $p < 0.0001$) and Heather index (0.1 ± 0.0 vs. 0.3 ± 0.0 $1/s^2$, $p < 0.0001$).

Discussion. Our results confirm that obesity is associated with sub-clinical and cardiovascular abnormalities that can be identified using non-invasive measures. The differences identified in those with obesity were in young and healthy individuals. It will be important to determine whether these findings can be used to predict future clinical abnormalities.

Key words: obesity, functionally single ventricle, Fontan procedure, congenital heart disease, tissue Doppler imaging, echocardiography

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Introduction

Obesity is a disease process, characterized by abnormal or excessive fat accumulation that presents a risk to health, typically considered as an imbalance between energy provision and expenditure or between intake of calories and physical activity [1–6].

The prevalence of obesity (body mass index [BMI] ≥ ≥ 30 kg/m^2) has increased dramatically worldwide. In Europe, the prevalence of obesity increases with age to peak at approximately 60 years. Childhood obesity is also becoming a major public health problem. The World Health Organization (WHO) has recognized obesity, as a global epidemic, which is representing a rapidly growing threat to the health of populations in an increasing number of countries. WHO suggests that at least 2.8 million people die each year as a consequence of obesity [1–6].

People with obesity are at a higher risk of significant medical conditions such as: diabetes, cardiovascular disease (hypertension, stroke, heart disease), sleep apnea and some cancers (including: pancreatic, renal, bladder, uterine cervical and prostate cancers) [7, 8].

Studies performed in both adults and children have confirmed that abnormalities of the autonomic nervous system are present in those with obesity and might explain at least in part the increased mortality seen in those with obesity. Obesity can affect the cardiovascular system in several ways, with hypertension being one of the most important adverse processes. The mechanisms underlying hypertension in people with obesity are not fully understood, but there is increasing evidence that obesity may provide the trigger for sympathetic nervous system activation as well as for changes in renal structure and function. Renal dysfunction plays a key role in increasing blood pressure and it is closely related to the renin-angiotensin and sympathetic nervous system [9, 10].

This study explores the hemodynamic, autonomic and cardiovascular function with those from a cohort of men of comparable age without obesity. The aim of the study was to objectively verify whether the presence of obesity is associated with sub-clinical changes in autonomic cardiovascular functions which occur in young obese subjects, even if they do not report any subjectively or objectively cardiovascular disturbances.

Materials and methods

Subjects

The present study was carried out on 35 volunteers, of whom 15 were young men with obesity and 20 were young male controls without obesity. Subjects were categorized as normal obese using BMI [(BMI) weight (kg)/height (m)^2]. No subjects were taking vasoactive medication, which could affect cardiovascular parameters and none had a history of diabetes, hypertension, hormonal disturbances, cardiovascular disease or neurological illness. Subjects underwent a comprehensive cardiac and neurologic clinical and diagnostic work-up prior to inclusion in the present study in order to rule out any abnormality of both the cardiovascular function and the autonomic nervous system.

In our study we investigated participants which fulfilled precise inclusion criteria. The examined group was distinguished on the base of medical and subjective examination. Body weight, BMI, and body composition were measured. Persons participating in the examination did not require the chronic treatment.

Data on lifestyle habits (smoking status, physical activity and alcohol intake), body weight, body height, waist and hip circumferences were measured using standardized protocols. This study examined a group of drinking no alcohol and never-smokers, who reported no regular physical activity. The obesity group and control group did not undergo any dietary restrictions.

Setting

The study was conducted in the Laboratory of Chronomedicine and Functional Examination of the Autonomic Nervous System (Department of Hygiene and Epidemiology, Department of Human Physiology), Collegium Medicum NCU, Bydgoszcz, Poland. The examination took place using our standard functional examination of the autonomic nervous conditions. Prior to the test, the patient rested for 15 minutes in a supine position. During the examination, room temperature was approximately 21°C and the room was quiet and darkened. The whole procedure was conducted according to the American Academy of Neurology and European Heart Association guidelines [11–13]. The study was approved by the Human Research Committee of the Nicolas Copernicus University in Torun. Written informed consent was signed by all subjects.

Measurement of cardiac hemodynamic and autonomic regulation

The subjects underwent examination using Task Force® Monitor (TFM — CNSystems, Medizintechnik, Gratz, Austria), a specialist device for non-invasive examination of the cardiovascular system and functional assessment of the autonomic nervous system. TFM includes the following components: digital photoplethysmography for the continuous measurement of blood pressure, electrocardiograph (ECG), impedance cardiograph (ICG), and oscillometric measurement of blood pressure. All parameters were collected in the non-invasive beat-to-beat mode.

The device for the continuous measurement of blood pressure determines the pressure of perivascular environment in the distal part of upper limb. In the case of TFM, the measurements are obtained with controlled pressure air cuff and plethysmograph, placed on the middle and index fingers.

Electrocardiograph registers the electrical activity of the myocardium detected as the voltage difference between two electrodes at the surface of the chest, and presents it graphically as the electrocardiographic curve.

Impedance cardiograph analyzes the components of impedance signal registered in the chest during one cardiac cycle.

The device for the oscillometric measurement of blood pressure senses the magnitude of oscillations caused by the blood flowing into the arm compressed with occluding cuff.

The last component of TFM system is pulse oximeter, monitoring the oxygen saturation of patient's blood.

The TFM obtains biological signals non-invasively and thus all of the procedures are safe for the participants of this study. The "beat to beat" measurements enable determination of arterial blood pressure, stroke volume, minute volume, peripheral resistance, heart rate variability (HRV), blood pressure variability (BPV), and spontaneous baroreceptor sensitivity. The autonomic function (HRV and BPV) is assessed by means of spectral analysis, while baroreceptor sensitivity (BR) is analyzed with the sequential method.

Data analysis

Data are presented as mean with the standard deviation. Group-wise comparison was performed with Student's *t*--test and linear relationships with Pearson's r. Statistical significance was set at < 0.05. Based on the correlation between the data and the corresponding normal scores, we used The Shapiro-Wilk test — the best choice for testing the normality of data. Linear regression models were built as theoretical models, containing those cardiovascular variables which would be expected to have an influence on the dependent outcome; as age can also influence autonomic function it was also included. Variables were excluded if they exceeded the tolerance level for multicollinearity. Analysis was performed with SPSS and Statistica.

Results

Details of the study group (with obesity) and control (without obesity) group are shown in Table 1. The obesity group had a significantly higher resting heart rate, systolic and diastolic blood pressure compared with the non-obesity group (Table 2). This was coupled with significantly reduced stroke volume (SV) that persisted, when the body surface area (BSA) was considered — the stroke index (SI). Cardiac output (CO) between the groups was not significantly different until it was corrected for BSA (the cardiac index), upon which the obesity group had a significantly reduced cardiac output compared with controls. Total peripheral resistance index (TPRI, corrected for BSA) was significantly increased in the obesity group compared with the controls (Table 2), whereas the preload (end diastolic index normalized for BSA) was significantly lower in the obesity group.

On comparing cardiac function and myocardial contractility between the two groups, all measures were lower in the obesity group with the index of contractility (IC — maximum blood flow during left ventricular ejection), acceleration index (ACI — the left ventricular–aortic systolic jet acceleration) and Heather's index (HI — a measure of positive inotropy of heart muscle) being significantly statistically lower. Interestingly, the parameters that might indicate heart failure, specifically systolic time ratio (STR) and left ventricular work index (LVWI) were not significantly different between the obesity group and controls. Alongside these cardiac changes was a significantly lowered thoracic fluid content (TFC) in the obesity group and this level was lower than the expected minimum value in the physiological conditions at this age.

The correlations between BMI and cardiovascular parameters are shown in Table 3. Among the cardioimpedance parameters, BMI correlated inversely with all contractility parameters and thoracic fluid content. In keeping with the higher mean ejection rate (ER) in the group comparison, there was a significantly positive correlation with ER and the BMI.

Linear regression models were constructed to identify whether BMI was independently associated with cardiac function. Controlling for age and the hemodynamic parameters measured, linear regression demonstrated an independent association between BMI and cardiac index, such that as BMI increased there was a reduction in the cardiac index — adjRsq 0.857, beta –0.037 (95% confidence interval [CI] –0.058 to –0.017), p = 0.001. In addition,

Table 1. Details of the two groups of participants: age, weight, height and body mass index (BMI)

Parameter	With obesity (N = 15)	Without obesity (N = 20)	p values
Age [years]	36.3 ± 7.3	33.7 ± 6.2	0.3
Weight [kg]	116.2 ± 17.6	75.4 ± 7.1	< 0.0001*
Height [m]	1.79 ± 0.07	1.7 ± 0.05	0.8
BMI [kg/m^2]	36.4 ± 5.0	23.4 ± 1.3	< 0.0001*

*Indicates significantly different results; all parameters are expressed as mean ± standard deviation, and p values

Table 2. Hemodynamic and cardiovascular parameters: heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), stroke volume (SV), stroke index (SI), diastolic index (EDI), cardiac output (CO), cardiac index (CI), total peripheral resistance index (TPRI), index of contractility (IC), acceleration index (ACI), Heather index (HI), systolic time ratio (STR), ejection rate (ER), left ventricular work index (LVWI), thoracic fluid content (TFC); at rest in the two groups of participants

Parameter	Obesity group	Non-obesity group	p
HR [n/1]	74.3 ± 11.8	56.0 ± 8.9	< 0.0001*
SBP [mm Hg]	128.1 ± 9.4	114.3 ± 7.0	< 0.0001*
DBP [mm Hg]	85.1 ± 8.2	70.7 ± 6.2	< 0.0001*
SV [ml]	81.3 ± 22.7	112.8 ± 20.3	< 0.0001*
SI [ml/m^2]	35.3 ± 10.2	58.3 ± 10.1	< 0.0001*
EDI [ml/m^2]	58.1 ± 14.4	94.5 ± 16.4	< 0.0001*
CO [l/min]	5.9 ± 1.5	6.2 ± 1.4	0.4971
CI [l/min/m^2]	2.5 ± 0.6	3.2 ± 0.7	0.0095*
TPRI [dyn × s × m^2/cm^5]	3181 ± 833.0	2158.4 ± 492.5	< 0.0001*
IC [1000/s]	31.7 ± 12.9	68.8 ± 16.1	< 0.0001*
ACI [100/s^2]	46.8 ± 18.8	95.1 ± 24.4	< 0.0001*
HI [1/ s^2]	0.1 ± 0.0	0.3 ± 0.0	< 0.0001*
STR [%]	37.3 ± 5.6	34.7 ± 4.8	0.2
ER [%]	36.2 ± 3.7	30.2 ± 4.0	< 0.0001*
LVWI [mm Hg × l/(min × m^2)]	3.3 ± 1.0	3.7 ± 0.9	0.3
TFC [1/Ohm]	28.5 ± 3.3	36.0 ± 3.3	< 0.0001*

*Indicates significantly different results; all parameters are expressed as mean ± standard deviation, and p values

Table 3. Matrix of correlations between body mass index (BMI) and cardiac functions: index of contractility (IC), acceleration index (ACI), Heather index (HI), diastolic index (EDI), systolic time ratio (STR), ejection rate (ER), left ventricular work index (LVWI) and thoracic fluid content: thoracic fluid content (TFC), significant correlations in bold, and p values

Parameter	BMI	p
IC [1000/s]	–0.70	< 0.05
ACI [100/s^2]	–0.64	< 0.05
HI [1/s^2]	–0.65	< 0.05
EDI [ml/m^2]	–0.64	< 0.05
STR [%]	0.24	> 0.05
ER [%]	0.48	< 0.05
LVWI [mm Hg × l/(min × m^2)]	–0.15	> 0.05
TFC (1/Ohm)	–0.74	< 0.05

BMI was associated with the IC, such that an increase in BMI was independently associated with a reduction in contractility of the heart — adjRsq 0.85, beta –0.847 (95% CI –1.592 to –0.101), p = 0.027.

Discussion

The results reported here confirm that there are significant cardiac abnormalities in young men with obesity compared with young men without obesity. Both measurements of cardiovascular hemodynamic and cardiac function were noted to be significantly different in those with obesity. These differences appear to be related to peripheral arterial abnormalities and significantly reduced cardiac inotropy. Those with obesity had significantly greater mean arterial blood pressure and a significantly reduced cardiac index which indicates that they have a reduced cardiac inotropy and an increase in vasoconstriction compared with controls (Fig. 1) [14]. Demonstrating these findings is of importance for two reasons. Firstly, obesity is now considered a global epidemic and as such, these results will be far reaching. Secondly, all the subjects in this study were young, healthy males with no clinical history of cardiac or vascular disease. Despite this, those with obesity demonstrated significant cardiac and cardiovascular differences when compared with those without obesity. These sub-clinical abnormalities may represent precursors to the increased risk of cardiovascular disease seen in people with obesity but may also contribute to the as yet unexplained increased risk of sudden cardiac death in young with obesity.

It is well known that obesity has a major impact on cardiovascular diseases, such as heart failure, coronary heart disease, atrial fibrillation and sudden cardiac death [15–18]. Studies suggest that obesity can exacerbate cardiovascular disease through a variety of mechanisms including activation of the sympathetic nervous system

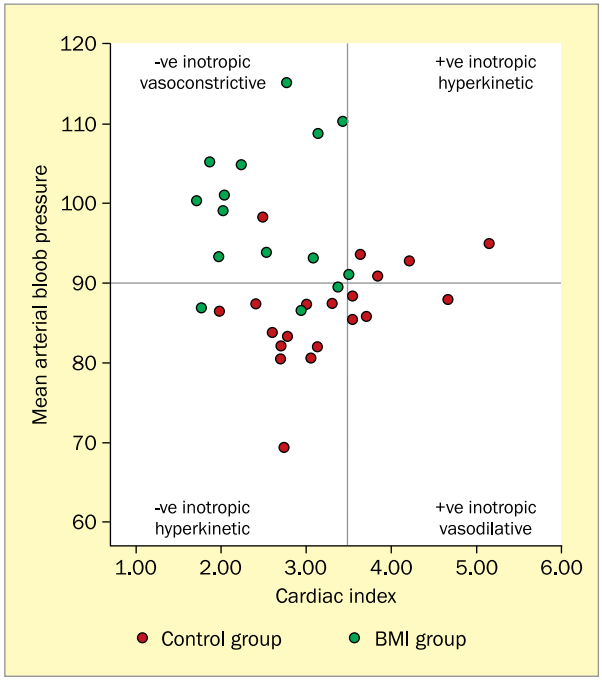

Figure 1. Reduced cardiac inotropy in the obesity; BMI — body mass index

and the renin–angiotensin systems [15, 16]. These results support the theory of increased sympathetic activity with those having obesity demonstrating an increased heart rate and increased peripheral vascular resistance. Unfortunately, the link between cardiac disease and obesity is complex, highlighted by the "obesity paradox" in which patients with obesity and established heart failure tend to have a more favorable prognosis than do lean subjects [17, 18]. Here, the complexity may arise from the interactions between renin and leptin both of which are increased in obesity and both of which can activate the sympathetic nervous system. Obesity may stimulate secretion by increasing sodium chloride reabsorption in the loop of Henle, thereby reducing sodium chloride delivery to the macula densa. Leptin influences changes in the central nervous system by stimulating receptors in neurons of the arcuate nucleus of the hypothalamus and increasing the activity of the sympathetic nervous system. Moreover positive correlation was observed between the concentration of leptin in blood and with thickness of the wall and mass of the left ventricle of the heart, what is indicating for the participation of this hormone in the process of the excess of the left ventricle [19].

Activation of the sympathetic nervous system plays an important role in the hypertension associated with obesity. Risk estimates from the Framingham Heart Study suggest that 65% of cases of hypertension in women and 78% of cases in men can be attributed to obesity. Furthermore, an increase in body weight of about 4.5 kg is associated with an increase in systolic pressure about 4.5 mmHg. But even in the absence of any blood pressure alteration, obesity is characterized by a marked sympathetic activation, possibly because of an impairment of reflex sympathetic restraint [20, 21].

Activation of the sympathetic nervous system can cause hypertrophy of cardiac muscle and remodeling of the vascular walls. Interestingly, obesity is also associated with greater left ventricular mass, wall thickness and chamber size. It is also associated with sub-clinical, functional changes in left ventricle systolic function that can be detected by strain and strain rate imaging. These early abnormalities in left ventricle structure and function are associated with increased cardiovascular morbidity and mortality [22]. The results presented in this study demonstrate sub-clinical changes in cardiac function in a cohort of otherwise young and healthy males. These parameters which were derived non-invasively offer the potential to identify early cardiac changes, which could predict increased cardiovascular risk, although this would need confirming in a longitudinal study.

Thoracic fluid content is a noninvasive bioelectrical impedance measure of the electrical conductivity of the chest cavity. Thoracic fluid content is a reliable measure of chest fluid status and can identify small shifts in the thoracic content of fluid. In this study, BMI correlated inversely with the TFC, such that an increased body mass was associated with a reduced thoracic fluid content. This is of importance because recent studies have suggested that thoracic impedance may identify patients with heart failure risk even in the absence of clinical structural and functional abnormalities [23].

Conclusions

Parameters such as SV, CO, CI, TPRI, HI, ACI, TFC in the last decade has attracted much interest in clinical settings as diverse as heart failure management and critical care. These hemodynamic variables define arterial blood pressure level and their modification is helpful in the selection of pharmacological therapy of hypertension. Reports from several clinical studies show that antihypertensive therapy based on hemodynamic measurements by cardiac impedance is more effective than recommendation based treatment in achieving blood pressure < 140/90 mm Hg [24–26].

Task Force® Monitor non-invasively measures changes in thoracic impedance generated by fluctuating blood volumes during the cardiac cycle, allowing calculation of stroke volume, cardiac output and other derived parameters. Task Force® Monitor derived also cardiac index (CI) and systemic vascular resistance index can help determine how current therapy is impacting that patient from a hemodynamic perspective [24–26].

Obesity is associated with sub-clinical cardiac and cardiovascular abnormalities that can be identified using

non-invasive measures. The differences identified in those with obesity were in young and healthy individuals. It will be important to determine whether these findings can be used to predict future clinical abnormalities.

Limitations

These findings may be limited by the relatively small size of the cohorts included. However, through the assessment of young and otherwise healthy males in the controlled environment of the cardiovascular laboratory the results demonstrated are reliable. As all the measurements are cross-sectional the study lacks the ability to assess risk of future events but does reveal important potential abnormalities which require further longitudinal investigation. One advantage of the indices used in this study as that the majority can be corrected for body surface area, however, the measurement of thoracic fluid content is based on models which was derived from non-obese individuals and therefore our TFC measurements may not be wholly reliable.

Conflicts of interest(s)

None declared.

Streszczenie

Wprowadzenie. Liczba otyłych osób zwiększa się gwałtownie na całym świecie. W badaniach przeprowadzonych wśród otyłych dorosłych i dzieci potwierdzono, że zaburzenia funkcji układu sercowo-naczyniowego i autonomicznego układu nerwowego mogą wyjaśniać zwiększoną śmiertelność w tej grupie.

Materiał i metody. W badaniach przedstawiono analizę wartości hemodynamicznych, autonomicznych i sercowo-naczyniowych w kohorcie dobrze scharakteryzowanych, młodych mężczyzn z otyłością w porównaniu z mężczyznami w podobnym wieku bez otyłości. Do badania użyto systemu *Task Force® Monitor*.

Wyniki. W grupie osób z otyłością znacznie wyższe były wartości tętna (74,3 ± 11,8 *v.* 56,0 ± 8,9 n/min; p < 0,0001), ciśnienia skurczowego (128,1 ± 9,4 *v.* 114,3 ± 7,0 mm Hg; p < 0,0001) i rozkurczowego (85,1 ± 8,2 *v.* 70,7 ± ± 6,2 mm Hg; p < 0,0001) niż w grupie osób bez otyłości. Ponadto wykazano obniżone wartości objętości wyrzutowej serca (81,3 ± 22,7 *v.* 112,8 ± 20,3 ml; p < 0,0001), pojemności minutowej (5,9 ± 1,5 *v.* 6,2 ± 1,4 l/min; p < 0,0001), zawartości płynu w klatce piersiowej (28,5 ± 3,3 *v.* 36,0 ± 3,3 1/Ohm; p < 0,0001), kurczliwości mięśnia sercowego (31,7 ± 12,9 *v.* 68,8 ± 16,1 1000/s; p < 0,0001) i wskaźnika Heather (0,1 ± 0,0 *v.* 0,3 ± 0,0 $1/s^2$; p < 0,0001) w grupie osób z otyłością.

Wnioski. Badania autorów potwierdzają, że otyłość wiąże się z zaburzeniami funkcji układu sercowo-naczyniowego, które mogą zostać zidentyfikowane na podstawie nieinwazyjnych wskaźników. Wartości te mogą mieć istotne znaczenie kliniczne, aby przewidzieć, jakiego typu zmiany w obrębie układu sercowo-naczyniowego mogą wystąpić u osób z otyłością.

Słowa kluczowe: otyłość, funkcjonalnie pojedyncza komora, motoda Fontana, wrodzone wady serca, obrazowanie metodą Dopplera tkankowego, echokardiografia

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