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Original Article

Heart rate variability and metabolic rate in healthy young adults with low birth weight

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Abstract: Objective: Low birth weight (LBW) is associated with obesity and a higher cardiovascular risk in adult life. Since autonomic dysfunction could be a pathophysiological factor for this association, we assessed the impact of LBW on cardiac autonomic activity and metabolic rate in young adulthood. We hypothesized that the autonomic tone could be coupled with the metabolic rate in subjects with LBW. Methods: Heart rate variability (HRV) from 24-hour Holter-electrocardiograms was measured in 15 healthy adults aged 20 to 30 years with LBW (<2500g at term) and 15 paired subjects with normal birth weight (NBW). The pairs were closely matched by gender, age, and body mass index. Resting energy expenditure was measured by indirect calorimetry and body composition by bioimpedance. Results: Global HRV parameters were significantly higher in the LBW group and a marked difference was observed in the long wave fluctuations of the frequency domain (very low frequency). These fluctuations were positively correlated with the resting energy expenditure per body weight in the LBW and negatively in the NBW group. Only in the LBW group HRV was closely related to body fat. Interpretation: This case-control study indicates that autonomous nervous function is not generally deteriorated in young adults with LBW and has a significant association with metabolic rate. Thus, it may be a determinant of the body weight regulation in this group. The higher cardiovascular risk in ageing individuals with LBW would therefore rather be a consequence of weight gain than of a primary autonomous nervous dysfunction.

Keywords: Low birth weight, autonomic nervous system, metabolic rate, weight gain

Introduction

Intrauterine growth retardation has been associated with increased cardiovascular morbidity and mortality [1]. This association may be explained by a higher incidence of cardiovascular risk factors such as obesity, diabetes, and hypertension found in subjects with low birth weight (LBW) in population based studies [2, 3]. The precise pathophysiological correlates, however, have thus far not been identified. Barker and co-workers postulated a “fetal programming” suggesting that neurohumoral alterations induced by adverse intrauterine events persist throughout life and result in adulthood disease [1]. Delayed intrauterine growth may also have an impact on the development of the central nervous system resulting in an altered autonomic nervous control in subjects with LBW.

Indeed, alterations of the sympathetic nervous system have been observed in animal studies. However, the results are conflicting: Both restrained [4, 5] and overshooting [6, 7] overall activity of the sympathetic nervous system has been described as a consequence to intrauterine growth restriction. Studies on sympathetic outflow in humans are also contradictious. A negative correlation of muscle sympathetic nerve activity and birth weight was found in Pima Indians [8]. A case-control study in a Brazilian population suggested higher muscle sympathetic nerve activity in subjects with LBW [9], whereas we were able to show that subjects with LBW have significantly lower muscle sym-

pathetic nerve activity as compared to a thoroughly matched control group with normal birth weight (NBW) [10].

The activity of the cardiac sympathetic nervous system is thought to be enhanced in subjects with LBW and this can be concluded from several observations: In one study a negative correlation between pulse rate assessed by field workers and birth weight in 449 adults aged 46 to 54 years was found [11]. A study in 114 adolescent twin pairs showed that pre-ejection period shortening (a marker of cardiac sympathetic stimulation) accounted for 63 to 83% of the association between birth weight and blood pressure [12]. Moreover, in psychological stress tests LBW was associated with a higher blood pressure and heart rate [13, 14], and a reduced baroreflex sensitivity [15]. However, latter relations could only be observed in women.

Most recently, lower parameters of heart rate variability (HRV) have been reported in children with LBW as compared to children with NBW [16]. HRV is a well-established non-invasive tool to study cardiac autonomic activity. Beyond this, HRV may also provide prognostic information: reduced heart rate variability predicts the onset of hypertension more accurately than the body mass index (BMI) [17] and is associated with the all-cause mortality in elderly [18]. A diminished autonomic modulation of heart rate in young adults with LBW could therefore be an indication of their higher cardiovascular risk in later life. On the other hand, the tone of autonomic control of the heart is also associated with thermogenesis [19] implicating that a decrease in long-wave modulation can go in line with a decrease in metabolic rate and, thus, with weight gain.

The regulation of blood pressure and heart rate has been shown to be altered in young adults with LBW and strongly interacts with BMI, insulin resistance, and the cortisol profile in these subjects in contrast to young adults with NBW [20]. In prepubertal children, a positive correlation between circadian blood pressure modulation and BMI could only be observed in the group with LBW but not in the controls with NBW [21]. Hence, autonomous rhythmicity and its association with metabolic rate may be regulated differently in subjects with LBW than in those with NBW. We therefore hypothesized that HRV might be associated to metabolic rate and body weight regulation differently in young adults with LBW as compared to a matched control with NBW and, hence, could be a factor promoting weight gain in this group.

Methods

Studied subjects

Singletons born after 37 completed weeks of gestation were considered to be too small for their gestational age when their weight at birth was less than 2500 g. Fifteen subjects with LBW aged 20 to 30 years were identified from the obstetric records of births of the Department of Gynaecology and Obstetrics of the University Clinic of Schleswig-Holstein, Campus Lübeck, and agreed to participate in the study. Exclusion criteria for participation in the study were drug treatment and any disease except for hypertension, glucose intolerance, and dyslipidemia which have been associated to LBW. The tracing process was the same as in previous studies from our group [10, 20].

For the control group, subjects were recruited by an advertisement in a local newspaper. Inclusion criterion was NBW (3200 to 3700 g after 37 completed weeks of gestation as verified by obstetric records) and exclusion criteria were the same as in the LBW group. Subjects were closely matched by gender, age (less than 5 years difference within the age range of 20 to 30 years), and BMI (less than 1 kg/m^2 difference). The matching subjects were also similar in terms of family history of hypertension, obesity, diabetes, physical activity, and diet. All 30 studied subjects were healthy and did not take any drugs. Health status was assessed by history, physical examination, and laboratory screening. Female subjects were examined in the follicular phase of the menstrual cycle. The study was approved by the local ethics committee, and all participants gave written informed consent.

Experimental procedure

All subjects were investigated by 24-hour ambulatory electrocardiogram recordings with three time-tracking Holter recorders (Cardioscan® DMS 300-6 SkanDisk; MTM multitechmed GmbH, Hünfelden, Germany) on a normal working day with a bedtime of approximately 11 p.m. and a wake up time of approxi-

Table 1. Characteristics of the subjects with LBW and NBW

	LBW (n=15)	NBW (n=15)	*P*
Birth weight [g]*	2346 ±41	3417 ±49	<.001
Age [years]	24.6 ±.8	26.2 ±.9	n.s.
Male/female [number]	7/8	7/8	n.s.
Weight [kg]	69.6 ±4.9	72.6 ±5.0	n.s.
Height [cm]	172.1 ±2.8	176.6 ±2.4	n.s.
BMI [kg/m²]	23.4 ±1.4	23.2 ±1.4	n.s.
Waist-to-hip ratio	.79 ±.02	.79 ±.02	n.s.

*P<.05.

Table 2. Endocrine and metabolic parameters of the studied subjects

	LBW (n=15)	NBW (n=15)	*P*
Glucose [mg x dL^{-1}]	87.1 ±1.4	86.3 ±1.8	n.s.
Insulin [mU x L^{-1}]	7.3 ±1.1	6.5 ±1.2	n.s.
Serum cortisol [µg x dL^{-1}]	16.7 ±2.1	13.9 ±2.2	n.s.
Adrenocorticotropin [µg x L^{-1}]	17.7 ±2.1	14.9 ±1.2	n.s.
Salivary cortisol 8 a.m. [nmol x L^{-1}]	.50 ±.06	.53 ±.05	n.s.
Leptin [µg x L^{-1}]	10.4±2.2	8.8 ±.1.1	n.s.
Plasma renin [pg x L^{-1}]	8.4 ±1.5	6.1 ±.7	n.s.
Aldosterone [ng x L^{-1}]	80.5 ±12.3	55.9 ±8.9	n.s.
Systolic blood pressure [mmHg]	116.2 ±3.0	111.7 ±1.6	n.s.
Diastolic blood pressure [mmHg]	68.3 ±1.9	66.2 ±1.5	n.s.
Fat mass [kg]	16.4 ±2.8	19.0 ±3.2	n.s.
REE [kcal x d^{-1}]	1639 ±73	1573 ±72	n.s.

There were no significant differences between the groups. REE = resting energy expenditure.

mately 7 a.m. and they were instructed not to exert excessive physical activity on the recording day. After an overnight fasting body height, weight, and circumferences of waist and hip were measured in each subject. Then the relative amount of fat free mass was assessed by bioimpedance analysis (Tanita®TBF-551; Tanita Europe GmbH, Sindelfingen, Germany) and subjects underwent calorimetry (Deltatrac II®; Datex - Ohmeda, Helsinki, Finland). Blood pressure and resting pulse were measured three times 2 min apart after a resting period of 30 min in supine position. Blood samples were collected and were immediately centrifuged at 4°C. The blood was either investigated by routine laboratory methods on the same day (plasma glucose, triglycerides, cholesterol) or stored at -80°C until assay for determination of cortisol, adrenocorticotropin, leptin and insulin. Salivary cortisol was collected on a free day shortly after awakening around 8 a.m. and before getting to bed at around 11 p.m. as previously described [26].

All Holter recordings were blinded to the status of the subjects and then manually edited for exclusion of artefacts and premature beats. Beats with a heart rate of greater than 30 beats/min and less than 160 beats/min, or beats with a prevailing RR interval less than 63% and greater than 175%, respectively, were automatically excluded from the analysis. Twenty-four-hour files of RR intervals were then processed on a personal computer using a special software package (Cadioscan® 6-Software H5 05 1173/1-V; MTM multitechmed GmbH, Hünfelden, Germany). Parameters of the time and frequency domain were computed for the day-time period (7 a.m. to 11 p.m.), the night-time period (11 p.m. to 7 p.m.) and the entire 24 hour recording period.

Statistical analysis

The group differences were assessed by Mann-Whitney-U rank tests. Spearman's bivariate correlation was used to test the correlation of values within a group. A *P* value less than .05 was considered significant. Data are presented as mean with the standard error of means.

Results

The anthropometric parameters of the 30 studied subjects are shown in **Table 1**. None of the studied subjects (LBW and NBW) had evidence of hypertension, diabetes or dyslipidemia. Three subjects in the LBW and one in the NBW group were smokers; the amount of physical activity was comparable in both groups. No difference was found in endocrine parameters, blood pressure, parameters of body composition or energy expenditure (**Table 2**). There was a trend for a lower resting pulse in the LBW group as compared to the controls (61.5 vs. 66.9 /min; *P*=.07).

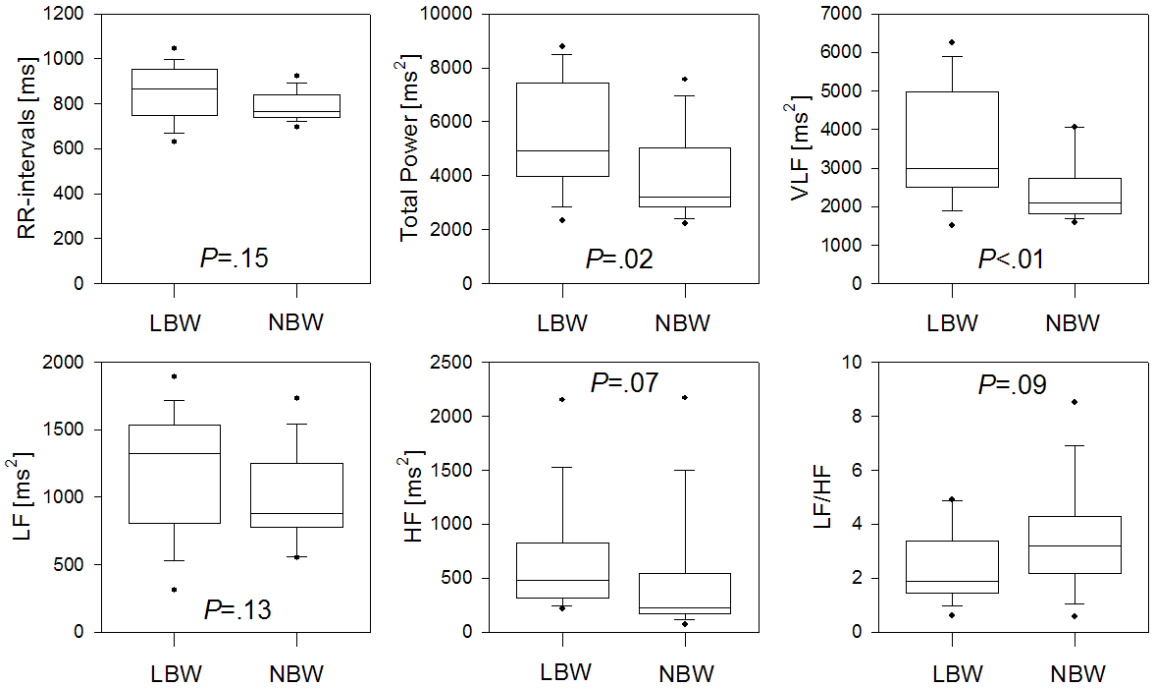

Figure 1. RR-intervals and heart rate variability parameters of the frequency domain. Plots with medians, 10th, 25th, 75th, and 90th percentiles. *P*-values of the comparison between the groups are given in each graph. VLF = very low frequency; LF = low frequency; HF = high frequency.

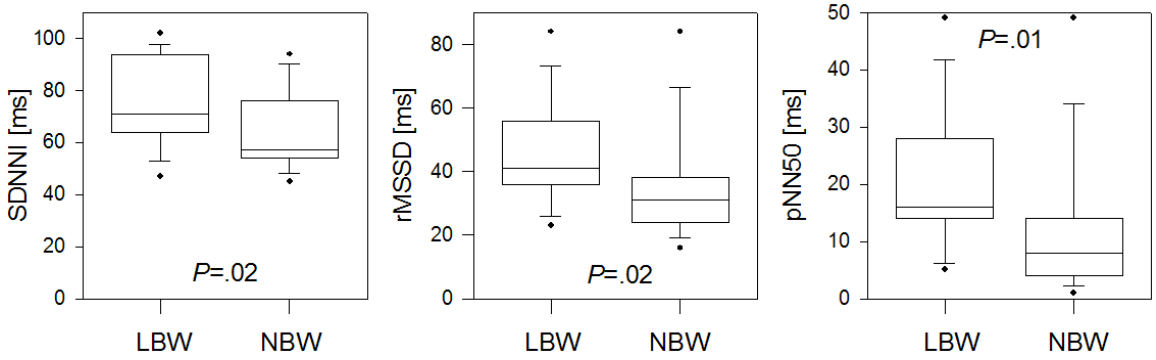

Figure 2. Parasympathetic heart rate variability parameters of the time domain. Plots with medians, 10th, 25th, 75th, and 90th percentiles. *P*-values of the comparison between the groups are given in each graph.

All subjects had valid electrocardiogram recordings over the entire 24-hour period and more than 90% of the RR-intervals entered the analysis. There was a trend towards higher mean RR-intervals in the LBW group as compared to the NBW group (**Figure 1**). The circadian variations of the HRV were comparable in both groups (data not shown). In the frequency domain, the total power and very low frequency fluctuations were significantly greater in the LBW group (**Figure 1**). There was a trend for greater low and high frequency fluctuations. However, this trend did not reach statistical significance (**Figure 1**). There was also a tendency for a lower sympathovagal balance (ratio low-to-high frequency) in the LBW group (**Figure 1**). In the time domain, the parameters of overall modulation SDNN and SDANN were similar in both groups (LBW versus NBW: SDNN 161±9 vs. 151±6 ms, P>.50; SDANN 139±8 vs. 138±6 ms, P>.50). The parasympathetic parameters SDNNI, rMSSD, and pNN50, however, were significantly higher in the LBW group (**Figure 2**). All of these effects could similarly be observed when data were separately analysed by gender. However, due to the smaller sample size of

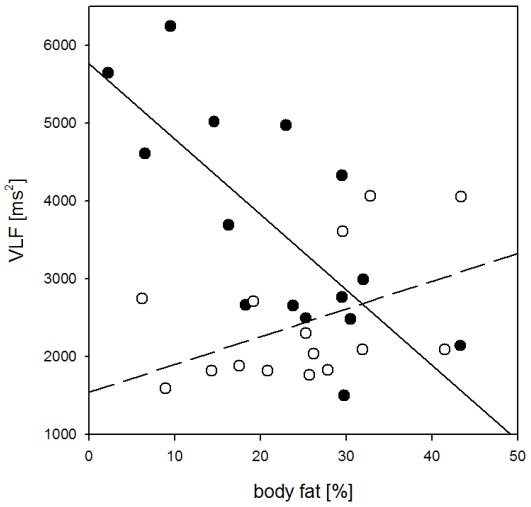

Figure 3. Correlations between the body fat fraction and the very low frequency (VLF) fluctuations of the HRV (LBW: R=-.75, P<.01; NBW: R=.45, P=.09). LBW: ●, solid line; NBW: ○, dashed line.

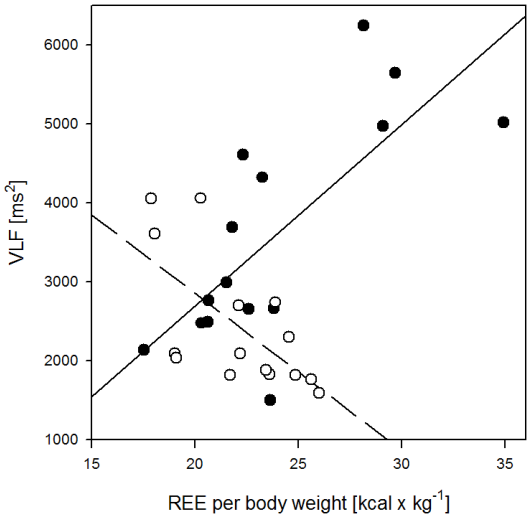

Figure 4. Correlations between the resting energy expenditure (REE) per body weight and the very low frequency (VLF) fluctuations of the HRV (LBW: R=.62, P=.01; NBW: R=-.65, P=.01). LBW: ●, solid line; NBW: ○, dashed line.

these subgroups the differences did not reach statistical significance.

Only in the LBW group there were inverse correlations between parameters of the HRV and parameters of body fat. These correlations were significant for the body fat fraction and RR-intervals (R=-.65, P<.01), total power (R=-.63, P=.01), very low frequency fluctuations (R=-.75, P=.001), and SDNNI (R=-.56, P=.03), respectively. In contrast, a trend for positive correlations could be observed in the NBW group (RR-intervals: R=.44; P=.11; total power: R=.46, P=.08; very low frequency fluctuations: R=.45, P=.09; SDNNI: R=.394, P=.15). The correlations between the body fat fraction and the very low frequency component are shown in **Figure 3**. Similar results were obtained when BMI was correlated with the same parameters of HRV in each group. Moreover, there were significant contrary correlations between the resting energy expenditure per body weight and the very low frequency fluctuations with a positive correlation in the LBW group and a negative correlation in the NBW group (**Figure 4**). No relations occurred between the parameters HRV and blood pressure, insulin resistance, and parameters of the hypothalamic-pituitary-adrenocortical axis, respectively.

Discussion

The primary finding of the present study is a higher HRV and a trend for higher RR-intervals, i.e. a lower heart rate, in the ambulatory 24-hour electrocardiogram of subjects with LBW as compared to a thoroughly matched control group with NBW. Accordingly, there was also a trend for a lower resting pulse in the LBW group. Higher HRV may in part be due to a lower heart rate. However, the trend for a lower heart rate in subjects with LBW is also a remarkable observation. Heart rate is an independent predictor of mortality in men and women with or without cardiovascular mortality [22] and was negatively correlated with birth weight when assessed in adults aged 46 to 54 years in an epidemiological survey [11]. In this age, however, established cardiac risk factors associated with LBW such as glucose intolerance, diabetes, and hypertension may have caused an impaired cardiac function. Our subjects were, in contrast, carefully selected to not have any interfering disease. In this group the autonomic control of heart rate had a rather favourable tendency compared to the control group. Thus, the view that the autonomic nervous function is generally deteriorated by adverse intrauterine events throughout life must be challenged.

The higher total power in the frequency domain of HRV was predominantly caused by long wave modulations in heart rate (i.e. very low frequency fluctuations). The very low frequency component accounts to approximately 95% of total power whereas only a relatively small amount

of variation is attributed to the high and low frequency components, respectively, which are known to be under parasympathetic and latter also sympathetic control [23]. Nevertheless, the very low frequency fluctuations also depend on vagal activity as they almost entirely abolish by the parasympatholytic action of atropine [24]. Although high and low frequency compounds were not significantly different in subjects with LBW as compared to controls, there was a trend for greater high frequency fluctuations and also for a shift of the low-to-high frequency quotient towards parasympathetic predominance in the LBW group. Moreover, the parasympathetic parameters of the time domain were significantly higher in the LBW subjects. In a previous study, Jones and coworkers specifically related alterations of parasympathetic function in adults to birth weight. They found a negative correlation between parasympathetic withdrawal during a stress test and birth weight in women but not in men [15]. No relation was found in the baseline characteristics. In respect to this parameter, a case control study as ours with a marked difference in birth weight between the groups might offer a more detailed view.

The very low frequency component of the HRV is also thought to be associated with the thermoregulation and the function of renin-angiotensin-aldosterone system [24]. Renin and aldosterone were not significantly different between the groups. Since we did not evaluate the activity of the renin-angiotensin-aldosterone system in detail we are unable to conclude an impact of the system on the HRV from these data. However, we have previously hypothesized that a lower muscle sympathetic nerve activity in subjects with low birth weight could be associated with lower thermogenesis [10]. We therefore also measured the resting energy expenditure in the present study. No significant difference between the groups was detectable. When related to each other, however, there were contrary correlations between the energy expenditure per body weight and the very low frequency fluctuations. The very low frequency component of the power spectrum is known to be enhanced after induction of thermogenesis by a carbohydrate rich meal [25]. It has been proposed that the slow wave modulation of the autonomic system is related to the activity of β3-receptor stimulation in the adipose tissue [26]. Our data demonstrate that high resting energy expenditure is associated with lower long wave fluctuations of heart rate in subjects with NBW; the opposite can be seen in subjects with LBW. Both the very low frequency component and the resting energy expenditure decline throughout life time [27]. The close and positive relation between both parameters in individuals with LBW could promote an unfavourable development when these subjects get older resulting in a stronger decrease of energy expenditure in combination with a stronger decrease in autonomous modulation.

Blood pressure, heart rate, and blood pressure modulation have previously been shown to be closely associated to BMI only in LBW but not in NBW subjects [20, 21]. Accordingly, we found a negative correlation between HRV and measures of body fat (including BMI) only in the LBW but not in NBW group. BMI and HRV do not correlate in subjects without evidence of heart disease [28]. Our findings underline the importance of body weight in subjects with LBW and could also explain why weight gain in this group is more detrimental than in subjects with normal fetal growth. Subjects with LBW tend to become obese [29] and the assumption that the autonomic nervous function is involved in the higher cardiovascular risk may be true if the weight gain in later life is taken into account. Our study groups, however, consisted of relatively young subjects only differing in birth weight while anthropometric characteristics were thoroughly matched. This approach takes age, gender, and the present body weight out of the equation. The higher HRV in the LBW group should therefore be interpreted in the light of the young age and the relatively low BMI of the probands. As indicated above, weight gain in later life might even invert the group differences in the autonomic nervous function.

In summary, when young and healthy adults with LBW are matched to same aged individuals with similar body proportions but with NBW, they are found to have more favourable measures of cardiac autonomous nervous function. Our study also shows that energy expenditure and body weight in individuals with LBW are more tightly associated with the autonomous nervous function than in normal controls. Thus, weight gain and the loss of autonomous modulation could progress more rapidly in ageing subjects with LBW than in their counterparts with NBW. We conclude that higher cardiovas-

cular risk in individuals with LBW is rather secondary to weight gain than to a primary autonomous nervous dysfunction.

Disclosure of conflict of interest

On behalf of all authors, the corresponding author states that there is no conflict of interest.

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