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Short-Term Heart Rate Variability in a Population-Based Sample of 10-Year-Old Children

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Abstract

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Heart rate variability (HRV) is a non-invasive quantitative marker of cardiac autonomic function derived from continuous electrocardiogram (ECG) recordings. Normative HRV values and development factors have not been established in pediatric populations. The objective was to derive referent time- and frequency-domain HRV values for a population-based sample of children. Children aged 9–11 years (N = 1,036) participated in the Québec Longitudinal Study of Child Development cohort cardiovascular health screening. Registered nurses measured anthropometrics (height, weight) and children wore an ambulatory Holter monitor to continuously record an ECG signal. HRV variables included time (SDNN, pNN50, RMSSD, SDANN) and frequency (HF, LF, LF/HF ratio) domain variables. Normative HRV values, stratified by age, sex, and heart rate, are presented. Greater heart rate (β_{avg} = −0.60, R^2_{avg}=0.39), pubertal maturation (β_{avg} = −0.11, R^2_{avg}=0.01), later ECG recording times (β_{avg} = −0.19, R^2_{avg}=0.07), and higher diastolic blood pressure (β_{avg} = −0.11, R^2_{avg}=0.01) were significantly associated with reduced HRV in 10-year-old children. The normative HRV values permit clinicians to monitor, describe, and establish pediatric nosologies in primary care and research settings, which may improve treatment of diseases associated with HRV in children. By better understanding existing values, the practical applicability of HRV among clinicians will be enhanced. Lastly, developmental (e.g., puberty) and procedural (e.g., recording time) factors were identified that will improve recording procedures and interpretation of results.

Keywords

Heart rate variability; Respiratory sinus arrhythmia; Vagal tone; Epidemiology; Children; Normative data

Introduction

Heart rate variability (HRV) is a non-invasive measure of cardiac autonomic function derived from continuous electrocardiogram (ECG) recordings [1]. In primary health care settings, ECG recordings and HRV are used by physicians as part of an initial screening tool, for early diagnosis of potentially detrimental illnesses (e.g., for suspected cardiac abnormalities), and to monitor physiological processes using HRV as a physiomarker [15]. The clinical relevance of HRV was first acknowledged when alterations in inter-beat intervals were observed prior to fetal distress [13]. Since then, reduced HRV, reflective of the inability or attenuation of the autonomic regulatory capacity to support flexible adjustments in response to the environment [40], has been implicated in a number of pediatric cardiac (e.g., arrhythmias, heart disease) [39] and non-cardiac pathologies (e.g., obesity; 6–7). Growing evidence suggests that cortico-subcortical networks which regulate autonomic balance, as indicated by low HRV, may structurally and functionally link psychological processes (e.g., negative affective states) with adverse health conditions, including immune dysfunction, emotional dysregulation, as well as poor use of cognitive resources [40].

Despite the increased use of HRV in the research literature, normative pediatric values are limited and few studies report referent values [18, 43]. Existing referent values are based on studies with methodological limitations including use of small samples (e.g., 10), combining

broad age ranges [18], use of convenience “healthy controls” [5, 35] or clinical samples [3], varying duration of ECG recording (e.g., 2 min to 24 h), inaccurate frequency bandwidths for spectral analysis parameters [7, 10, 26], and reporting HRV values using inconsistent units (e.g., beats/min^2, log transformed, absolute, normalized). Further, important developmental factors are often not considered. Limited findings suggest younger age [19, 37], pubertal status [5], greater physical activity [5, 26], and consolidated sleep [18, 19] are associated with a predominance of parasympathetic activity and reduced sympathetic modulation; yet, these have not been considered when deriving normative values. Collectively, these limitations hinder and bias interpretation and their practical applicability among clinicians.

In sharp contrast, numerous adult population-based studies report referent HRV values, stratified by sex, age, and heart rate, and account for factors including adiposity, blood pressure, medication use, and physical activity [2, 21, 38, 39, 42]. Unique developmental changes and pediatric milestones preclude these adult findings from being extrapolated to children. Altogether, the state of knowledge regarding “normal” HRV values in children is rather haphazard [8, 23, 37, 43]. The objectives of the present study were twofold. The first objective was to provide time- and frequency-domain HRV values for a population-based sample of 10-year-old children. The second objective was to comprehensively assess associations with developmental factors on HRV.

Method

Participants

Children (N = 1,052) participated in the population-based Québec Longitudinal Study of Child Development (QLSCD), an ongoing longitudinal study conducted by the Institut de la statistique du Québec [14]. Using a multistage cluster (by region and municipality) random sampling strategy, the original birth cohort was selected from the Quebec Ministry of Health birth registry, which was representative of singleton births from 1996 to 1998. Exclusion criteria included serious medical pathology, infants born <24 or >42 weeks gestation (0.1 %) or those with unknown gestational age (1.3 %), families living in Aboriginal territories or remote regions of Québec, and parents who did not understand French or English. The original QLSCD sample represented 97.8 % of the target population and was approved by the ethics review boards of the Institut de la statistique du Québec, the Centre Hospitalier Universitaire Sainte-Justine, the Louis-Hippolyte Lafontaine Hospital, and the Université de Montréal Faculty of Medicine. Present data are derived from the cross-sectional, cardiovascular health screening at age 10, conducted between 2006 and 2008, as part of the QLSCD annual follow-up. (Further information on methodology http://www.jesuisjeserai.stat.gouv.qc.ca/default_an.htm).

Measures

ECG Signal Acquisition—Following a 20 min resting period, continuous raw ECG data were acquired, digitized, and recorded (8500 Marquette MARS Holter monitor; GE Marquette Medical Systems, Milwaukee, Wisconsin, USA) during a standardized procedure. Following skin preparation, pre-gelled silver chloride electrodes were attached in a Lead II

configuration. The recording protocol was standardized and lasted an hour in duration (SD = 21 min). All monitors were calibrated, and start and end times were noted and recorded by the nurse (i.e., event marker); the majority of recordings took place between 8 and 11 am.

ECG Signal Processing—ECG data were uploaded on the MARS® Holter Analysis Workstation (GE Marquette Medical Systems, Milwaukee, Wisconsin, USA) for signal interpretation and analysis. Beat-by-beat visual inspection of the shape, trend, and length of each QRS complex was identified based on standard Marquette algorithms for QRS labeling and further verified by visual inspection from a qualified trained professional. ECG data were sampled at 1,024 samples/300 s, and RR intervals were automatically filtered. The removal of artifacts was based on a 20 % change from the previous signal as a criterion [17].

Data were processed by Fast Fourier Transform (FFT) spectral analysis method. Frequency-domain variables included very low frequency (VLF, 0.0033–0.04 Hz), low frequency (LF, 0.04–0.15 Hz), high frequency (HF, 0.15–0.4 Hz), and LF:HF ratio; these were quantified and expressed in absolute units. Time-domain variables included standard deviation of all normal sinus RR intervals (SDNN), standard deviation of the averaged normal sinus RR intervals for all 5-min epochs (SDANN), SDNNi (mean of the standard deviations of all normal sinus RR intervals for all 5-min epochs), root mean square of the successive normal sinus RR interval difference (rMSSD), and percentage of successive normal sinus RR intervals <50 ms (pNN50).

Blood Pressure

A pediatric- or appropriately-sized occlusion cuff was attached to the medial surface of the right arm over the brachial artery using an oscillometric instrument (BpTRU, model BPM-100, VSM MedTech Ltd, Vancouver, Canada) according to standardized procedures [47]. Units were routinely calibrated with a mercury sphygmomanometer to ensure precision. Following a seated resting baseline, five readings were taken at 1 min intervals; the mean of the last four readings was calculated for systolic and diastolic blood pressure (SBP, DBP).

Anthropometrics

A registered nurse assessed anthropometrics. Waist circumference was measured at the narrowest part of the abdomen, midway between the lowest rib and the iliac crest. Height (shoes off) and weight (dressed in light clothing) were measured in duplicate; triplicate measures were taken if measures differed by 0.5 cm or 0.2 kg, respectively. The mean of the two closest measurements was used. Body mass index (BMI) [weight kg/(height m^2)] was calculated and converted to age-and sex-specific BMI *Z* scores [28].

Puberty

Using a validated self-report measure of puberty (Growing and Changing Questionnaire; [29]), two stages of pubertal development were assessed: gonadarche (breast and genital development) and adrenarche (pubic hair). Youth indicated their pubertal stage based on sex-specific illustrations corresponding to Tanner stages I–V of prepubertal to complete sexual

maturity. This method has good reliability and validity against gold-standard physician examination (r = 0.77–0.91) [25, 27].

Sleep

Parents reported the child's usual bed- and wake-times over the week (includes school and non-school nights). Typical sleep duration was calculated as the difference between bed- and wake-times. Subjective estimates of sleep duration show significant correlations with objective measures of sleep duration in youth (actigraphy: r = 0.53–0.79) [41, 49].

Gestational Age at Birth

Gestational age at birth (i.e., sum of pregnancy duration and chronological age of the child, calculated in weeks), birth weight (in grams), and pregnancy status (full-term vs. premature) were obtained from medical birth records.

Physical Activity, Medication, and Caffeine Intake

Parents reported whether their child exercised vigorously, consumed caffeine products (e.g., chocolate, energy drinks), or took medication 24 h prior to the ECG recording (response options yes or no).

Statistical Analyses

Data were entered, verified, and analyzed with IBM SPSS Statistics v.20 software (SPSS, Inc., Chicago, IL). Frequency-domain variables (VLF, LF, HF) were natural log transformed due to skewness. To yield normative values, mean and standard deviations were first derived for HRV parameters stratified by sex and heart rate reference ranges based on age at the 5th, 25th, 50th, 85th, and 95th percentiles [44]. Next, linear regression analyses were used to determine the unique variance explained by each covariate for the HRV parameters. Finally, stepwise regression models were used to identify the most salient covariates, when all were entered simultaneously.

Results

Of the original 1,052 participants completing the cardiovascular screening at the QLSCD follow-up visit, 16 children were excluded due to missing ECG recordings (n = 12) or insufficient recording duration (<30 min, n = 4), yielding a final sample of 1,036. Participant demographics are presented in Table 1. Average gestational age at birth was 60.7 weeks (SD = 1.1), birth weight was 3,420.1 g (SD = 510.1), and 94.8 % were full-term. Children had no cardiovascular pathology (e.g., bradycardia, fibrillation, premature contraction) based on ECG review by a board-certified cardiologist (PP). ECG recordings were of excellent quality: >97 % of data were analyzable, artifact time was <8 min (0.09 %), and no recordings had >20 % noise or ectopic beats. Most children refrained from strenuous physical activity (96.4 %), caffeine (87.6 %), and medication use (82.0 %) for 24 h prior to the ECG recording.

Mean values and standard deviations for heart rate, RR intervals, and HRV variables are presented in Table 1. Sex differences were observed; boys had significantly greater HRV

values for all time-and frequency-domain variables. Due to age-related changes in heart rate [9, 44], normative HRV values are age- and sex-stratified and presented for the 5th, 25th, 50th, 85th, and 95th heart rate percentiles (see Table 2).

Regression analyses revealed several significant covariates for HRV parameters. Overall, female sex, higher SBP, DBP, and heart rate, later recording start time, advanced pubertal development, and shorter sleep duration were associated with reduced HRV (Table 3). When all covariates were included in the models simultaneously, heart rate (β_{avg} = −0.60, R^2_{avg}=0.39), ECG recording start time (β_{avg} = −0.19, R^2_{avg}=0.07), gonadarche puberty stage (β_{avg} = −0.11, R^2_{avg}=0.01), and DBP (β_{avg} = 0.11, R^2_{avg}=0.01) emerged as the most pronounced covariates across all the HRV parameters (data not shown for parsimony).

Discussion

Existing pediatric HRV normative values are limited, and developmental factors have not been systematically evaluated in children. The first objective was to provide time-and frequency-domain HRV values for a large, population-based sample of 10-year-old children. Compared to previously reported HRV values with short-term recordings (2–60 min) in same-aged children, the present study had comparable values for SDNN (*M* = 87 ms vs. range 60–72 ms) [19, 31, 45, 46], LF (in ms^2: *M* = 1,493 ms^2 vs. range 38.7–1,011 ms^2 [19, 31, 48]; log transformed: *M* = 7.1 vs. range 3.5–6.4 [4, 5, 26, 31]), HF (in ms^2: *M* = 829 ms^2 vs. range 52–1,559 ms^2 [19, 31, 48]; log transformed: *M* = 6.4 vs. range 3.9–6.3 [5, 26, 31]), and LF:HF ratio (*M* = 2.1 vs. range 0.8–4.51) [16, 31, 45, 48]. Compared to past studies, the present study obtained smaller values for rMSSD (*M* = 43 ms vs. range 55–72 ms) [19, 31, 45, 48] and pNN50 (*M* = 19.7 % vs. range 26–64 %) [19, 48]. No comparisons could be made for SDANN and SDNNi, as they are infrequently reported in studies.

These discrepancies may be attributable to prior studies' small sample sizes (e.g., *N* = 12; 36), posture (e.g., seated vs. supine) [5], time of recording (e.g., upon awakening from sleep) [18], presentation of data reduction techniques (e.g., HRV values presented through graphs only) [8], inconsistencies in units (e.g., beats/min^2, Hz) [7], and failure to adhere to the Task Force [39] recommendations for spectral analyses [7, 8]. Notedly, previously reported values fell within the 5th and 95th percentile values observed in the present population-based sample.

The second objective was to comprehensively assess the influence of developmental factors on HRV parameters. When covariates were assessed singularly, age, sex, pubertal stage, sleep duration, blood pressure, heart rate, and recording start time (i.e., time of day) all influenced HRV, which is consistent with previous adult findings [30, 36, 42]. However, when all covariates were considered together simultaneously, heart rate, gonadarche pubertal status, DBP, and ECG recording start times emerged as the most salient.

Age-related changes in HRV are likely attributable to age-related changes in heart rate [9, 49]. Consistent with previous studies [4, 31, 37], sex differences emerged. Boys had lower heart rate and greater HRV, particularly HRV indices reflecting parasympathetic activity (SDNN, rMSSD, pNN50, HF) [6, 45]. Girls evidenced higher heart rate and greater

sympathovagal imbalance (LF:HF ratio) [31]. It was hypothesized that these sex differences were partly attributable to pubertal onset, as girls typically enter puberty 2 years earlier than boys [34]. Further, gestational age at birth, birth weight, and pregnancy status were not associated with any time- or frequency-domain variables.

Advanced pubertal development was associated with increased sympathovagal imbalance and reduced parasympathetic activity across time- and frequency-domain HRV variables (rMSSD, pNN50, HF; LF:HF ratio). These results are similar to previous research and support the notion that the timing of pubertal development coincides with the emergence and maturation of neural autonomic mechanisms [5, 6, 19, 29]. Similar to the limited pediatric data of other studies, shorter sleep duration was associated with reduced HRV [24, 32]. DBP was stronger than SBP at predicting VLF, SDNN, SDNNi, and rMSSD.

Also, later recording time (vs. earlier) was associated with reduced HRV parameters and sympathovagal imbalance, except rMSSD and pNN50. These findings may reflect circadian variations in the autonomic nervous system and HRV [50] and are consistent with past findings of decreasing HRV parameters over the day [12, 24].

Interestingly, when assessed separately, a significant association between 24-h physical activity and diminished sympathovagal imbalance in children was observed [5, 48]. However, while larger BMI was not associated with HRV, larger waist circumference was related to reduced VLF, which is partly consistent with past pediatric findings of greater obesity linked to reduced HRV [16, 22, 33].

Strengths, Limitations, and Future Recommendations

The first limitation included the use of 10-year-old children, limiting the generalizability of the results. However, unlike previous cross-sectional studies, with small sizes, wide age ranges, or clinical samples, this was the first study to present normative HRV values in a large, population-based sample of children. Given the prognostic significance of HRV for the progression of disease [1], repeated measures of HRV and covariates would be valuable to establish whether HRV is a stable intra-individual difference, which may increase its clinical utility (e.g., monitor risk stratification).

The second limitation was the use of, several covariates that were based on self- or parent-report rather than objective assessment (e.g., accelerometer, pubertal development) [20, 45]. However, these self- or parent-report measures have demonstrated reliability and validity with objective measures [27]. Further, physiological covariates (e.g., blood pressure) were objectively assessed following standardized protocols.

Conclusion

Normative time- and frequency-domain HRV values for a large, population-based sample of 10-year-old children are provided. Pediatric reference ranges of short-term HRV parameters permit comparison to assess values and may help promote use in clinical settings.

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Abbreviations

HRV	Heart rate variability
SBP	Systolic blood pressure
DBP	Diastolic blood pressure
SDNN	Standard deviation of all normal sinus RR intervals
SDANN	Standard deviation of the averaged normal sinus RR intervals for all 5-min epochs
SDNNi	Mean of the standard deviations of all normal sinus RR intervals for all 5-min epochs
rMSSD	Root mean square of the successive normal sinus RR interval difference
pNN50	Percentage of successive normal sinus RR intervals <50 ms
VLF	Very low frequency
LF	Low frequency
HF	High frequency

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Table 1

Heart rate variability time-and frequency-domain variables in children

	Boys (*n* = 481, 46.4 %)		Girls (*n* = 555, 53.6 %)		Total	
	***M* (*n*)**	**SD (%)**	***M* (*n*)**	**SD (%)**	***M* (*n*)**	**SD (%)**
Age (years)	10.2	0.3	10.2	0.3	10.2	0.3
Gonadarche pubertal stage	1.8	0.6	1.9	0.7	1.9	0.6
BMI %ile[a]	61.7	28.1	58.4	27.4	60.0	27.8
Waist circumference (cm)	64.8	9.7	63.9	9.1	64.3	9.4
Weight (kg)	36.5	7.9	36.6	8.2	36.5	8.1
Height (cm)	140.2	6.6	140.5	7.1	140.4	6.9
Sleep duration (HH:MM)	9:50	0:42	9:54	0:40	9:52	0:40
Physical activity (yes)	(21)	(5.3)	(18)	(2.1)	(49)	(3.6)
SBP (mmHg)	97	10	97	10	97	10
DBP (mmHg)	62	9	61	8	62	8
Recording start time (HH:MM)	10:32	3:06	10:49	3:17	10:41	3:13
Mean RR (ms) *	691.0	71.7	669.5	63.3	679.5	68.2
Mean heart rate (beats/min) *	79.1	10.5	81.1	9.8	80.2	10.2
Time-domain						
SDNN (ms) *	89.4	26.1	84.4	23.1	86.7	24.7
SDANN (ms) *	42.3	17.1	39.3	15.2	40.7	16.2
SDNNi (ms) *	77.4	22.9	73.0	21.0	75.0	22.0
rMSSD (ms) *	45.1	13.7	41.1	12.9	42.9	13.4
pNN50 (%) *	21.3	11.4	18.3	10.8	19.7	11.2
Frequency-domain						
VLF (ms^2) *	1,621.9	1,139.5	1,448.3	840.8	1,528.9	994.0
LF (ms^2) *	1,587.7	1,040.1	1,411.2	934.4	1,493.1	988.3
HF (ms^2) *	896.3	684.4	770.7	622.2	828.0	654.5
lnVLF	7.2	0.6	7.1	0.5	7.2	0.6
lnLF *	7.2	0.6	7.1	0.6	7.1	0.6

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	Boys (*n* = 481, 46.4 %)		Girls (*n* = 555, 53.6 %)		Total	
	***M* (*n*)**	**SD (%)**	***M* (*n*)**	**SD (%)**	***M* (*n*)**	**SD (%)**
lnHF *	6.5	0.8	6.4	0.8	6.4	0.8
LF:HF ratio *	2.1	0.8	2.2	0.9	2.1	0.9

SBP systolic blood pressure, *DBP* diastolic blood pressure, *mmHG* millimeters of mercury, *bpm* beats per minute, *HH:MM* hours:minutes, *RR* R–R interval, *Ln* natural log transformed, *ms* milliseconds

* Indicate significant sex difference at $p < 0.01$

[a] *Z* scores used in statistical models

Table 2

Normative heart rate variability percentile values adjusted for age and heart rate, by sex

	Boys					Girls				
	5th	**25th**	**50th**	**85th**	**95th**	**5th**	**25th**	**50th**	**85th**	**95th**
Time-domain										
SDNN (ms)	71.1	83.9	95.5	111.7	124.9	76.4	89.9	100.3	117.0	128.5
SDAN*N* (ms)	15.1	20.0	24.5	31.1	36.3	17.8	23.3	27.2	33.9	38.8
SDNNi (ms)	84.0	95.8	106.7	121.6	134.4	89.0	101.3	110.8	126.3	136.5
rMSSD (ms)	41.2	49.0	56.0	65.9	73.9	45.4	53.6	59.9	70.1	77.1
pNN50 (%)	31.7	38.0	43.7	51.8	58.3	34.9	41.6	46.7	55.0	60.7
Frequency-domain										
VLF (ms^2)	2,936.8	3,363.0	3,756.2	4,293.0	4,749.6	3,131.4	3,573.7	3,914.1	4,474.7	4,843.7
LF (ms^2)	3,882.1	4,316.6	4,713.3	5,270.7	5,765.8	4,079.9	4,541.8	4,892.4	5,448.8	5,801.6
HF (ms^2)	1,668.4	1,946.6	2,202.3	2,559.9	2,857.2	1,797.2	2,094.6	2,322.4	2,695.9	2,945.9
lnVLF	2.6	2.9	3.2	3.5	3.9	2.7	3.0	3.3	3.6	3.9
lnLF	3.4	3.7	3.9	4.3	4.7	3.5	3.8	4.0	4.4	4.7
lnHF	2.9	3.3	3.7	4.2	4.6	3.1	3.5	3.8	4.3	4.6
LF:HF ratio	0.0	0.1	0.2	0.4	0.5	0.0	0.1	0.2	0.4	0.6

Ms milliseconds, *ln* log-transformed value

Table 3

Covariates of heart rate variability frequency- and time-domain variables in 10-year-old children

Covariates	Standardized beta coefficients								
	Time-domain variables					Frequency-domain variables			
	SDNN	SDANN	SDNNi	rMSSD	pNN50	lnVLF	lnLF	lnHF	LF/HF ratio
Age (years)	0.1	0.1	0.0	**0.1***	**0.1***	0.0	−0.0	0.0	**−0.1***
Sex (male)	**0.1****	**0.1****	**0.1****	**0.1*****	**0.1*****	**0.1***	**0.1****	**0.1*****	**−0.1****
Gestational age at birth (weeks)	0.0	−0.0	0.0	0.0	0.0	0.0	0.0	−0.0	0.0
Birth weight (g)	−0.0	−0.0	−0.0	−0.0	−0.0	−0.0	−0.0	−0.0	0.0
Premature status (yes)	0.0	0.0	0.0	0.0	0.0	0.0	−0.0	0.0	−0.0
SBP (mmHg)	**−0.2*****	**−0.2*****	**−0.2*****	**−0.2*****	**−0.1*****	**−0.2*****	**−0.2*****	**−0.1*****	0.0
DBP (mmHg)	**−0.2*****	**−0.1*****	**−0.2*****	**−0.2*****	**−0.2*****	**−0.2*****	**−0.2*****	**−0.1*****	0.0
Heart rate (bpm)	**−0.7*****	**−0.4*****	**−0.7*****	**−0.7*****	**−0.7*****	**−0.7*****	**−0.6*****	**−0.6*****	**0.3*****
Recording start time (HH:MM)	**−0.2*****	**−0.2*****	**−0.2*****	−0.0	−0.0	**−0.3*****	**−0.2*****	**−0.1***	**−0.1*****
Gonadarche pubertal stage	−0.0	0.0	−0.0	**−0.1****	**−0.1****	−0.0	−0.0	**−0.1***	**0.1****
BMI %ile[a]	0.0	−0.0	0.0	0.1	0.1	0.0	0.0	0.0	−0.0
Waist circumference (cm)	−0.0	**−0.1**$^{+}$	−0.0	0.0	0.0	**−0.1***	−0.0	−0.0	−0.0
Sleep duration (HH:MM)	**0.1***	**0.1**$^{+}$	**0.1**$^{+}$	0.1	0.1	**0.1***	**0.1**$^{+}$	**0.1**$^{+}$	−0.0
Physical activity (yes)	−0.0	**−0.1**$^{+}$	−0.1	0.0	0.0	−0.1	−0.0	0.0	**−0.1****

Bold values are statistically significant

SBP systolic blood pressure, *DBP* diastolic blood pressure, *mmHG* millimeters of mercury, *bpm* beats per minute; *HH:MM* hours:minutes

$^{*}p < 0.05$;

$^{**}p < 0.01$;

$^{***}p < 0.001$;

$^{+}p < 0.08$