Original Paper

Lower Heart Rate Variability Is Associated with Lower Pulse Pressure Amplification: Role of Obesity

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Keywords

Heart rate variability · Pulse pressure amplification · Pulse pressure · Obesity · Artery

Abstract

Background: Heart rate variability (HRV), pulse pressure amplification, and obesity represent risk factors for cardiovascular events. The aims of the present study are (1) to explore the impact of HRV on pulse pressure amplification and (2) to investigate whether the association between HRV and pulse pressure amplification differs in obese and lean subjects. **Methods:** A total of 342 patients (age 61 ± 11 years) were enrolled. HRV was analyzed concerning both the frequency and time domain as well as concerning the HRV triangular index. Pulse pressure amplification was estimated as the ratio between brachial and carotid pulse pressure, the latter measured with SphygmoCor. **Results:** Time domain HRV indices were directly correlated with pulse pressure amplification (the lower the HRV indices, the lower the pulse pressure amplification). This association was stronger in obese than in lean subjects after controlling for age and sex. **Conclusion:** Larger controlled studies are needed to provide a more detailed insight into the relation between HRV and pulse pressure amplification and to determine which pathways are differentially activated in lean and obese subjects.

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Introduction

The pulse wave generated by the heart at each beat travels along the arterial system. Its amplitude (pulse pressure [PP]) has been related to greater cardiovascular (CV) risk, particularly in women [1], and aortic remodeling [2] predisposing to systolic hypertension [3]. At

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a younger age, physiologically, the amplitude (i.e., PP) of the pressure wave increases gradually from the aorta/carotid arteries to the brachial/radial arteries. This phenomenon has been referred to as PP amplification. The lower the central PP and the greater the PP amplification, the more beneficial the effect on the CV system, because of a lower load on the left ventricle. PP amplification decreases with age [4, 5]. Observational studies also reported that obesity and other classical CV risk factors are associated with reduced PP amplification [4, 5].

Heart rate variability (HRV), i.e., the beat-by-beat fluctuations in heart rate (HR) reflecting the autonomic nervous system balance, has emerged as an indicator of CV risk in adults [6, 7]. In general, increased cardiac sympathetic drive is detrimental, while increased cardiac parasympathetic activity is cardioprotective [8]. Conventionally, measures of HRV are in both the time and frequency domains. In the time domain, the square root of the mean squared differences of successive normal-to-normal (NN) intervals (RMSSD), the proportion of beat-to-beat (RR) intervals having a difference of >50 ms (pNN50), and the HRV index have been shown to be useful indices of vagal activity. In the frequency domain, both low-frequency (LF; 0.04–0.15 Hz) and high-frequency (HF; 0.15–0.40 Hz) spectral powers have been used as indices of vagal activity. Regardless of the autonomic function selectively explored by those functions (sympathetic versus parasympathetic) [9], lower values of these indices are associated prospectively with death and disability.

Obesity significantly impacts on pulse wave properties [10–14]. In overweight and obese individuals, particularly in children and teenagers, reduced HRV [15, 16] has been documented.

The aims of the present study are (1) to explore the impact of HRV on PP amplification and (2) to investigate whether the association between HRV and PP amplification differs in obese and lean subjects.

Methods

Study Population

A total of 342 outpatients who came to our attention during a campaign for the assessment of CV risk were enrolled in this study. All patients filled in a brief questionnaire concerning their medical history. No blood samples were drawn.

Office brachial blood pressure (BP) was measured by a physician using a mercury sphygmomanometer after the subjects had rested for 10 min, according to standard procedures. Mean BP was defined as diastolic BP + 1/3 (systolic – diastolic BP).

PP Amplification

Measurement of central pressures was determined from radial waveforms using the validated SphygmoCor device (AtCor Medical) [17]. All measurements were made in duplicate by a single operator.

PP amplification is usually defined by the ratio between the distal (brachial) PP and the central (aortic) PP. Alternatively, it can be expressed as the difference (in mm Hg) between PP at the distal and PP at the central sites, usually ranging from 5 to 20 mm Hg. The PP amplification ratio is considered less dependent on calibration errors [18], and, thus, it has been adopted as the primary index for the purposes of the present study.

Assessment of HRV

HRV was measured with the AtCor Medical HRV software to assess sympathetic/parasympathetic autonomic function. A standard 5-min electrocardiogram recording was performed with the patient in supine position, with a regular and calm breathing pattern (5-min resting study) in a quiet room.

Assessment of overall HRV included HRV triangular index (the integral of the density distribution, i.e., number of all NN intervals plotted in a histogram, divided by the maximum of the density distribution).

Table 1. Impact of lower and upper levels of indices of HRV on pulse pressure amplification ratio

	Pulse pressure amplification ratio			Reduced pulse pressure amplification ratio, %		
	1st quartile	4th quartile	<i>p</i>	1st quartile	4th quartile	<i>p</i>
pNN50, %	124.4±1.4	129.1±1.4	0.02	34.5	15.5	0.01
RMSDD, m/s	125.4±1.4	131.2±1.4	0.004	32.9	14.0	0.004
HRV index	124.6±1.4	129.9±1.4	0.008	37.8	19.1	0.004
LF	128.8±1.4	128.5±1.4	0.83	18.4	17.5	0.88
HF	127.0±1.4	128.8±1.4	0.36	25.7	19.0	0.33
LF/HF ratio	128.3±1.4	126.4±1.4	0.37	19.7	23.7	0.54

HRV, heart rate variability; pNN50, proportion of RR intervals having a difference of >50 ms; RMSDD, square root of the mean squared differences of successive NN intervals; LF, power spectral density at the low-frequency range (0.04–0.15 Hz); HF, power spectral density at the high-frequency range (0.15–0.4 Hz).

Time domain measures are the means and standard deviations of RR intervals recorded by the continuous electrocardiogram, where NN intervals represent all the RR intervals. The time domain of HRV was evaluated using:

- RMSSD (m/s), which provides an estimate of the short-term components of HRV; the lower this vagal index, the greater the CV burden; and
- pNN50 (%), which reflects alterations in autonomic function that are primarily vagally mediated and that are virtually independent of circadian rhythms.

The frequency domain of HRV consists of the spectral analysis of a series of consecutive RR intervals in order to quantify sympathetic and vagal influences on the heart. The evaluated parameters were [9, 19]:

- power spectral density at the HF range (0.15–0.4 Hz);
- power spectral density at the LF range (0.04–0.15 Hz) – a composite index of cardiac sympathetic and parasympathetic activity; and
- the LF:HF ratio as an indicator of the relative contribution of the sympathetic and parasympathetic components to the autonomic control of the HR.

Statistical Analysis

All analyses were performed using the SAS package for Windows (version 9.1, Cary, NC, USA). Data are presented as means ± standard deviations unless otherwise specified. Differences in mean values for each of the measured variables between groups were compared by ANOVA, followed by the Bonferroni test for multiple comparisons. ANCOVA analysis was adopted to compare means across groups after controlling for age and sex. A 2-sided *p* value <0.05 indicated statistical significance.

Results

The subjects participating in the study were 61 ± 11 years old. The prevalence of hypertension and diabetes was 89 and 73%, respectively. Lower values of time domain measures were associated with lower PP amplification (Table 1, left columns) and with a greater proportion of subjects with a reduced PP amplification ratio (defined as the lower quartile of PP amplification ratio distribution within the study population) (Table 1, right columns). No significant difference in PP amplification was observed in subjects with low or high values of indices exploring the HRV frequency domain (Table 1).

Since obesity was more common in subjects with HRV indices in the lower quartile than in those with HRV indices in the upper quartile (on average 4% greater prevalence in the lower quartiles), we compared lean and obese subjects. Obese subjects were on average 5

Table 2. HRV indices in lean and obese subjects

	Control (n = 239)	Obese (n = 103)	t test p value
Age, years	63.5±9.3	58.1±10.8	<0.001
Men, %	60	54.4	<0.05
Hypertension, %	80.3	89.5	0.32
Diabetes mellitus, %	70.4	77.2	0.27
Brachial SBP, mm Hg	140.4±13.4	142.3±11.4	0.30
DBP, mm Hg	77.5±8.0	79.8±8.4	<0.05
MBP, mm Hg	100.2±9.0	101.9±8.3	0.12
Brachial PP, mm Hg	63.1±11.9	62.3±11.4	0.64
HR, bpm	66.8±8.7	68.9±8.8	0.12
Carotid SBP, mm Hg	130.1±13.4	129.8±10.9	0.89
Carotid PP, mm Hg	52.8±11.4	49.8±10.6	0.07
PP amplification ratio	125±10	132±13	<0.0001
pNN50, %	7.3±8.5	11.7±14.8	<0.05
RMSDD, m/s	36.4±25.8	43.4±34.3	0.23
HRV index	6.7±2.4	6.8±2.7	0.76
LF	1,193±1,569	992±1,274	0.69
HF	619±799	832±1,076	0.37
LF/HF ratio	2.79±1.74	2.02±1.37	<0.01

Values are means ± standard deviations unless otherwise specified. HRV, heart rate variability; SBP, systolic blood pressure; DBP, diastolic blood pressure; MBP, mean blood pressure; PP, pulse pressure; HR, heart rate; pNN50, proportion of RR intervals having a difference of >50 ms; RMSSD, square root of the mean squared differences of successive NN intervals; LF, power spectral density at the low-frequency range (0.04–0.15 Hz); HF, power spectral density at the high-frequency range (0.15–0.4 Hz).

years younger than lean subjects (58.1 ± 13.2 vs. 63.5 ± 15.1 years, respectively) and more likely women (45.6 vs. 41.4%).

The PP amplification ratio was greater in obese than in lean subjects (Table 2). Though average HR did not significantly differ between lean and obese subjects, resting HR influenced both time domain HRV and PP amplification. Therefore, to investigate potential differences in the impact of HRV indices on PP amplification between lean and obese subjects, baseline HR was introduced as a covariate together with age and sex. Additional models controlled also for diabetes mellitus and BP levels. As illustrated in Table 3, the impact of HRV indices on PP amplification differed between lean and obese subjects (significant interaction term HRV × obesity). For example, in lean subjects, being in the lower quartile of RMSSD was associated with an average, significant, 5% greater PP amplification as compared with lean subjects in the upper quartile of RMSSD. In obese subjects, the opposite effect was observed.

Discussion

The present study found that (1) time domain HRV indices were directly correlated with the PP amplification ratio (the lower the HRV indices, the lower the PP amplification ratio) and (2) the association was stronger in obese than in lean subjects after controlling for age and sex. The study has 2 major limitations. Subjects were recruited during a local screening campaign for CV disease. Thus, our study population is composed predominantly of high-risk subjects (the prevalence of hypertension and diabetes was 89 and 73%, respectively). Additionally, no blood samples were available, nor detailed information about medication use.

Table 3. Least square means ($\pm$ standard error) of pulse pressure amplification ratio in lean and obese subjects by HRV domains (upper vs. lower quartile)

	Lean subjects (<i>n</i> = 239)		Obese subjects (<i>n</i> = 103)		<i>p</i> value		
	1st quartile	4th quartile	1st quartile	4th quartile	HRV	obesity	HRV $\times$ obesity
a <i>Adjusted for age, sex, and heart rate</i>							
pNN50, %	129.0 $\pm$ 1.7	122.6 $\pm$ 1.5	127.6 $\pm$ 1.8	131.2 $\pm$ 2.0	0.40	<0.001	<0.01
RMSDD, m/s	128.7 $\pm$ 1.4	122.5 $\pm$ 1.5	126.7 $\pm$ 1.8	135.1 $\pm$ 1.9	0.12	<0.0001	<0.0001
HRV index	128.8 $\pm$ 1.4	122.4 $\pm$ 1.5	128.7 $\pm$ 1.9	129.9 $\pm$ 2.0	0.30	<0.001	<0.05
LF	124.0 $\pm$ 1.3	128.2 $\pm$ 1.5	134.1 $\pm$ 2.6	128.9 $\pm$ 1.6	0.10	<0.001	<0.05
HF	126.1 $\pm$ 1.6	125.9 $\pm$ 1.4	128.4 $\pm$ 1.7	130.7 $\pm$ 2.0	0.44	<0.01	0.48
LF/HF ratio	123.8 $\pm$ 1.4	126.2 $\pm$ 1.6	136.1 $\pm$ 2.9	128.6 $\pm$ 1.7	0.24	0.36	<0.01
b <i>Adjusted for age, sex, heart rate, MBP, and diabetes mellitus</i>							
pNN50, %	128.8 $\pm$ 1.4	122.4 $\pm$ 1.4	127.8 $\pm$ 1.7	130.6 $\pm$ 1.9	0.45	<0.001	<0.01
RMSDD, m/s	128.8 $\pm$ 1.4	122.4 $\pm$ 1.5	127.1 $\pm$ 1.7	133.9 $\pm$ 1.9	0.32	<0.0001	<0.001
HRV index	129.0 $\pm$ 1.3	122.4 $\pm$ 1.3	128.9 $\pm$ 1.8	130.0 $\pm$ 1.8	0.18	<0.001	<0.01
LF	124.1 $\pm$ 1.2	127.4 $\pm$ 1.5	133.9 $\pm$ 2.5	129.2 $\pm$ 1.5	0.12	<0.0001	<0.05
HF	125.7 $\pm$ 1.5	126.0 $\pm$ 1.3	128.6 $\pm$ 1.6	131.1 $\pm$ 1.9	0.40	<0.001	0.44
LF/HF ratio	124.1 $\pm$ 1.3	125.3 $\pm$ 1.6	135.7 $\pm$ 2.7	129.0 $\pm$ 1.6	<0.05	0.36	<0.01

HRV, heart rate variability; pNN50, proportion of RR intervals having a difference of >50 ms; RMSDD, square root of the mean squared differences of successive NN intervals; LF, power spectral density at the low-frequency range (0.04–0.15 Hz); HF, power spectral density at the high-frequency range (0.15–0.4 Hz); MBP, mean blood pressure.

The use of specific antihypertensive drug classes might have a role. In fact, antihypertensive drugs with vasodilating effects increase PP amplification as compared to β -blockers [19]. Similarly, angiotensin-converting enzyme inhibitors [20] and anti-aldosterone [21] have been reported to positively impact on HRV. Controlling for resting HR may have reduced the limitation deriving from a lack of detailed records about medication use.

An additional limitation may be represented by the adoption of body mass index to define obesity rather than waist circumference, a measure of visceral adiposity and “metabolically active” adipose tissue [13]. In fact, it has been reported that central adiposity, measured by waist circumference, but not overall adiposity, measured by body mass index, was associated with decreased HRV – assessed as standard deviation of successive differences in NN intervals and RMSDD [22].

Nonetheless, the present study calls attention to potential novel pathophysiological pathways that may contribute to arterial aging [23] and may promote CV disease onset and progression [24, 25]. Larger controlled studies are needed to provide more detailed insight into the role of HRV and PP amplification, an index of arterial aging, and to determine which pathways are differentially activated in lean and obese subjects.

Additional studies will also clarify whether the detrimental effects of obesity on reduced HRV and PP amplification, risk factors for CV disease, may be minimized by active healthy behaviors [26]. For instance, physical activity has been associated with more favorable HRV indices, especially those reflecting increased vagal modulation and reduced sympathetic activity [27, 28]. Similarly, a dose-response relationship between physical activity and improved HRV has been reported, and it is observable even in the presence of heart failure [29]. Thus, behaviors that alter this autonomic imbalance toward a more salubrious profile may serve to prevent or at least minimize the effects of certain risk factors (HRV as well as obesity) for CV events.

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