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PAPER

Early impairment of two arms of the baroreflex response in young normotensive patients with obesity

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Abstract

Objective. Hypertension increasingly affects younger populations alongside rising obesity rates, and impaired baroreflex (BR) function could contribute to its development. This study investigated changes in BR control of the cardiac chronotropic (ccBR) and vascular resistance (vrBR) arms in young normotensive patients with obesity and explored associations with sex- and age-independent anthropometric measures (body mass index (iso-BMI) and waist to hip ratio (OSS of WHR)), insulin resistance ($HOMA_{IR}$), and arterial stiffness index $CAVI_0$. *Approach.* Twenty-three normotensive adolescents and young adults with obesity (17 females, median age: 17.1 years) and twenty-two sex- and age-matched healthy lean participants (16 females, median age: 17.4 years) were examined during four phases: supine rest, head-up-tilt (HUT), supine recovery, and mental arithmetics task (MA). The causal coupling and gain in the frequency-domain of the ccBR and vrBR arms were assessed non-invasively from the spontaneous variability series of arterial pressure, heart period, and peripheral vascular resistance using a partial spectral decomposition method in the low frequency band (0.04–0.15 Hz). *Main results.* Patients with obesity showed lower ccBR gain during HUT and persistently lower vrBR gain during supine rest and HUT. No significant associations were found between iso-BMI, OSS of WHR, $HOMA_{IR}$, $CAVI_0$, and spectral parameters during supine rest, except for a significant negative correlation between iso-BMI and changes in ccBR spectral gain as a response to MA. *Significance.* Advanced non-invasive methods accounting for causality in evaluating two BR arms revealed early BR impairment in young participants with obesity, affecting both the ccBR arm and the less-explored vrBR arm.

1. Introduction

Hypertension is widely recognized as the primary factor that contributes to the onset of cardiovascular diseases, leading to worldwide dominating cardiovascular mortality (Fuchs and Whelton 2020, Aune *et al* 2021). Traditionally viewed as a condition affecting older adults, hypertension is now recognized as a significant issue also in younger populations. Over recent decades, the escalating prevalence of hypertension among children and young adults has mirrored the rise in obesity prevalence (Kolanowski 1999, Genovesi and Pieruzzi 2006, Rahmouni 2010, Brady 2017). It is important to address the link between obesity and hypertension early in life, as timely identification and intervention can play a critical role in preventing long-term cardiovascular complications (Rajinikanth *et al* 2023). Previous studies suggest that individuals

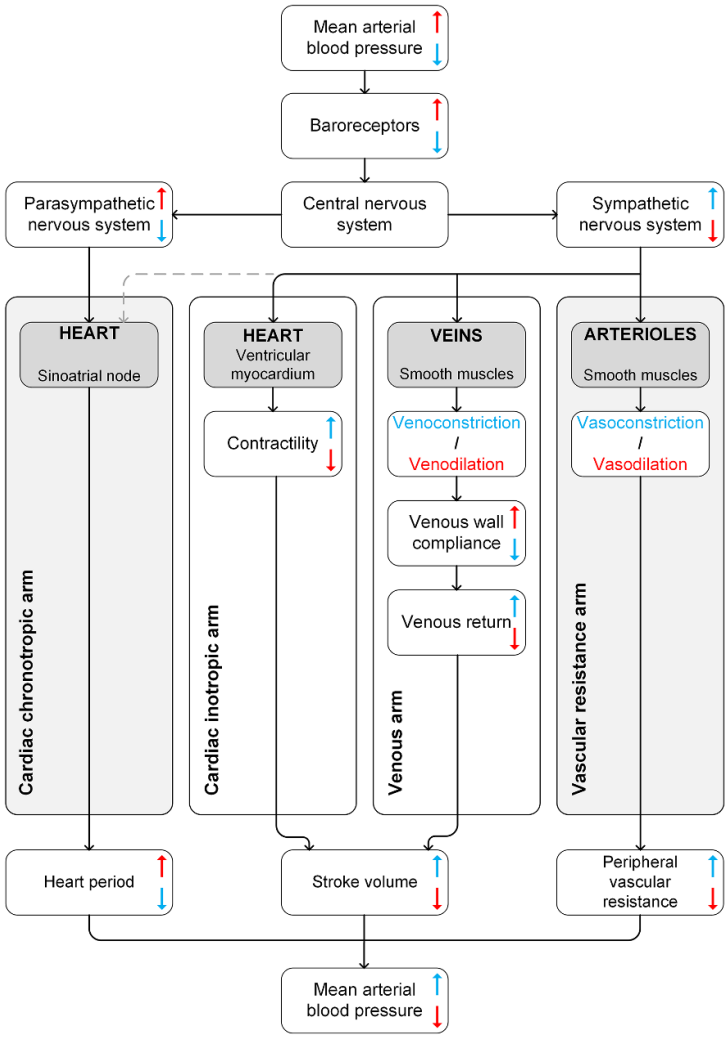

Figure 1. Flowchart illustrating the baroreflex regulation of blood pressure. Red arrows indicate responses to increased blood pressure, while blue arrows show changes associated with decreased blood pressure. This study focused on the cardiac chronotropic pathway (left grey rectangle) and the vascular resistance pathway (right grey rectangle). Adapted with permission from Kittnar and Mlcek (2009).

with obesity are more likely to develop hypertension at a younger age compared to those with normal weight (Li *et al* 2022, Fan and Zhang 2023). A recent study by Fan and Zhang (2023) showed that the earlier the onset of overweight or obesity, the greater the risk of developing hypertension. Specifically, individuals who became overweight between the ages of 18–39 faced a significantly higher risk than those who became overweight later or remained at a normal weight. However, pathophysiological mechanisms behind the observed associations remain at least partially unclear.

An increased sympathetic nerve activity is one of the key factors contributing to the development of obesity-related hypertension and it is often associated with impaired baroreflex (BR) function (Kolanowski 1999, Bravo *et al* 2006, Hesse *et al* 2007). The BR is considered as one of the most important reflex mechanisms for maintaining cardiovascular homeostasis in the human body (Skrapari *et al* 2007). It plays a very important role in short-term arterial blood pressure regulation and involves a coordinated response of several physiological components to maintain blood pressure within a normal range. The BR reacts to perturbations in blood pressure through its cardiac chronotropic (ccBR), cardiac inotropic, venous, and vascular resistance (vrBR) components/arms (figure 1), related respectively to changes in heart rate, cardiac contractility, venous return and vascular resistance (La Rovere *et al* 2011). The evaluation of the BR function (e.g. performed through the analysis of baroreflex sensitivity (BRS)) provides valuable prognostic information and insights into neural cardiovascular regulation (Skrapari *et al* 2007, Lazarova *et al* 2009, Brinth *et al* 2013, Chapleau 2023). Reduced BRS is linked to several pathological conditions, including hypertension and obesity (Skrapari *et al* 2007). This reduction may stem from autonomic nervous system (ANS) dysfunction or alterations in the mechanical properties of the arterial wall (arterial distensibility),

where the arterial baroreceptors are located (Miller *et al* 1999, Monahan *et al* 2001, Tanaka *et al* 2001, Lazarova *et al* 2009).

Obesity can significantly affect various components of the BR mechanism, but previous research was mainly focused on the analysis of the ccBR arm, where significantly lower BRS was observed compared to lean young participants (Lazarova *et al* 2009, Javorka *et al* 2013, Honzikova and Zavodna 2016). In young participants with obesity, BR function assessment faced several important limitations, including the non-causal evaluation of BR function using spontaneous arterial blood pressure (as an input signal) and heart rate oscillations (as an output signal) overlooked the closed-loop nature of cardiovascular interactions (i.e. blood pressure influences heart rate, but heart rate also influences blood pressure), emphasising the need to use causal methods (Javorka *et al* 2013). Moreover, evaluation of the BR function is typically performed analyzing the variability series in the time domain, thus incorporating a wide range of oscillatory components including those related to confounding factors (related, e.g. to respiration); to overcome this limitation, frequency-domain evaluation of the BR is recommended (Faes *et al* 2013).

Importantly, BR analyses have thus far been almost exclusively limited to the ccBR arm. However, the vrBR arm—responsible for the modulation of peripheral vascular resistance (PVR)—may be independently or differently affected by obesity. Simultaneous assessment of both ccBR and vrBR components enables a more comprehensive evaluation of BR function and may reveal previously undetected patterns of dysregulation (Borgers *et al* 2014, Porta *et al* 2018). This approach is particularly relevant in obesity, where complex and potentially divergent impairments in autonomic control of heart rate and PVR could contribute to increased cardiovascular risk (Konstantinidou *et al* 2022).

The assessment of the vrBR component was performed only rarely in adults with obesity, and was based on invasive recording of muscle sympathetic nerve activity (MSNA) from peroneal nerve (Holwerda *et al* 2016), which is technically demanding, provides information on the sympathetic control only from a limited portion of the circulation (Krohova *et al* 2020), and due to the invasive nature of this technique, it is not suitable for paediatric research (Litwin 2024). Therefore, in recent studies, the time series of PVR measured non-invasively was used as the output signal for the evaluation of the vrBR arm (Reyes Del Paso *et al* 2017, Krohova *et al* 2020, Cernanova Krohova *et al* 2022b). PVR reflects systemic sympathetic activity to vessels, unlike MSNA, which specifically measures sympathetic nerve traffic to blood vessels directed to a limited part of the circulation and thus reflects only local sympathetic activity.

In an attempt to overcome the limitations mentioned above, the primary aim of this study was to simultaneously examine potential alterations in the function of the ccBR and vrBR arms in young normotensive patients with obesity applying up-to-date causal spectral methods from non-invasively obtained spontaneous cardiovascular oscillations under various physiological conditions (including orthostatic and cognitive loads). In addition, we tried to verify the previously observed associations between parameters characterizing the BR function and obesity severity, fat distribution, insulin resistance, and arterial stiffness using more recent BR analysis methods assessing both ccBR and vrBR arms. Preliminary data were presented at the 12th Conference of the European Study Group on Cardiovascular Oscillations (Cernanova Krohova *et al* 2022a).

2. Material and methods

2.1. Participants and experimental protocol

Our study included 45 normotensive participants (12m and 33f; age range 13.7–25.4 years; median age: 17.2 years) divided into group with obesity (group O) and control group (group C) based on body mass index (BMI) adjusted for sex and age (iso-BMI). All participants were healthy, with no current or recent infectious disease (during last 3 weeks), cardiovascular disease (including hypertension, verified via 24 h ambulatory blood pressure monitoring), respiratory disease, diabetes mellitus, psychiatric disorders, or hypothyroidism. Participants were not on any medication and were instructed to avoid substances influencing ANS or cardiovascular system activity (caffeine, alcohol, energetic beverages) 24 h before examination. The protocol was approved by the Ethics Committee of the Jessenius Faculty of Medicine in Martin, Comenius University Bratislava (approval no. EK 1257/2013, revised. EK 1834/2016). Written informed consent was obtained from all participants or their parents/guardians before participation.

The experimental protocol (figure 2) included four phases: supine rest (15 min), head-up tilt (HUT) to 45° (8 min), supine recovery (10 min), and non-verbal mental arithmetics task (MA, 6 min). All measurements took place in the morning hours (8–11 am) from 25 April 2014, to 26 November 2020.

2.2. Data acquisition and analysis

Before recording the cardiovascular signals, fasting blood samples were taken to analyze biochemical parameters. Glucose, total cholesterol, triacylglycerol (TAG), high-density lipoprotein (HDL), low-density

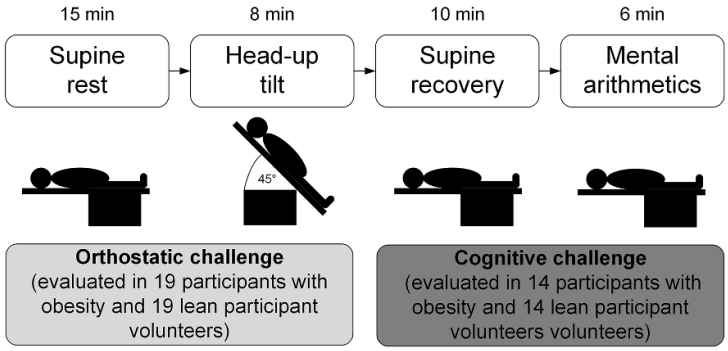

Figure 2. Flowchart of the experimental protocol.

lipoprotein (LDL), and insulin were measured by the Department of Clinical Biochemistry, Jessenius Faculty of Medicine in Martin, Comenius University Bratislava and University Hospital Martin, Martin, Slovakia. The values of glucose and insulin were used to calculate fasting insulin resistance using the $HOMA_{IR}$ model (Matthews *et al* 1985, Jimenez-Maldonado *et al* 2020).

Anthropometric data were obtained by the body composition analyzer (InBody J10 device, InBody, South Korea). Iso-BMI values were calculated using a method described by Naess *et al* (2021). The circumferences of the waist and hips were measured using measuring tape and the waist-hip ratio (WHR) was calculated. To standardize the WHR comparison across age and sex (based on Polish reference data (Kulaga *et al* 2023)), the 'Ordinal' standard score (OSS) of WHR was used (Carifio 2006). The OSS of WHR was calculated using the median and interquartile range values, instead of mean and standard deviation considering the non-Gaussian distribution of this measure (Carifio 2006).

During the four phases of the protocol, we simultaneously and non-invasively recorded beat-to-beat R–R intervals (RR, a measure of the cardiac cycle duration representing a reciprocal value of heart rate) by ECG (CardioFax ECG-9620, NihonKohden, Japan). Arterial blood pressure values for each heart beat (systolic (SBP), diastolic (DBP), and mean blood pressure (MBP)) were obtained by the photoplethysmographic volume-clamp method (Finometer Pro, FMS, The Netherlands). Cardiac output (CO) was acquired by impedance cardiography (CardioScreen® 2000, Medis, Germany). The beat-to-beat values of PVR were calculated as the ratio of MBP and CO. Furthermore, the updated cardio-ankle-vascular index $CAVI_0$, which estimates arterial stiffness from the pulse wave velocity independently from blood pressure, was estimated in the supine position using VaSera device (VS-1500, Fukuda Denshi, Japan).

Stationary 300-beat segments used for further analysis were extracted as follows: for the supine rest phase, the analyzed segment started 8 min after the beginning of this phase, for the HUT phase 3 min after the change of position, for the supine recovery phase 7 min before starting the MA task, and for the MA phase 2 min after starting of this phase.

In some cases, due to the presence of noise and artefacts, the algorithm was not able to detect the correct location of the specific reference points in the recorded impedance cardiograph waveform and thus to calculate the hemodynamic parameters (CO) on a beat-to-beat basis. Therefore, only participants with segments containing at least 285 artefact-free heart beats and no more than 4 missed values in a row were included for further analysis. Missing values were substituted by cubic spline interpolation. The exclusion of some recordings led to a reduction of the number of probands in the study group. Accordingly, the effect of orthostasis was analyzed in 38 participants (19 participants with obesity and 19 lean participants, matched by sex and age) and the effect of cognitive challenge was analyzed in 28 participants (14 individuals with obesity and 14 matched controls). These two subsets of participants were partially overlapped.

The function of the ccBR and vrBR arms was assessed in the frequency domain using the partial spectral decomposition method (Baselli *et al* 1997, Faes *et al* 2019, Pernice *et al* 2021). Using this approach, we are able to quantify the effectiveness of the reflex (the strength of the relation between output signal and the blood pressure input signal, reflecting how closely the output signal follows changes in blood pressure) by means of the spectral causal coupling measure, as well as the responsiveness of the BR to blood pressure variations (i.e. BRS, the magnitude of the output signal response to unit blood pressure change (1 mmHg)) by means of the spectral causal gain measure. Specifically, this method quantifies the strength of the causal spectral coupling (SC) and gain (G) based on the decomposition of the transfer function from the input to the output series, followed by evaluation of coupling and gain relevant to specific oscillatory components of the two series (details of the procedure are in Pernice *et al* 2021). For the analysis of ccBR and vrBR

arms, the MBP was taken as a source (input) signal and RR and PVR as target (output) signals, respectively. The selection of source (input) signals for BR analysis was based on the results of previous study (Cernanova Krohova *et al* 2022b). Frequency-specific analysis was performed focusing on the oscillatory components of MPB, RR and PVR located in the low frequency (0.04–0.15 Hz) band of the spectrum, to avoid the confounding effects of nonbaroreflex mechanisms involved in the connection between breathing and oscillations in blood pressure and heart rate. More details on data pre-processing and analysis are presented elsewhere (Krohova *et al* 2020, Cernanova Krohova *et al* 2022b).

Mean values of beat-to-beat recorded cardiovascular variables (SBP, MBP, DBP, RR, and PVR) were also calculated for each phase. Change in mean values (ΔSC ccBR, ΔG ccBR, ΔSC vrBR, ΔG vrBR) in response to orthostatic load (mean value from the HUT phase minus mean value of the supine rest phase) and cognitive load (mean value from the MA phase minus mean value of the supine recovery phase) were calculated for each participant.

2.3. Statistical analysis

All data were tested for normality using a Shapiro–Wilk's test. The paired *t*-test was used for a comparison of SC and G between the supine rest phases and the following stress phases (HUT, MA). Differences between groups (group O vs. group C) were evaluated using the two-sample *t*-test. If a violation of normality occurred, the Wilcoxon signed rank test or the Mann–Whitney test was applied, respectively. The correlations between the variables were analyzed using Pearson's (normal distribution) or Spearman's (non-normal distribution) correlation analysis. All results were considered statistically significant at a P value < 0.05. Statistical analysis was performed using SYSTAT 13 (Systat Software Inc., USA). Effect sizes were calculated using Cohen's d for normally distributed data and the effect size r for non-normally distributed data when comparing the parameters derived from the spectral causal analysis between the groups C and O. For normally distributed variables, Cohen's d was computed as the difference between group means divided by the pooled standard deviation. For non-normally distributed variables, the effect size r was calculated by dividing the absolute value of the standardized test statistic (Z) by the square root of the sample size ($n = 38$ or $n = 28$). According to Cohen's criteria, effect sizes of 0.1, 0.3, and 0.5 represent small, medium, and large effects, respectively.

3. Results

As expected, all anthropometric measures (weight, BMI, iso-BMI, WHR, OSS of WHR, visceral fat area (VFA), relative fat mass (FM), and skeletal muscle mass (SMM)) were significantly higher in group O. Biochemical parameters, such as TAG, insulin and homeostasis model assessment of insulin resistance ($HOMA_{IR}$) were also higher in group O, whereas HDL was lower in this group (table 1). $CAVI_0$ (parameter reflecting arterial stiffness) was significantly lower in group O.

Differences in the mean values of the cardiovascular time series are presented in table 2. Although participants with obesity were normotensive, their systolic, mean and diastolic blood pressure values were significantly higher during HUT than those of age-matched controls ($P \leqslant 0.010$). DBP was also higher in this group during the following supine recovery phase ($P = 0.031$). The duration of R–R intervals was similar in both groups during orthostatic and mental loads ($P \geqslant 0.169$). During the supine rest phase, RR was significantly lower in group O ($P = 0.039$). Throughout the entire study protocol, PVR was significantly lower in group O ($P = 0.000$).

The results of spectral causal analysis are reported in figure 3, showing the distributions of SC and G for the ccBR (from MBP to RR, figures 3(a) and (b)) and the vrBR arms (from MBP to PVR, figures 3(c) and (d)).

The between-group comparison revealed that significant differences were observed exclusively in spectral gain indices, with no group differences in SC strength ($P > 0.050$) in both BR arms. Most notably, participants in the group O exhibited consistently lower G values in the vrBR during both the supine rest and HUT phases (figure 3(d), $P \leqslant 0.014$, effect sizes 0.637–0.836), with persistently lower values during supine recovery phase on the border of significance ($P = 0.081$, effect size 0.681). In addition, the G characterizing the ccBR arm was significantly lower in group O during HUT (figure 3(b), $P = 0.002$, effect size 1.062).

Comparison of the impact of the two different stress phases on the SC parameters (supine rest vs. HUT and supine recovery vs. MA) was performed within each group, along with computation of the magnitude of this change for each group (Δ values of spectral causal parameters calculated as mean value of stress phase (HUT or MA) minus the mean value of preceding rest phase). This analysis revealed significantly lower SC values in the ccBR arm during MA in the group O ($P = 0.030$), and the magnitude of this change (ΔSC ccBR) was also more negative in this group, with borderline significance ($P = 0.085$). A similar response to

Table 1. Between-groups comparison of anthropometric, biochemical measures and arterial stiffness index ($CAVI_0$).

	C ($n = 22$)	O ($n = 23$)
Age [years]	17.4 [2.5]	17.1 [2.2]
Weight [kg]	**60.4 (11.1)**	**95.3 (13.0)**
BMI [kg m^{-2}]	**21.1 [2.2]**	**32.6 [4.4]**
iso-BMI [kg m^{-2}]	**21.3 [2.4]**	**32.8 [4.6]**
WHR	**0.76 (0.06)**	**0.82 (0.07)**
OSS of WHR	**0.14 (0.96)**	**1.35 (1.24)**
VFA [cm^2]	**35.9 (19.1)**	**129.5 (28.8)**
FM [%]	**21.3 (6.9)**	**41.8 (6.1)**
SMM [kg]	**23.3 [8.7]**	**29.5 [9.6]**
Glucose [mmol l^{-1}]	5.09 (0.50)	4.85 (0.68)
Total cholesterol [mmol l^{-1}]	3.92 [1.33]	3.72 [0.65]
TAG [mmol l^{-1}]	**0.77 [0.30]**	**0.95 [0.68]**
HDL [mmol l^{-1}]	**1.38 [0.38]**	**1.08 [0.28]**
LDL [mmol l^{-1}]	2.06 (0.61)	2.18 (0.53)
Insulin [mU/L]	**6.75 [5.30]**	**14.65 [14.10]**
$HOMA_{IR}$	**1.41 [1.19]**	**3.00 [2.92]**
$CAVI_0$	**7.51 [0.91]**	**6.61 [0.76]**

Values are presented as mean (SD) for normally distributed variables, median and interquartile range [IQR] for non-normally distributed variables. Statistically significant differences between groups are indicated in bold. Abbreviations: C, control group; O, group of participants with obesity; BMI, body mass index; iso-BMI, adjusted body mass index; WHR, waist-hip ratio; OSS of WHR, 'Ordinal' standard score of WHR; VFA, visceral fat area; FM, relative fat mass; SMM, skeletal muscle mass; TAG, triacylglycerol; HDL, high-density lipoprotein; LDL, low-density lipoprotein; $HOMA_{IR}$, homeostasis model assessment of insulin resistance; $CAVI_0$, updated cardio-ankle-vascular index.

MA was observed in the vrBR arm, but in the group C ($P = 0.003$), where greater negative magnitude of the change (ΔSC vrBR) was observed, reaching statistical significance ($P = 0.024$).

Spectral gain values in the ccBR arm tended to be lower during HUT in both groups, although this difference was statistically significant only in the group O ($P = 0.013$). On the contrary, a significant increase in G values was observed in the vrBR arm in group O during HUT ($P = 0.001$). During MA, a statistically significant decrease in G was found in the ccBR arm in group C ($P = 0.019$). The between-group comparison of the magnitude of the response to orthostatic and mental load (ΔG ccBR, ΔG vrBR) did not reveal any significant differences ($P > 0.05$).

Correlation analysis (table 3) between selected sex- and age-independent anthropometric characteristics (iso-BMI, OSS of WHR), $HOMA_{IR}$, arterial stiffness index $CAVI_0$, and BR-related characteristics (SC strength and G of ccBR and vrBR arms) obtained in group O during supine rest phase did not reveal any significant correlation ($P > 0.05$). Additionally, we examined correlations between obesity-related parameters and changes in the mean values of SC and G (ΔSC ccBR, ΔG ccBR, ΔSC vrBR, ΔG vrBR) characterizing magnitude of response to orthostatic and mental loads. A significant negative correlation was observed between the response to mental load in G in the ccBR arm (ΔG ccBR) and iso-BMI (rho $= -0.60$; $P = 0.023$).

4. Discussion

The results of this study point to the manifestation of an early BR impairment in young patients with obesity, detected by novel methods for the analysis of spontaneous cardiovascular oscillations considering frequency-domain content and directionality of interactions. This main finding is documented by the observed significantly lower values of the spectral gain relevant to interactions driven by MBP variability, not only in the widely studied ccBR arm of the baroreflex (ccBR, with RR variability as the target), but even more visible in the less explored vrBR arm (vrBR, with PVR variability as the target).

Previous research on BR function in young patients with obesity has predominantly focused on the ccBR arm. Our results align with previous studies (Honzikova *et al* 2006, Lazarova *et al* 2009, Javorka *et al* 2013), which reported significantly lower BRS values along the ccBR arm in patients with obesity (with or without hypertension) compared to lean participants, in both supine and sitting positions. Although it might seem that the assessment of the ccBR component provides sufficient information about the BR function, all four

Table 2. Differences in the mean values of observed cardiovascular parameters between groups of subjects.

	Supine rest		HUT		Supine recovery		MA	
	C ($n = 19$)	O ($n = 19$)	C ($n = 19$)	O ($n = 19$)	C ($n = 14$)	O ($n = 14$)	C ($n = 14$)	O ($n = 14$)
SBP [mmHg]	119.3 (8.3)	123.6 (7.9)	**112.4 (8.9)**	**120.2 (8.7)**	121.9 (9.1)	126.3 (8.1)	132.7 (10.7)	132.9 (9.0)
DBP [mmHg]	70.2 (6.1)	74.3 (6.8)	**70.6 (6.7)**	**77.0 (6.4)**	**70.2 (5.4)**	**74.7 (5.2)**	78.3 (5.3)	79.9 (4.8)
MBP [mmHg]	89.4 (5.6)	92.7 (7.4)	**87.0 (6.6)**	**93.6 (6.5)**	90.2 (5.3)	94.1 (6.1)	100.3 (6.3)	100.0 (5.8)
RR [ms]	**924.8 (146.1)**	**842.5 (78.4)**	730.4 (121.0)	682.3 (87.6)	965.7 (123.2)	881.7 (97.7)	801.0 [200.5]	760.7 [200.6]
PVR [mmHg (L·min)$^{-1}$]	**15.4 (2.6)**	**10.6 (2.1)**	**16.5 (2.4)**	**11.6 (2.2)**	**15.3 (2.6)**	**10.9 (1.6)**	**16.0 (3.2)**	**11.4 (1.7)**

Values are presented as mean (SD) for normally distributed variables, median and interquartile range [IQR] for non-normally distributed variables. Statistically significant differences between groups are indicated in bold. Abbreviations: C, control group; O, group of participants with obesity; SBP, systolic blood pressure; DBP, diastolic blood pressure; MBP, mean blood pressure; RR, R-R interval; PVR, peripheral vascular resistance.

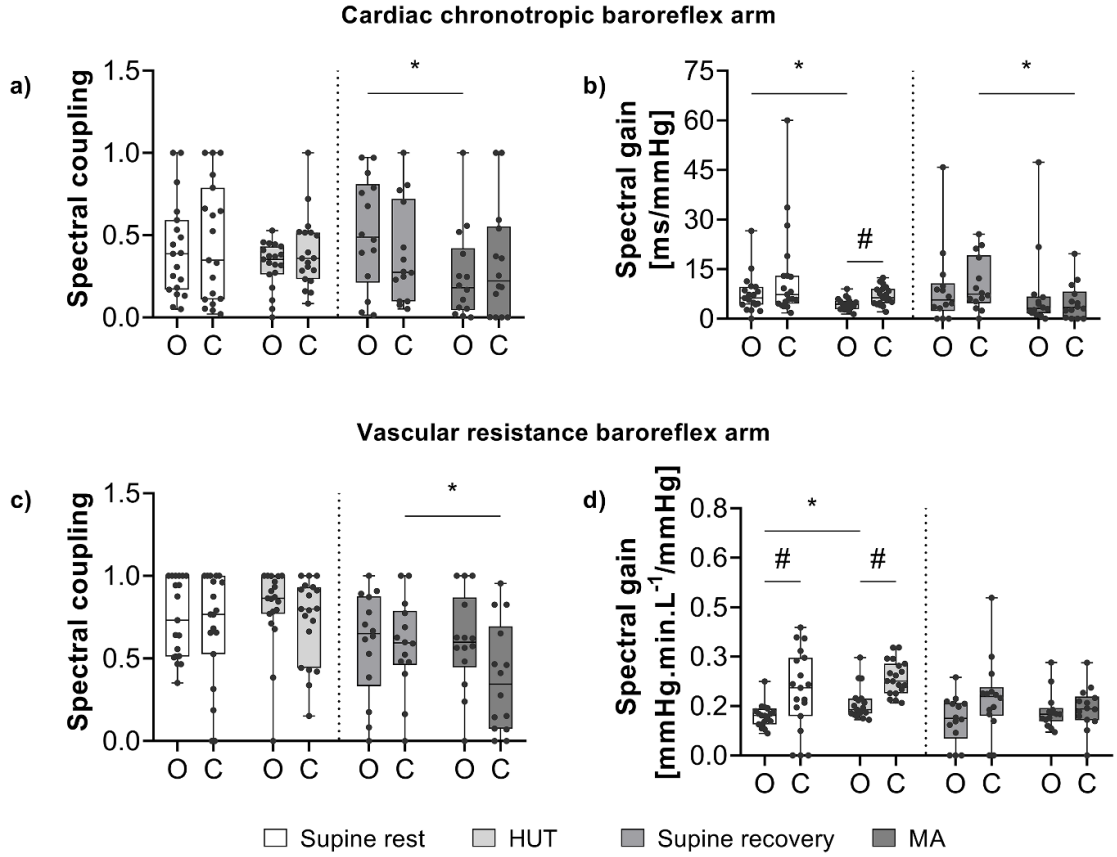

Figure 3. Spectral causal coupling strength and gain in the low frequency band measured along the direction of interaction from MBP to RR (ccBR arm, (a) and (b)) and from MBP to PVR (vrBR arm, (c) and (d)) during the supine rest, HUT, supine recovery and MA phases. Distributions are plotted as individual values superimposed to boxplots reporting minimum and maximum values (whiskers) and (25, 50, 75)th percentiles (box with central line). * denotes a statistically significant difference between stress and preceding rest phase. # indicates a statistically significant difference between group of participants with obesity (O) and healthy control (C) participants.

BR components share a common goal—i.e. to minimize short-term fluctuations in systemic arterial blood pressure. However, their effects are not redundant, as each component plays a relatively independent role in the BR response (Taylor *et al* 2015, Marchi *et al* 2016). Therefore, simultaneous evaluation of multiple BR components is important to provide a more comprehensive and insightful characterization of the overall human BR regulation (Dutoit *et al* 2010).

The vrBR component assessment has been limited in paediatric studies (Litwin 2024), as studies focusing on this arm of BR response in adults with obesity have mainly used invasive measures of MSNA as the output signal. While MSNA provides a direct measure of sympathetic nerve activity, it is invasive, technically demanding and time-consuming. Moreover, it provides information on the sympathetic control only from a limited portion of the circulation (Krohova *et al* 2020). To address the limitations of using invasive MSNA measurement in paediatric patients, we developed a non-invasive method using impedance cardiography (in connection with volume-clamp photoplethysmographic blood pressure measurement) to obtain the beat-to-beat variations in PVR as the output signal for the assessment of the vrBR component with greater feasibility and comfort for the measured subject (for details, see (Krohova *et al* 2020)).

Impedance cardiography offers a non-invasive, continuous, and operator-independent method for assessing hemodynamic parameters, such as stroke volume (SV) and CO. Since SV, together with heart rate, determines CO from which the PVR is calculated as the ratio of MBP and CO, accurate monitoring of SV or CO is essential for reliable PVR estimation. Several studies have demonstrated that impedance cardiography can reliably track changes in CO or SV across various physiological conditions (Gujjar *et al* 2008, Blohm *et al* 2014, Fellahi and Fischer 2014), including in individuals with elevated BMI (Stelfox *et al* 2006). Although obesity may introduce variability in thoracic impedance due to increased amount of adipose tissue, potentially affecting signal quality and accuracy, with appropriate calibration and attention to electrode placement, ICG remains a valuable tool for monitoring CO or SV trends in populations with obesity.

In comparison to previous studies, our findings provide additional nuance to the understanding of the BR function in young individuals with obesity, particularly focusing on the vrBR component. Previous

Table 3. Correlation coefficients among spectral coupling parameters (spectral coupling strength and gain of ccBR and vrBR arms), their response to orthostatic and cognitive loads and obesity severity (iso-BMI), fat distribution (OSS of WHR), insulin resistance ($HOMA_{IR}$), and arterial stiffness ($CAVI_0$) during rest phase in the group with obesity.

	Supine rest				Response to HUT				Response to MA			
	SC ccBR	G ccBR	SC vrBR	G vrBR	ΔSC ccBR	ΔG ccBR	ΔSC vrBR	ΔG vrBR	ΔSC ccBR	ΔG ccBR	ΔSC vrBR	ΔG vrBR
iso-BMI	−0.07	0.15	0.03	−0.07	0.16	0.03	0.20	−0.05	−0.14	**−0.60**	−0.02	0.38
OSS of WHR	0.28	0.22	−0.10	−0.38	−0.19	−0.23	0.26	0.20	−0.09	0.46	0.24	0.05
$HOMA_{IR}$	−0.31	0.33	−0.01	−0.30	0.42	−0.25	−0.08	0.10	−0.35	0.00	0.33	−0.04
$CAVI_0$	0.19	−0.27	−0.03	0.28	−0.34	0.17	0.12	−0.14	0.27	−0.13	0.28	0.05

Statistically significant correlations ($P < 0.05$) are indicated in bold. Abbreviations: SC ccBR, spectral coupling in cardiac chronotropic baroreflex arm; G ccBR, spectral gain in cardiac chronotropic arm; SC vrBR, spectral coupling in vascular resistance arm; G vrBR, spectral gain in vascular resistance arm; Δ, change in mean values (ΔSC ccBR, ΔG ccBR, ΔSC vrBR, ΔG vrBR) as a response to orthostatic (mean value from the HUT phase minus mean value of the supine rest phase) and mental load (mean value from the MA phase minus mean value of the supine recovery phase); iso-BMI, BMI adjusted for sex and age; OSS of WHR, 'Ordinal' standard score of WHR; $HOMA_{IR}$, homeostasis model assessment of insulin resistance; $CAVI_0$, updated cardio-ankle-vascular index.

studies in adults—employing a pharmacological approach, using vasoactive drug application to induce controlled changes in blood pressure—found either no effect of obesity on BRS in the vrBR component assessed by MSNA analysis (Holwerda *et al* 2016) or significantly higher BRS values (Al-Khateeb *et al* 2017). By comparison, Grassi *et al* (2000, 2004), also employed pharmacological techniques, showing a consistent pattern of impaired BRS and increased sympathetic nerve activity in individuals with obesity, regardless of hypertension status.

Using our non-invasive causal approach, we observed contrasting results compared with some previous studies: we found that changes in MBP elicit a weaker response in PVR, both in the supine rest phase and during HUT, in participants with obesity compared to lean individuals. This highlights the importance of using proper methodological settings for non-invasive assessment of BR function. Our study shows that causal analysis, combined with the use of a more appropriate output signal, can be a sensitive method to detect an impaired function of the vrBR component in children and young adults with obesity.

We ascribe the differences with previous findings in the literature to methodological aspects of time series analysis. Most previous studies employed noncausal analysis, thus overlooking the closed-loop interactions between cardiovascular variability series, which leads to potential misinterpretation of results (Porta *et al* 2000). In addition, the analysis was performed in the LF band, where the response of the heart rate is primarily mediated by the BR. The PVR response to blood pressure changes is modulated almost exclusively by the sympathetic branch of the ANS. Because of norepinephrine kinetics and the slow conduction velocity of sympathetic nerves, PVR dynamics are largely confined to the low- and very-low-frequency bands (Rosenbaum and Race 1968, Janssen *et al* 1997, Julien 2006, Porta *et al* 2018, Krohova *et al* 2020). To achieve a more objective assessment of the BR function, we analyzed the strength of spectral causal coupling and spectral gain from the input signal MBP to the output signal (RR or PVR) using the partial spectral decomposition method, enabling frequency-specific analysis of low-frequency directed causal interactions between time series. The selection of input and output signals for BR analysis was based on the results of previous study (Cernanova Krohova *et al* 2022b). Moreover, although our study identified significantly lower BRS values in the vrBR component among young individuals with obesity, these results cannot be directly compared with previous studies that reported similar impairment (Grassi *et al* 2000, 2004). In addition to differences in the studied population (adults vs. young individuals)—our cohort consisted of younger individuals—the methodologies also diverged. Prior studies typically relied on invasive assessments of MSNA, often involving the administration of vasoactive agents. Such agents have been shown to inhibit central nuclei involved in sympathetic outflow in animal models and may also modify vascular responsiveness to MSNA. These pharmacological effects raise concerns that BRS estimates obtained using these approaches may not fully reflect physiological BR function (Hart *et al* 2010).

Blunted BRS is often associated with an increased arterial stiffness (or reduced arterial compliance) (Skrapari *et al* 2006, Konstantinidou *et al* 2022), which impairs baroreceptor stimulation by limiting arterial wall stretching and potentially reducing BR sensitivity. However, despite observing decreased BRS in both BR arms, this cannot be attributed to reduced arterial compliance. In fact, we detected an increased arterial compliance in our group of patients with obesity, as demonstrated by a lower value of the $CAVI_0$ index. The $CAVI_0$ index, estimating arterial stiffness independently from blood pressure changes, was significantly lower in another group of young participants with obesity (Mestanik *et al* 2017, Czippelova *et al* 2019). Moreover, Svec *et al* (2022) reported higher arterial compliance in young participants with obesity using a novel approach analyzing blood pressure decay during diastole. We can conclude that, despite the reduced arterial stiffness observed in our study group, BR impairment is still present, further highlighting the presence of reflex autonomic dysfunction in obesity.

The BR plays a crucial role in maintaining blood pressure during the HUT by triggering compensatory adjustments in the ANS. After the transition from a supine to upright (tilted) position, gravity causes blood pooling in the lower extremities, reducing venous return to the heart, leading to a temporary decrease in CO and mean arterial pressure. The BR-mediated response triggers changes in ANS activity, increasing heart rate and PVR to maintain baseline mean arterial pressure (O'Leary *et al* 2003). Similarly, the MA task induces ANS changes, specifically an increase in sympathetic activity, resulting in elevated blood pressure, heart rate, and vasoconstriction in the renal and splanchnic regions, alongside vasodilation in skeletal muscles (Kuipers *et al* 2008). Comparison of the effects of two stressors (supine rest vs. HUT and supine recovery vs. MA) confirmed preserved reactivity of BRS in individuals with obesity. During HUT, the spectral gain in ccBR arm decreased and in vrBR arm increased in both groups, reaching statistical significance in patients with obesity only. During mental load, lean subjects exhibited a significant decrease in ccBR arm spectral gain. Previous study employing a noncausal method found similar results: a decrease in ccBR gain and an increase in vrBR gain (using MSNA as the output signal) in lean adult participants during 60° HUT (O'Leary *et al* 2003).

During MA, we observed a significant reduction in spectral coupling values in the ccBR arm in participants with obesity, with a more pronounced change in its gain, reaching borderline significance. A

similar pattern was noted in the vrBR arm, but in lean participants, where a more pronounced decrease was observed. Comparable findings were reported in young healthy participants using noncausal methods, showing reduced BR effectiveness (coupling strength) in both arms among sedentary individuals, but not in physically active group (Reyes Del Paso *et al* 2017). These findings suggest that while both groups demonstrated altered BR responsiveness under mental load, the changes were more pronounced in the vrBR arm of lean participants, indicating potential differences in BR modulation between participants with obesity and healthy individuals.

The correlation analysis did not reveal any association between the spectral coupling parameters and sex- and age-independent anthropometric characteristics (iso-BMI and OSS of WHR), insulin resistance ($HOMA_{IR}$), arterial stiffness index $CAVI_0$, regarding both BR components assessed during the resting phase in the group with obesity. However, a significant negative correlation was found between the response to mental load of the spectral gain in the ccBR arm and the iso-BMI index; this result suggests that greater severity of obesity is associated with a more pronounced decrease in BRS along the ccBR component during this stressor. Our results are consistent with a previous study by Holwerda *et al* (2016) where no significant correlations were noted between vrBR gain and BMI or waist-to-hip ratio. Other studies found a negative association between BRS in ccBR arm and severity of obesity in children and adolescents (Dietrich *et al* 2006, Honzikova *et al* 2006, Lazarova *et al* 2009) and adults (Laederach-Hofmann *et al* 2000, Man *et al* 2021), as well as a negative correlation between ccBR sensitivity and WHR in adults with obesity (Indumathy *et al* 2015). Ryan *et al* (2013) also reported a negative association between $HOMA_{IR}$ and BRS assessed in the ccBR arm. This association was not confirmed in our study, despite higher insulin levels and insulin resistance found in subjects with obesity, which are commonly associated with changes in ANS activity (Frontoni *et al* 2003). We could attribute the difference in results to the noncausal method used in evaluating BRS in previous studies and the use of iso-BMI and OSS of WHR in our study, which are independent of sex and age, unlike the previously used BMI and WHR.

The identification of early BR dysfunction holds potentially significant clinical relevance in various populations, including young individuals with obesity. We assume that impaired BR function may be indicative of future development of cardiovascular diseases (including, e.g. hypertension) in children, adolescents, and young adults with obesity. Previous studies indicate that weight loss and regular physical activity improves BR function in individuals with obesity (Loimaala *et al* 2003, Alvarez *et al* 2005), highlighting the importance of initiating early preventive strategies. Given that not all individuals with obesity progress to hypertension, the non-invasive assessment of BR function may help identify those at higher risk, thereby supporting the implementation of targeted preventive strategies at an early stage.

Future research should focus on longitudinal studies tracking BR sensitivity across time in individuals with varying grades of obesity, as well as controlled intervention studies aimed at evaluating the efficacy of lifestyle modifications—including exercise programs and dietary interventions—on improving BR function and reducing cardiovascular risk.

5. Study limitations

While this study provides novel and potentially valuable information about the obesity-related impairment of the BR function in young normotensive patients, certain limitations must be considered when interpreting the findings.

Although impedance cardiography is a non-invasive and user-friendly method for beat-to-beat CO monitoring, its effectiveness in our study was limited, likely due to detection errors or signal artefacts. Future improvements in filtering and detection algorithms may help to improve data quality and reliability. Together with the fact that the evaluated group could not include participants with additional comorbidities, this resulted in a relatively small sample size, which represents study limitation, reducing statistical power and increasing the risk of Type II error.

A post-hoc power analysis was conducted for the spectral gain measures, yielding a mean statistical power across phases of 0.476 for the ccBR arm and 0.704 for the vrBR arm. These values reflect limited power in the between groups analysis of ccBR arm and moderate power in the vrBR arm, potentially constraining our ability to detect statistical differences. It is also important to note that prior studies evaluating the vrBR arm using MSNA as the output signal (Holwerda *et al* 2016, Al-Khateeb *et al* 2017) analyzed smaller cohorts—specifically, 9 patients with obesity and 10 control participants in the former, and 6 patients with obesity and 7 controls in the latter. In contrast, our study includes a substantially larger and more diverse sample. While this improves generalizability, the moderate statistical power remains a relevant limitation.

Moreover, the imbalance in sex distribution among the participants, with 12 male subjects and 33 female subjects, could also alter our results. In a previous study performed on young healthy subjects (Krohova *et al* 2020), the SC strength in both arms was similar, but they found some sex differences in spectral gains (the

spectral gain in ccBR arm was significantly higher and in vrBR arm was significantly lower in male participants). In our case, even though the groups are not perfectly balanced in terms of sex, we ensured that the comparison between groups was conducted with equal representation of sexes within each individual group. To assess the potential effect of sex-related differences on the results of our study, we compared the SC strength and gain values in both arms across phases and groups (group O and group C separately). This analysis revealed no statistically significant differences in BR indices between males and females (results not shown). These findings suggest that, despite the sex imbalance, sex did not have a measurable effect on the outcomes in our current dataset. Nonetheless, we recognize that the small number of male participants may limit the power to detect subtle sex-related effects. We therefore highlight the importance of future studies with larger sample sizes and more balanced sex representation to validate these findings and explore potential sex-specific differences in BR function, particularly in the context of obesity.

Another limitation regards the age range of the study group, which involved participants in the pubertal stage—a period characterized by considerable and dynamic hormonal changes known to modulate autonomic control and BR function, potentially contributing to interindividual variability in our findings. Although the study cohort was generally within a normal fitness range (individuals who regularly participated in intensive training programs were excluded) unmeasured interindividual variability in physical conditioning likely existed and could have contributed to the observed variability in autonomic responses. The absence of these data in the current study represents a limitation; incorporating such variables in future research will be valuable for a more comprehensive understanding of autonomic regulation in young individuals with obesity.

Moreover, the findings may not be fully generalizable to older adults, individuals from different ethnic backgrounds, or those with comorbidities (e.g. diabetes mellitus, cardiovascular disease). The current cohort represents a relatively healthy, homogeneous sample. In particular, hypertensive individuals were not included in this study, preventing us from comparing BR function between hypertensive individuals with obesity, normotensive individuals with obesity and hypertensive individuals without obesity—a distinction that may yield important physiological insights. Future studies involving larger and more diverse populations, including participants with common comorbid conditions such as hypertension, are needed to confirm and extend these results across broader clinical and demographic contexts.

6. Conclusions

BR dysfunction is one of the factors that could contribute to the obesity-related development of hypertension, through an imbalance in the sympathetic-vagal outflow directed to the heart and to blood vessels. In this study, we applied a novel, fully non-invasive approach to simultaneously evaluate both the ccBR and vrBR arms using simultaneous beat-to-beat measurement of heart rate and vascular resistance as well as advanced causal spectral analysis. Our analysis performed in young individuals with obesity revealed an early impairment of the BR in both the ccBR and vrBR arms, with the latter documented for the first time. These results underscore the importance of early detection of blood pressure dysregulation in young patients with obesity, potentially evoking early therapeutic intervention helping to prevent the long-term consequences of hypertension.

Future studies with larger sample size are needed to confirm our findings and explore whether early therapeutic interventions, including lifestyle modifications could restore BR function and reduce cardiovascular risk. This approach may offer valuable opportunities for targeted prevention strategies in at-risk populations with obesity.

Data availability statement

The data cannot be made publicly available upon publication because they contain sensitive personal information. The data that support the findings of this study are available upon reasonable request from the authors.

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Conflict of interest

All authors declare that they have no conflicts of interest.

Ethical statement

The study protocol was approved by the Ethics Committee of the Jessenius Faculty of Medicine in Martin, Comenius University Bratislava (Approval No. EK 1257/2013; revised EK 1834/2016) and conducted per the Declaration of Helsinki. Written informed consent was obtained from all participants or their guardians, who were informed of their right to withdraw at any time.

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