

# Vasomotor sympathetic outflow in the muscle metaboreflex in low birth weight young adults

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**Abstract:** A growing body of evidence suggests that low birth weight (LBW) offspring are associated with long-term structural and functional changes in cardiovascular and neuroendocrine systems. We tested the hypothesis that muscle metaboreflex activation produces exaggerated responses in cardiac autonomic tone (represented by heart rate variability ratio) and cutaneous vascular sympathetic tone (represented by plethysmography pulse wave amplitude) in LBW compared to normal birth weight (NBW) young adults. We recruited 23 LBW (18 females and five males) and 23 NBW (14 females and nine males) University of Zimbabwe students with neonatal clinical cards as proof of birth weight at term. Resting electrocardiogram, pulse waves, and blood pressures were recorded. Participants then underwent a static/isometric handgrip exercise until fatigue and a post-exercise circulatory arrest period of 2 minutes. We observed (results mean  $\pm$  standard deviation) a greater mean increase in heart rate variability ratio from baseline to exercise for LBW compared to NBW individuals ( $1.015 \pm 1.034$  versus [vs]  $0.119 \pm 0.789$ , respectively;  $P < 0.05$ ). We also observed a greater mean decrease in plethysmography pulse wave amplitude from baseline to exercise ( $-1.32 \pm 1.064$  vs  $-0.735 \pm 0.63$ ;  $P < 0.05$ ) and from baseline to post-exercise circulatory arrest ( $-0.932 \pm 0.998$  vs  $-0.389 \pm 0.563$ ;  $P < 0.05$ ) for LBW compared to NBW individuals. We conclude that LBW may be associated with an exaggerated sympathetic discharge in response to muscle metaboreflex.

**Keywords:** blood pressure, heart rate variability, plethysmography pulse

## Introduction

A growing body of evidence suggests that low birth weight (LBW) offspring are associated with an increased risk for coronary artery disease,<sup>1</sup> hypertension,<sup>2</sup> and heart failure.<sup>3</sup> Previous studies have also shown that exaggerated vasoconstrictive and neuroendocrine responses are associated with development of hypertension in adults and may function as markers for preclinical or pathophysiologic phases of hypertension.<sup>4,5</sup> LBW is associated with an increased sympathetic nerve activity and therefore predisposing LBW individuals to development of hypertension in adulthood.<sup>6-8</sup>

Static/isometric handgrip exercise evokes an increase in heart rate, mean arterial pressure, muscle and skin sympathetic nervous activity. Forearm blood circulatory arrest just before cessation of the exercise causes blood pressure (BP) to remain above resting levels.<sup>6,9</sup> These responses are evoked by two neural mechanisms, components of the muscle metaboreflex, which are: central command (neural signals of central origin) and the exercise pressor reflex (EPR, a reflex arising from exercising muscle).<sup>10</sup> The central command has a minor role in cardiovascular regulation during exercise. The EPR is a feedback system arising from thinly myelinated mechanosensitive (group III/A $\delta$ -fibers)

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and unmyelinated metabosensitive (group IV/C-fibers) afferents in the skeletal muscle.<sup>10</sup> When oxygen delivery to active skeletal muscle is insufficient to meet the metabolic demands, metabolites, eg, lactic acid, adenosine, diprotonated phosphate, potassium, H<sup>+</sup>, and arachidonic acid products among others, accumulate within active muscle and stimulate group III and group IV afferent neurons leading to a reflex sympathetic discharge (the muscle metaboreflex).<sup>1,2,10</sup> The EPR is exaggerated in hypertension and related conditions like heart failure, with the over activity of the afferent arms (mechanosensitive and metabosensitive afferents) of this reflex being the cause of the exaggeration.<sup>3</sup>

Pulse wave amplitude (PWA) is useful in monitoring sympathetic influences on skin blood flow in the finger and heart rate variability (HRV) ratio monitors the cardiac autonomic tone.<sup>9,11</sup>

Studies have assessed the modulation of the sympathetic outflow by the muscle metaboreflex.<sup>9,12</sup> However, no study has compared the modulation of the sympathetic nerve activity to the cardiovascular system by the muscle metaboreflex, between individuals with LBW and normal birth weight (NBW). In this study, we hypothesized that individuals born with LBW would respond with exaggerated sympathetic discharge to the heart and the vascular system during stimulation of the muscle metaboreflex, compared to NBW individuals.

## Methodology

### Participants

The study was conducted in the Exercise Laboratory in the Department of Physiology, University of Zimbabwe. Forty-six healthy voluntary participants were drawn from students at the University of Zimbabwe. Before the actual day of study, all participants were provided with the full details of the study and we familiarized each subject with the protocol. Informed consent was sought and obtained from the participants. The study participants were screened using a self-administered questionnaire. Participants were recruited on the basis of documented proof of birth weight in the form of a Ministry of Health, Child Health Card. The exclusion criteria were 1) age <18 or >25 years; 2) a history of cardiovascular disease or hypertension (defined as the current use of antihypertensive medication or resting BP  $\geq$ 140/90 mmHg); 3) previous endurance training; 4) pre-term birth; 5) body mass index (BMI) more than 24.5 kg/m<sup>2</sup>. The participants were assigned into two groups, LBW and NBW. LBW was defined as birth weight <2,500 g at term. Participants in the two groups were matched for BMI. Ethical permission was granted by Joint Parirenyatwa Hospital

and College of Health Sciences Research Ethics Committee and the Medical Research Council of Zimbabwe.

### Anthropometric and resting measurements

Weight and height were measured with the participants putting on light clothing and without shoes. BMI for each participant was calculated (kg/m<sup>2</sup>). Resting BPs were measured. Resting computerized electrocardiogram (ECG) recording was obtained from lead II and resting pulse wave recordings were obtained from the finger pulse plethysmography for 5 minutes, using iWorx research system hardware (IWX/214) (iWorx Systems, Inc., Dover, NH, USA) and the Labscribe 2 software.

### Exercise protocol

In the 24 hours before exercise, participants were asked to abstain from taking alcohol, energy drinks, and caffeinated products. Participants underwent a static/isometric handgrip exercise performed with the dominant hand using a handgrip dynamometer (Lab BSL 3.7.7; BIOPAC, Goleta, CA, USA) at 40% maximum voluntary contraction (MVC) until fatigue to ensure that they have all reached a common metabolic end point. This level of force was chosen since it has been previously shown that handgrips sustained at 40% and 60% of MVC elicited a comparable increase in muscle sympathetic nerve activity.<sup>12</sup> Once the exerted force declined to <80% of the desired force (40% MVC) for >2 seconds, a 2-minute post-exercise circulatory arrest (PECA) phase began using an arm cuff inflated to a pressure >200 mmHg. During the static handgrip exercise and PECA participants were instructed to avoid breath holding. After PECA period, participants were given a 5-minute recovery period. ECG and pulse wave recordings were obtained during the period of exercise, PECA, and recovery.

### Data analysis

Frequency domain measures of ECG R-R variability were used to estimate the high frequency (HF, 0.15–0.4 Hz) and low frequency (LF, 0.04–0.15 Hz) power. The HF power peak represents modulation of efferent parasympathetic (vagal) activity by ventilation, but only in the presence of sinus rhythm. The LF power peak represents combined modulation of efferent parasympathetic and efferent sympathetic nervous system activity by baroreflex activity. Overall the amplitudes of LF and HF power reflect modulation of sinus node firing rate and the LF/HF ratio (HRV ratio) has been proposed as an index of sympathovagal balance.<sup>9,13</sup> However, very LF indices could not

**Table 1** Baseline demographic characteristics of the study sample

	Total (n=46) Mean ± SD	NBW (n=23) Mean ± SD	LBW (n=23) Mean ± SD	P-value
Age (years)	20.24±0.95	20.13±1.01	20.35±0.89	0.443
Body mass index (kg/m <sup>2</sup> )	20.88±2.0	20.38±2.22	21.88±1.65	0.091
Mean systolic BP (mmHg)	113±11.66	112±11.4	115±12	0.403
Mean diastolic BP (mmHg)	73±9.27	71±8.5	74±10	0.213
Mean heart rates (beats/min)	83±10.47	82±11.3	84±9.7	0.532
Birth weight (grams)	2.744±0.89	3.248±0.43	2.241±0.19	0.0001*

**Note:** \*Indicates that birth weight was the only baseline variable where there was a significant difference between the two groups.

**Abbreviations:** NBW, normal birth weight; LBW, low birth weight; BP, blood pressure.

be used since they require power spectra that are more than 5 minutes long, which was not in keeping with our experimental protocol. The IWORX Labscribe 2 software which is part of the physiological system was used to analyze these variables (iWorx Sytems, Inc.). SPSS software version 16.0 (SPSS Inc., Chicago, IL, USA) was used to analyze the data. Independent samples two-tailed Student's *t*-test at 5% level of significance was used to compare the various means of the cardiovascular parameters between NBW and LBW individuals ( $P < 0.05$  was considered significant). The data are represented as mean ± standard error of the mean on figures and as mean and standard deviation (SD) in tables.

## Results

A total of 23 LBW (18 females and five males) and 23 NBW (14 females and nine males) black adults, with a median age of 20 years (18–25 years), successfully completed the experiment. The baseline characteristics and mean MVC, time to fatigue as well as the heart rate changes are shown in Tables 1 and 2, respectively.

### HRV ratio

The trends of mean HRV ratios for LBW and NBW individuals during the experimental protocol are shown in Figure 1. The mean increase in HRV from baseline to exercise was greater

for LBW compared to NBW individuals (1.015±1.034 versus [vs] 0.119±0.789, respectively;  $P < 0.05$ ). However, the mean increase in HRV ratio from baseline to PECA and from baseline to recovery was not significantly different between LBW and NBW individuals (Table 3).

### PWA

The trends of the mean PWA for LBW and NBW individuals during the experimental protocol are shown in Figure 2. The mean decrease in PWA from baseline to exercise was greater for LBW compared to NBW individuals (−1.32±1.064 vs −0.735±0.63, respectively;  $P < 0.05$ ). The mean decrease in PWA from baseline to PECA was also greater for LBW compared to NBW individuals (−0.932±0.998 vs −0.389±0.563, respectively;  $P < 0.05$ ). However, the mean change in PWA from baseline to PECA was not significantly different between LBW and NBW individuals (Table 3).

## Discussion

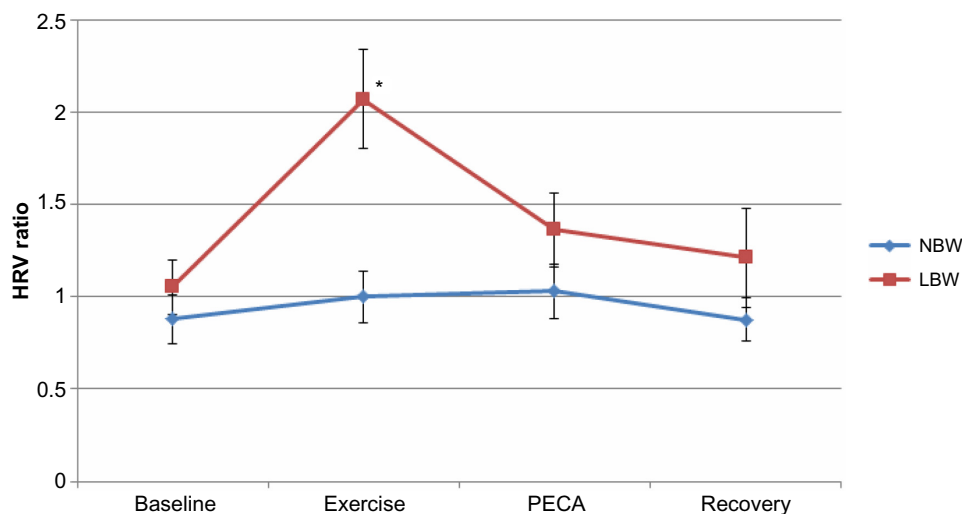
HRV ratio and PWA responses to activation of the muscle metaboreflex are exaggerated in LBW compared to NBW individuals. This suggests that the EPR, which is involved in tight regulation of the cardiovascular response to exercise, is persistently dysregulated into early adulthood for LBW individuals.<sup>10,14</sup>

**Table 2** Mean heart rates during entire protocol and mean maximum voluntary contraction and time to fatigue

	Total (n=46) Mean ± SD	NBW (n=23) Mean ± SD	LBW (n=23) Mean ± SD	P-value
MVC (kg)	46.1±13.4	45.7±13.4	46.5±13.7	0.829
TTF (seconds)	141.1±13.9	141.8±13.8	141.2±14.3	0.884
HR-B (beats/min)	83±10.47	82±11.3	84±9.7	0.532
HR-E (beats/min)	94.9±10.9	86.4±8.7	103.4±4.1	0.0001*
HR-PECA (beats/min)	89.8±8.2	88.1±7.6	91.6±8.6	0.148
HR-R (beats/min)	84.6±9.3	83.9±9.8	85.3±8.9	0.595

**Note:** \*Indicates a significant difference.

**Abbreviations:** MVC, maximum voluntary contraction, TTF, time to fatigue; NBW, normal birth weight; LBW, low birth weight; SD, standard deviation; PECA, post-exercise circulatory arrest; HR-B, heart rate at baseline; HR-E, heart rate during exercise; HR-R, heart rate during recovery.



**Figure 1** Mean heart rate variability (HRV) ratio responses during rest, static/isometric handgrip exercise, post-exercise circulatory arrest (PECA) and recovery period, in NBW and LBW individuals.

**Note:** \* $P < 0.05$ .

**Abbreviations:** NBW, normal birth weight; LBW, low birth weight.

HRV ratio for LBW was modestly elevated at rest, although there was no significant difference between the HRV ratios of the two groups. This may be due to LBW individuals being prenatally programmed to increase sympathetic nerve activity secondary to the adverse intra-uterine conditions that the fetus will be subjected to.<sup>14</sup> Studies have shown that the EPR is exaggerated in hypertensive rats, in part due to over activity of the afferents.<sup>3,13</sup> We investigated the efferent component of the EPR; the afferent pathway has not been investigated in LBW subjects. In hypertensive subjects, exercise evokes an excessive increase in BP from a chroni-

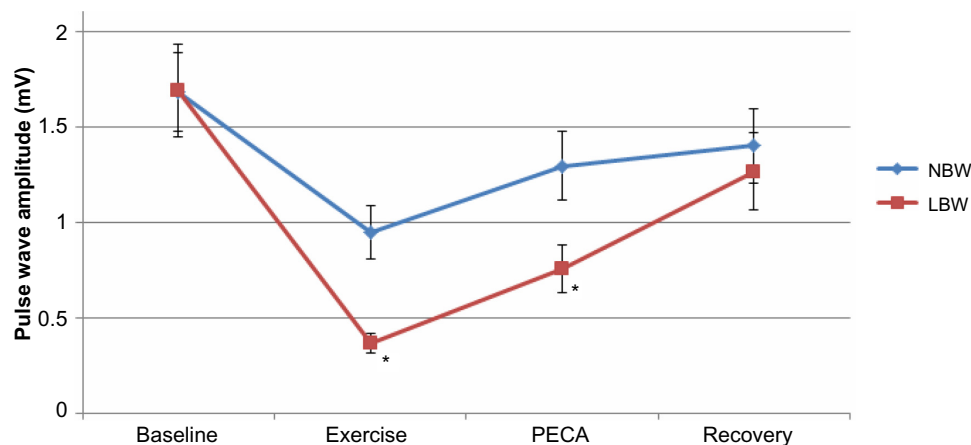
cally elevated resting value.<sup>14</sup> During exercise, compared to baseline, LBW individuals experienced an exaggerated sympathetic response to the static handgrip. This was indicated by a significant mean increase in HRV ratio (increased HRV ratio reflects an increase in sympathetic tone compared to the vagal tone) as well as a significant mean decrease in PWA (Table 3). LBW and NBW individuals had an increased sympathetic discharge to the heart and the peripheral vessels, although that of LBW individuals was exaggerated. The increased sympathetic discharge we observed in both groups is in keeping with the findings by Jarvis et al<sup>12</sup> and Ichinose et al<sup>2</sup> who described an increase in sympathetic discharge in normal individuals. However, in these two studies birth weight was not considered as a variable while in our study it was.<sup>9,12</sup> The mean increase in HRV ratio from baseline to PECA decreased but was not significantly different between the two groups (Table 3), whilst the mean decrease in PWA showed a significant difference between the two groups (LBW and NBW). This indicated a potentiated sympathetic discharge in response to accretion of metabolites in the once active muscle, with the differences in the sympathetic discharge to the heart and the peripheral vessels during PECA being probably due to the fact that there is organ specific sympathetic nerve activity and regional differences in this nerve activity as is experienced particularly in cardiovascular diseases.<sup>12,15,16</sup> Animal models in which there was ganglionic and  $\alpha$ -adrenergic blockage using hexamethonium and phentolamine, respectively, showed an abolishment of the exaggerated pressor response to exercise, suggesting that these exaggerated hemodynamic responses were mediated,

**Table 3** Mean changes in HRV ratio and PWA from baseline to exercise, PECA, or recovery

	LBW	NBW	P-value
Mean change in HRV ratio from B-E $\pm$ SD	1.015 $\pm$ 1.034	0.119 $\pm$ 0.789	0.002*
Mean change in HRV ratio from B-PECA $\pm$ SD	0.311 $\pm$ 0.679	0.15 $\pm$ 0.71	0.436
Mean change in HRV ratio from B-R $\pm$ SD	0.157 $\pm$ 1.275	-0.003 $\pm$ 0.638	0.593
Mean change in PWA from B-E (mV) $\pm$ SD	-1.320 $\pm$ 1.064	-0.735 $\pm$ 0.63	0.028*
Mean change in PWA from B-PECA (mV) $\pm$ SD	-0.932 $\pm$ 0.998	-0.389 $\pm$ 0.563	0.029*
Mean change in PWA from B-R (mV) $\pm$ SD	-0.421 $\pm$ 1.134	-0.284 $\pm$ 0.635	0.615

**Notes:** \* $P < 0.05$  showing a significant difference between LBW and NBW. B-E represents mean change in PWA/HRV ratio from baseline to exercise; B-PECA represents mean change in PWA/HRV ratio from baseline to PECA; B-R represents mean change in PWA/HRV ratio from baseline to recovery.

**Abbreviations:** HRV, heart rate variability; PWA, pulse wave amplitude; PECA, post-exercise circulatory arrest; SD, standard deviation; NBW, normal birth weight; LBW, low birth weight.



**Figure 2** Mean pulse wave amplitude during rest, static/isometric handgrip exercise, post-exercise circulatory arrest (PECA) and recovery period, in NBW and LBW individuals.

**Note:** \* $P < 0.05$  NBW versus LBW.

**Abbreviations:** NBW, normal birth weight; LBW, low birth weight.

in part, by the abnormally large EPR-induced sympathetic nerve activity.<sup>14</sup> This might be the same reason why the LBW individuals in our study had an exaggerated response to the EPR. Exaggerated neuroendocrine and vasoconstrictive responses have been shown to predict the development of hypertension in adults.<sup>4</sup> Therefore, the exaggerated EPR response, in our study, may function as a marker for the pathophysiological phases of hypertension.

The insignificant difference in mean increase in HRV ratio and significant difference in mean decrease in PWA during PECA may also suggest an increase in cardiac parasympathetic tone caused by buffering by the arterial baroreflex.<sup>9</sup> Insensitivity of baroreceptors, which buffer BP increases during exercise, has been reported in hypertensive individuals and individuals with heart failure.<sup>13</sup> This might also be present in LBW individuals since they are predisposed to these conditions; therefore, future studies to investigate the baroreceptor sensitivity in LBW individuals are warranted.

Overall, the totality of these findings support the hypothesis that LBW young adults have an exaggerated EPR response that is measurable long before progression to the cardiovascular disorders that LBW individuals are prenatally programmed to develop. The EPR is dysfunctional in cardiovascular disorders such as heart failure and hypertension. This leads to an increased sympathetic discharge underlying the exaggerated increase in BP, heart rate, and peripheral resistance during acute physical activity.<sup>3,10,13</sup>

## Conclusion

We concluded that LBW may be associated with an exaggerated vasomotor sympathetic outflow during the muscle

metaboreflex activation during exercise in normotensive young adults. LBW individuals may have an exaggerated EPR response.

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## Disclosure

The authors report no conflicts of interest related to this paper.

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