ORIGINAL ARTICLE

Resting heart rate: Its correlations and potential for screening metabolic dysfunctions in youth

Short title: Pediatric tachycardia and metabolic dysfunction

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Abstract

**Background:** In pediatric populations, the use of resting heart rate as health index remains unclear, mainly in epidemiological settings. **Objective:** The purpose of this study was to analyze the potential of resting heart rate for screening metabolic dysfunction, as well as, to identify its correlation in pediatric populations. **Methods:** The sample was composed of 971 randomly selected schoolchildren, of both genders. Resting heart rate was measured with oscillometric devices using two types of cutoffs according to the arm circumference. Biochemical parameters triglycerides, total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol and glucose were measured. Body fatness, sleep disorders, smoking, alcohol consumption and physical fitness were analyzed. **Results:** Resting heart rate was significantly related to sleep disorder ($r = 0.12; \beta = 0.005, p = 0.039$) and maximal oxygen uptake ($r = -0.09; \beta = -0.207, p = 0.001$). The receiver operating characteristic indicated significant potential for the resting heart rate in the screening of youth at increased values of fasting glucose (area under curve= $0.611 \pm 0.039 \ [0.534 – 0.688]$) and triglycerides (area under curve= $0.618 \pm 0.044 \ [0.531 – 0.705]$). Moreover, resting heart rate was associated with abnormalities in high density lipoprotein (OR= 1.97 [1.07-3.60]) and fasting glucose (OR= 3.82 [1.11-13.1]). **Conclusion:** Tachycardia constitutes a significant and independent risk factor for the development of dysfunctions from early in life.

**Keywords:** heart rate; adipose tissue; sleep; physical fitness; lipid; glucose; adolescent
Background

Early life is a determinant period in the prevention [1,2] and development [3] of chronic diseases in adulthood and, therefore, the development of cheap tools to identify youth at an increased risk are useful in epidemiological and clinical settings. As a result of this point of view, anthropometric variables have been tested and widely used for screening increased cardiovascular risk [4-6]. More recently, resting heart rate (RHR) has been suggested as a valuable indicator of early cardiovascular risk. Palatini [7] has demonstrated that among adults there is scientific evidence to suggest that tachycardia should no longer be viewed as an innocent clinical feature. Similarly, Julius et al. [8] have evidenced that increased values of RHR constitute a significant risk factor in the development of cardiovascular outcomes, such as heart failure, myocardial infarction, sudden cardiac death and stroke (independent of blood pressure and a variety of other risk factors).

However, in pediatric populations this issue has been less investigated. Previous study [9] found a significant relationship between tachycardia and elevated blood pressure in 356 male children and adolescents. Surprisingly, they observed that this association occurred in both obese and lean youths. Rabbia et al. [10] also found a positive association between RHR and elevated blood pressure in adolescents of both sexes. Similarly, Freitas Junior et al. [11] identified a significant relationship between RHR and lipid variables in a sample composed of 180 obese youths. The above mentioned data is promising in support of the use of RHR as an index for screening the pediatric population for increased cardiovascular risk. However, in pediatric populations this issue remains unclear, mainly in epidemiological settings, as well as, the determinants of RHR in these populations.
The purposes of this study were to analyze the RHR potential for screening metabolic dysfunction in a school based sample (RHR treated as independent variable), as well as, to identify its correlation in pediatric populations (RHR treated as dependent variable).

Methods

Sample

This was a school based study, in which the sample was composed of adolescents (11 – 17 years-old) of both genders from Londrina, Brazil; which is a medium-sized city (~500,000 inhabitants) located in South Brazil with a high human development index (0.824). The minimum sample size was estimated using an equation for correlation coefficients, adopting a power of 80% and alpha error of 5% (Z=1.96). Among obese youth, Freitas Junior et al. [11] identified that RHR was significantly related to triglycerides ($r=0.21; p=0.004$) and total cholesterol ($r=0.18; p=0.011$). Therefore, the lowest correlation coefficient was used to estimate our sample size ($r=0.18$), which indicated the necessity of at least 241 youths. This minimum sample size was increased by 100% due to the design effect of the study (because all students in the chosen classes were invited to participate) and by 30% for predictable losses, giving a final minimum required sample size of 554 youths.

The sample of schoolchildren was selected in 2011, through a sampling process involving two random stages. The city was divided into five geographical regions (east, west, north, south and center) and two/three schools (in each geographical region) were randomly selected to participate in the survey. In each of the selected schools,
individual classes were randomly selected and thereafter all students in the chosen
classes were invited to participate. The inclusion criteria were: (i) self-report of health;
(ii) aged between 11-17 years-old; (iii) parent signature on a written consent form. The
study protocol was approved, prior to the study, by the Ethical Research Committee of
the State University of Londrina, Brazil.

Independent variables

In this study, six independent variables were taken into account: body fatness percentage (%BF), sleep pattern, sport practice, cardiorespiratory fitness, cigarette and alcohol consumption. %BF was estimated through an equation based on skinfold thickness specifically for youth [12]. Sleep pattern was assessed through a question (“Do you have trouble sleeping?”) with responses based on the likert scale (never [score 1], sometimes [score 2], very often [score 3] and always [score 4]). Sport practice was assessed by the score from section 2 of the Baecke questionnaire [13] and cardiorespiratory fitness by a maximal multistage 20-meter shuttle run test, in which the maximum oxygen uptake was estimated by a specific equation [14,15]. The number of cigarettes and alcoholic drinks consumed in the previous week was computed.

Potential confounders

Chronological age, pubertal stage and gender were used as potential confounders and, therefore, adjusted for in the multivariate models. Chronological age was determined as a decimal variable using the difference between the birthday and the date of the assessment. Pubertal stage was identified by the peak height velocity, which was
used to estimate biological maturity. The technique estimates time before or after the peak height velocity from the chronological age and anthropometric measures (height, sitting height, estimation of leg length and body weight) as described by Mirwald et al.[16].

**Resting heart rate**

Oscillometric devices (Omron MX3 Plus), clinically validated for measuring blood pressure in adolescents [17], were used to measure RHR (expressed as beats per minute [beats/min]) and two types of cutoffs were used according to the arm circumference. All measurements were registered in a quiet room with the adolescents resting in the sitting position for 5 minutes with their back supported and feet on the ground. Two measures were taken and the mean value of both was utilized. There are not widely accepted RHR cutoffs, therefore, RHR values were stratified into quartiles provided by previous study [9]: <70 beats/min; 70-77.4 beats/min; 77.5-85.9 beats/min; ≥86 beats/min.

**Blood samples**

After fasting for 10-12 hours, the patients’ blood samples were collected in tubes containing ethylene-diamine-tetraacetic acid (EDTA) as an anticoagulant and antioxidant, kept on melting ice during transfer, and immediately processed to obtain plasma, using a refrigerated centrifuge 4°C (Fanem®), and stored at -80°C (Indrel®) until the assay was performed. All collected blood samples (performed by nurses) were performed at the patients’ school and biochemical analyses were done at the University
Hospital at the Center of Health Sciences from the Universidade Estadual de Londrina. Biochemical parameters, including serum triglycerides, total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), and glucose were evaluated by a biochemical autoanalyser (Dimension ©, RXL, Newark, NJ, USA) and were used in conjunction with Dade Behring – Siemens kits. Modifications in lipid profile (TC ≥170 mg/dL, LDL ≥130 mg/dL, HDL < 45 mg/dL and triglycerides ≥130 mg/dL) and fasting glucose (≥100 mg/dL) were identified [18].

**Statistical Procedures**

The Kolmogorov-Smirnov test analyzed the distribution of the numerical variables and, when necessary, logarithm transformation was used in variables with non-parametric distribution. Pearson correlation analyzed the relationship between numerical variables and linear regression was elaborated with variables statistically significant in the Pearson correlation (RHR treated as dependent variable). Chi-square test analyzed association among categorical variables and the binary logistic regression (odds ratio [OR] and its 95% confidence interval [OR95%CI]) indicated the magnitude of these associations (RHR treated as independent variable). Moreover, gender, age and maturational status adjusted both multivariate models (linear regression and binary logistic regression). The receiver-operating characteristic (ROC) curve (expressed as area under the ROC curve [AUC]) analyzed the potential of RHR for screening metabolic dysfunctions. Statistical significance was set at \( p < .05 \) and statistical software BioEstat version 5.0 (BioEstat, Tefé, Amazonas) was used for all analyses.
Results

Initially, 1396 youths of both genders agreed to participate and returned the completed, signed consent form. However, 425 boys and girls were later excluded (e.g. absence in the fasting blood sample measurement; lack of 10-12 hours of fasting; refusal to participate in the running test). Therefore, after the field work, 971 youths (Male: 42.2% [n= 410] and Female: 57.8% [n= 561]) composed the sample. The mean age and mean RHR were 12.9±1.4 years-old and 82.7±12.5 beats/min, respectively.

RHR was positively and significantly related to %BF ($r= 0.10; p= 0.001$) and sleep disorder ($r= 0.12; p= 0.001$). Similarly, RHR was negatively and significantly related to cardiorespiratory fitness, sport practice and alcohol consumption. The number of cigarettes was not related to RHR values. Age ($r= -0.24; p= 0.001$) and pubertal status ($r= -0.09; p= 0.002$) were negatively related to RHR, on the other hand, male gender ($r= 0.14; p= 0.001$) was significantly and positively related to RHR. In the multivariate model, independent of the other variables, only cardiorespiratory fitness and sleep disorder remained significantly related to RHR (Tables 1 and 2).

Increased values of LDL-C and HDL-C were not significantly related to RHR (Table 2). On the other hand, RHR was significantly related to triglycerides ($r= 0.08; p= 0.011$), TC ($r= 0.08; p= 0.007$) and glucose values ($r= 0.07; p= 0.017$). In the multivariate model, triglycerides and glucose maintained the significant relationship with RHR, except TC.

Compared to bottom RHR quartile, highest quartile was associated with increased values of glucose (OR= 3.82 [OR$_{95\% CI}$: 1.11-13.1]; $p= 0.034$) and decreased
values of HDL-C (OR= 1.97 [OR_{95\% CI}: 1.07-3.60]; p= 0.028), independently of age, sex and pubertal stage (Table 3).

The ROC curve indicated significant potential for the RHR in screening youth at an increased value of fasting glucose (AUC= 0.611±0.039 [AUC_{95\% CI}: 0.534 – 0.688]) and triglycerides (AUC= 0.618±0.044 [AUC_{95\% CI}: 0.531 – 0.705]) (Figure 1). On the other hand, the potential for screening increased values of HDL-C (AUC= 0.518±0.026 [AUC_{95\% CI}: 0.467 – 0.568]), LDL-C (AUC= 0.525±0.023 [AUC_{95\% CI}: 0.479 – 0.570]) and TC (AUC= 0.539±0.028 [AUC_{95\% CI}: 0.483 – 0.594]) was limited.

Discussion

A school based study involving adolescents with age ranging from 11 to 17 years-old, in which cardiorespiratory fitness and sleep pattern were significantly related to increased RHR. Moreover, RHR presented the potential for screening youth at an increased risk of abnormalities in glucose, HDL-C and triglycerides values.

In our study, tachycardia was related to lower cardiorespiratory fitness, independent of obesity, maturational status and gender. The close inverse relationship between physical fitness and RHR has been demonstrated in previous reports by other authors\textsuperscript{10}. The recognized effect of cardiorespiratory fitness in autonomic nervous system activity and subsequent adaptations in neurohumoral control (decrease in circulating levels of catecholamines and changes in number or affinity of receptors)[19]seems to be independent of body composition\textsuperscript{20} and could offer support to our results.
Felber Dietrich et al.

Felber Dietrich et al. [20] found that parasympathetic indexes of obese adults engaged in ≥2 hours per week of physical exercises were higher than those observed in sedentary adults of normal weight. Moreover, this protective effect is identified from an early age. Gutin et al. [21] in an intervention protocol of eight months with obese children identified an improvement in parasympathetic activity, which decreased after subsequent detraining (changes in parasympathetic activity were not related to modifications in body fatness). In our study, the positive effect of sports practice in RHR was mediated by cardiorespiratory fitness and, therefore, as previously observed in other cardiovascular and metabolic outcomes [1,2], the physical activity practice during early life could be useful in the promotion of bradycardia and hence the prevention of cardiovascular diseases in adulthood.

Additionally, tachycardia was also associated with sleep pattern. Recently, Gallicchio and Kalesan [22] in a systematic review/meta-analysis identified that people with both short and longer periods of sleep are at an increased risk of all-cause mortality. However, the actual pathway by which sleep is linked to cardiovascular complications [23] is not clear, although it is plausible to believe that a pathway exists. Adolescents are prone to perform many activities at night (TV viewing and computer usage) and thus they are more exposed to shorter periods of sleep. Short sleep may act as a stressor in the acute and chronic setting and, therefore, affect the sympathetic activity of the organism and lead to tachycardia [24]. Moreover, the concentration of pro-inflammatory agents (interleukine-6, tumor necrosis factor – alpha and C-reactive protein) is increased in people with short sleep periods [24]. Our findings highlight the fact that health professionals must target the promotion of adequate sleep patterns.
among pediatric populations, because this harmful relationship between sleep pattern and tachycardia seems significant from an early age.

RHR had significant potential for screening increased fasting glucose values. Concurring with this, Oda and Kawai [25] identified the same relationship among Japanese adults. Researches have indicated that insulin resistance has an important relationship with sympathetic activation [26,27], which significantly affects the RHR. Similarly, dysfunction in lipid metabolism was also related to tachycardia. Freitas Junior et al. [11] found a significant relationship between the RHR with triglycerides and TC among obese youth. On the other hand, the same authors point out that the causality/pathway by which tachycardia is linked to lipid dysfunction cannot be clearly determined. It is plausible to believe that insulin resistance could also be relevant in this process [26]. In fact, insulin resistance affects the process of energy production, leading to an increased use of lipids as fuel and a higher production of reactive oxygen species in the brain (by the activation of the nicotine adenine dinucleotide hydrogen phosphatase oxidase), which increases the oxidative stress in rostral ventrolateral medulla, the region that determines the basal sympathetic activity [27,28]. Apparently, this inflammatory process occurs irrespective of the presence of obesity and ratifies the potential of RHR for screening youth at an increased cardiovascular risk.

Our study has strengths, such as the sample size calculation and random process for selecting the schools/classes. However, the limitations must be recognized too. Initially, the absence of cutoffs for RHR in pediatric populations constitutes a significant weakness in our study and a target for further investigations. Although Palatini [7] pointed out that there is no doubt that an RHR ≥80 to 85 beats per minutes implies an increased risk for health, this cutoff seems not to be true in pediatric
populations, because previous studies (and also our study) have reported a significant RHR variation according to age groups [9,11,29]. Therefore, future cutoffs tables should be developed to take into account adjustments for gender and age. The absence of measures related to adipokines and insulin resistance must be recognized and recommended as important in future investigations. Finally, the low magnitude of the correlation coefficient found should be taken into account in further inferences, because it denotes the action of other variables in the outcome.

Conclusions

In summary, our findings indicate that tachycardia constitutes a significant and independent risk factor to the development of dysfunctions related to glucose and lipid metabolism from early in life, but the development of RHR cutoffs is necessary. Moreover, cardiorespiratory fitness and sleep disturbances were significantly correlated to the RHR, independent of a variety of potential confounders.
Contribution of the Authors

RAF and ESC: (1) conception and design of the study, (2) acquisition, analysis and interpretation of data, (3) draft of the article and selection of manuscripts to discuss the results. DV, DRPS, CMTC, MSC and MBB: (1) Acquisition, analysis and interpretation of data, (2) draft of the article and selection of manuscripts to discuss the results, DSB, MJCS, LBS and ERVR: (1) conception and design of the study (2) review and approval of the final version to be submitted. All authors read and approved the final manuscript.

List of Abbreviations:

RHR-resting heart rate; %BF-body fatness percentage; EDTA-ethylene-diamine-tetraacetic acid; TC-total cholesterol; HDL-C-high-density lipoprotein cholesterol; LDL-C-low-density lipoprotein cholesterol; ROC-receiver-operating characteristic; AUC-area under the ROC curve; 95%CI-95% confidence interval; OR= odds ratio.

Competing interests

The authors declare that they have no competing interests
References


Figure Legend:

Figure 1. Potential of resting heart rate for screening metabolic variables among the pediatric population.
Table 1. Relationship between resting heart rate and independent variables among adolescents (Brazil, n = 971).

<table>
<thead>
<tr>
<th>Independent Variables</th>
<th>Correlation coefficient</th>
<th>Linear Regression</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$r$</td>
<td>$p$</td>
</tr>
<tr>
<td>%BF</td>
<td>0.10</td>
<td>0.001</td>
</tr>
<tr>
<td>Cardiorespiratory fitness</td>
<td>-0.09</td>
<td>0.004</td>
</tr>
<tr>
<td>Sport practice</td>
<td>-0.08</td>
<td>0.008</td>
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<tr>
<td>Alcohol</td>
<td>-0.08</td>
<td>0.014</td>
</tr>
<tr>
<td>Cigarettes</td>
<td>-0.04</td>
<td>0.162</td>
</tr>
<tr>
<td>Sleep pattern</td>
<td>0.12</td>
<td>0.001</td>
</tr>
</tbody>
</table>

*Multivariate model in which all independent variables were entered simultaneously in the model, in addition to being adjusted by age, pubertal status and gender. %BF= percentage of body fatness; VO$_2$= maximum oxygen uptake; Alcohol= number of drinks per week; Cigarettes= number of cigarettes per week.
Table 2. Relationship between resting heart rate and metabolic variables among adolescents (Brazil, n = 971).

<table>
<thead>
<tr>
<th>Independent Variables</th>
<th>Correlation’s coefficient</th>
<th>Linear Regression</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>r</td>
<td>p</td>
</tr>
<tr>
<td>LDL-C</td>
<td>0.05</td>
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<td>HDL-C</td>
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<td>0.783</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>0.08</td>
<td>0.011</td>
</tr>
<tr>
<td>TC</td>
<td>0.08</td>
<td>0.007</td>
</tr>
<tr>
<td>Glucose</td>
<td>0.07</td>
<td>0.017</td>
</tr>
</tbody>
</table>

*Multivariate model adjusted by age, pubertal status and gender; LDL-C = low density lipoprotein cholesterol; HDL-C = high density lipoprotein cholesterol; TC = total cholesterol.
Table 3. Association between resting heart rate and metabolic variables among adolescents (Brazil, n = 971).

<table>
<thead>
<tr>
<th>RHR (beats/min)</th>
<th>LDL-C OR (OR&lt;sub&gt;95%CI&lt;/sub&gt;)</th>
<th>HDL-C OR (OR&lt;sub&gt;95%CI&lt;/sub&gt;)</th>
<th>Triglycerides OR (OR&lt;sub&gt;95%CI&lt;/sub&gt;)</th>
<th>TC OR (OR&lt;sub&gt;95%CI&lt;/sub&gt;)</th>
<th>Glucose OR (OR&lt;sub&gt;95%CI&lt;/sub&gt;)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;70</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>70-77.4</td>
<td>1.27</td>
<td>1.60</td>
<td>1.58</td>
<td>1.23</td>
<td>1.82</td>
</tr>
<tr>
<td></td>
<td>(0.70-2.27)</td>
<td>(0.83-3.08)</td>
<td>(0.14-17.7)</td>
<td>(0.56-2.52)</td>
<td>(0.46-7.23)</td>
</tr>
<tr>
<td>77.5-85.9</td>
<td>1.06</td>
<td>1.79</td>
<td>7.20</td>
<td>1.19</td>
<td>3.17</td>
</tr>
<tr>
<td></td>
<td>(0.60-1.87)</td>
<td>(0.97-3.31)</td>
<td>(0.91-56.6)</td>
<td>(0.56-2.52)</td>
<td>(0.89-11.2)</td>
</tr>
<tr>
<td>≥86</td>
<td>1.33</td>
<td>1.97</td>
<td>5.56</td>
<td>1.38</td>
<td>3.82</td>
</tr>
<tr>
<td></td>
<td>(0.78-2.27)</td>
<td>(1.07-3.60)</td>
<td>(0.70-43.7)</td>
<td>(0.68-2.81)</td>
<td>(1.11-13.1)</td>
</tr>
</tbody>
</table>

Binary logistic regression adjusted by age, pubertal status and gender; OR = odds ratio; 95%CI = 95% confidence interval; LDL-C = low density lipoprotein cholesterol; HDL-C = high density lipoprotein cholesterol; TC = total cholesterol.
Figure 1

The figure illustrates the AUC ± 95% CI for various metabolic variables: Glucose, Total Cholesterol, HDL-C, LDL-C, and Tryglicerides. The reference line is indicated.

- **Glucose**: p = 0.007
- **Total Cholesterol**: p = 0.195
- **HDL-C**: p = 0.491
- **LDL-C**: p = 0.293
- **Tryglicerides**: p = 0.030