Obesity and Cardiac Autonomic Nerve Activity in Healthy Children: Results of the Toyama Birth Cohort Study

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Abstract

Objectives: To determine the relationship between obesity and cardiac autonomic nerve activity in healthy children.

Methods: 16 healthy male children comprising of 9 nonobese and 7 obese subjects (body mass index > 19.1 kg/m2) aged 8–9 years were selected. Electrocardiograms were measured for 10 min. under controlled ventilation (0.25 Hz) in the supine position. Consecutive 256-second RR interval data were transformed by the Fast Fourier Transform method into power spectral data. Very low frequency (VLF; 0.003–0.04 Hz), low frequency (LF; 0.04–0.15 Hz), high frequency (HF; 0.15–0.40 Hz), and total power (TP; 0.003–0.40 Hz) were calculated and transformed into a natural logarithm (ln). Normalized units (nu) were also calculated as follows: LFnu = LF / (TP - VLF) x 100. HFnu = HF / (TP - VLF) x 100. Low/high-frequency ratio (LHR) was calculated as LF divided by HF. Unpaired t-test was performed to compare the 2 groups.

Results: TP ln and HFnu, reflecting cardiac parasympathetic nerve activity, in obese children were significantly lower than those in nonobese children. In contrast, LFnu and LHF, reflecting cardiac sympathetic nerve activity, in obese children were significantly higher than those in nonobese children.

Conclusions: These findings suggest that obese children have higher sympathetic nerve activity and lower parasympathetic nerve activity than nonobese children.

Key words: obesity, children, autonomic nerve activity, heart rate variability, the Toyama Birth Cohort Study

Introduction

Long-term follow-up studies have revealed that obese children have higher mortality and morbidity for all causes and coronary heart diseases12). Obese children have a higher prevalence of hyperinsulinemia3), hyperlipidemia4), and hypertension5). About 40% of obese children continue to be obese as adults6). The long-term continuation of these abnormalities could make the prognosis of obese children poorer7).

In animal and clinical studies, the autonomic nervous system has been shown to play an important role in glucose intolerance, dyslipidemia, the development of obesity and hypertension89). Recently, frequency domain analysis of heart rate variability has been used in the estimation of cardiac autonomic nerve activity1012). In this technique, two dominant frequency bands were identified; a low frequency peak reflecting mixed activity of both the sympathetic and parasympathetic nervous systems and a high frequency peak reflecting parasympathetic activity.

While previous studies have indicated that there is a significant change in cardiac autonomic nerve activity in obese adults1315), there is a lack of information concerning obese children. In obese children, a more active renin-angiotensin-aldosterone (RAA) system and higher plasma catecholamine levels have been reported16). Therefore, there is a possibility that obese children have higher activity in the sympathetic nervous system. We have now examined the relationship between obesity and cardiac autonomic nerve activity in healthy children without regular exercise habits.

Methods

Subjects

We are currently conducting a birth cohort study of children born in 198917). Study subjects were 3rd grade elementary school children aged 8 or 9 years when we carried out this study between December, 1998 and March, 1999. A screening questionnaire was sent to 115 male children belonging to 3 elementary schools in a district in Toyama prefecture. Of 112 respondents, 30 sedentary subjects without chronic diseases were selected. An introductory letter was sent to the parents/guardians of the children. In total, 16 children agreed to participate as study subjects and provided written informed consent. We defined subjects with a body-mass index (BMI; body weight(kg) divided by square of height(m)) of
less than 19.1 as nonobese and subjects with a BMI of greater than 19.1 as obese subjects, on the basis of the proposed international definition for child obesity\(^\text{[10]}\). The study subjects consisted of 9 nonobese and 7 obese male children.

**Study protocol**

All measurements were performed between 3:30 p.m. and 4:30 p.m., 3 or more hours after a school lunch, and in an air-conditioned, quiet, comfortable room. Room temperature and humidity were 20–21°C and 48–52%, respectively. Subjects did not consume beverages containing caffeine, including Japanese tea, after 9:00 p.m. on the day preceding the study. Subjects did not take any refreshment, except for water, after school lunch. Subjects did not take vasoactive or neuroactive medications. Subjects urinated immediately before the study. The heights and weights of children were measured wearing shorts. The heights of children were measured using a stadiometer, to the nearest 0.1 cm. The weights of children were measured using a balance scale to the nearest 0.1 kg. The stadiometer was checked for accuracy and the balance scale was calibrated before the study. Bilateral subscapular and triceps skinfolds were measured twice using an Eiyokentype caliper (Yagami Co., Nagoya, Japan). The mean of four measurements at each skinfold site was calculated. Cardiac auscultation showed no abnormality in any of the study subjects. The subjects were attached to a Holter electrocardiograph (RAC1202, Nihon Coden Co., Japan) and a blood pressure monitoring device (90207 Spacelabs, USA) while in the supine position. After a 5-minute bed rest, blood pressure was measured twice and the mean blood pressure reading was calculated. After a 20-minute bed rest, the subjects were instructed to synchronize their breath gently with a metronome at a frequency of 0.25 Hz for 10 minutes. The anthropometric and physiological measurements were performed by one investigator.

**Time and frequency domain analysis**

During 10 minutes of controlled ventilation, RR intervals were measured at an accuracy of 1 millisecond and recorded on the IC card in the Holter electrocardiograph. Consecutive 256-second RR intervals with a normal sinus rhythm were selected for analysis. Time series data were transformed into time and frequency domain indices using a personal computer (Digital HiNoteVP, Digital Equipment Co., USA) with a pentium MMX microprocessor.

For time domain analysis, we calculated 3 time domain indices including standard deviation of the RR interval (SD), the coefficient of variance (CV\(_{\text{RR}}\); the standard deviation divided by mean RR interval), and the root mean square of successive differences (rMSSD; the square root of the mean of the sum of the square of the adjacent RR intervals). These indices were considered to reflect cardiac parasympathetic nerve activity\(^{[9,20]}\).

For frequency domain analysis, RR interval data were interpolated using a cubic-spline interpolation method and resampled at 2 Hz. The resampled 512-point equidistant data were treated with a Hanning window function and transformed into power spectral data using a Fast Fourier Transform method\(^{[12]}\). Very low frequency power (VLF; 0.003–0.04 Hz), low frequency power (LF; 0.04–0.15 Hz), high frequency power (HF; 0.14–0.4 Hz), and total power (TP; 0.003–0.4 Hz) were calculated. These indices were transformed into the natural logarithm (ln), because the indices did not show normal distribution. Low/high-frequency ratio (LHR) was calculated as LF divided by HF. HF and LF were considered to arise from cardiac parasympathetic nerve activity and combined sympathetic and parasympathetic nerve function, respectively\(^{[10,12]}\). The consensus is that LHR reflects cardiac sympathetic nerve activity\(^{[10,12]}\). In addition, normalized units (nu) of two spectral components were calculated as follows\(^{[11,14]}\):

\[
\text{LFnu} = \frac{\text{LF}}{(\text{TP} - \text{VLF})} \times 100, \quad \text{HFnu} = \frac{\text{HF}}{(\text{TP} - \text{VLF})} \times 100.
\]

Normalized units of HF and LF were suggested to highlight sympathovagal balance\(^{[11,14]}\).

**Statistical analysis**

All statistical analyses were performed using SPSS (SPSS 7.5.1J, SPSS Inc., Chicago, Ill). Values were expressed as means ± SD. Unpaired t test was performed to compare anthropometric measurements, blood pressure, and time and frequency domain indices between the 2 groups. A two-tailed P value of less than 0.05 was considered significant.

**Results**

Representative samples of tachogram and spectrogram data obtained from two study subjects are shown in Fig. 1. Spectrograms obtained from obese children showed higher LF and lower HF than those of nonobese children.

The anthropometric measurements, blood pressure, and heart rate are shown in Table 1. Height, weight, BMI, triceps and subscapular skinfolds, and heart rate were significantly higher in obese children than those in nonobese children. There were no significant differences in age and systolic and diastolic blood pressure between the 2 groups. Comparisons of time domain indices between the 2 groups are presented in Table 2. There were no significant differences in SD, CV\(_{\text{RR}}\), and rMSSD between the 2 groups, while the mean RR interval was significantly lower in obese children than that in nonobese children. Comparisons of the frequency domain indices are presented in Table 3. Obese subjects had significantly lower TP ln, VLF ln, and HFnu than nonobese children. In contrast, LFnu and LHR in obese children were significantly higher than those in nonobese children.

**Discussion**

In the present study, it was demonstrated that obese children had higher LHR and LFnu reflecting an increase in cardiac sympathetic nerve activity and lower TP ln and HFnu reflecting a decrease in cardiac parasympathetic nerve activity. These results were consistent with those of previous studies in adults\(^{[13,14]}\). Moreover, obese children tended to have higher systolic blood pressure and heart rate than lean children. The higher sympathetic nerve activity observed in obese children could be associated with higher blood pressure and heart rate in obese children.

It has been suggested that the autonomic nervous system plays a crucial role in the development of obesity and prevents further weight gain through energy substrate homeostasis\(^{[21,23]}\). However, previous studies concerning autonomic nervous system activity in obese adults have produced conflicting results\(^{[24]}\). Measurements of plasma and urinary catecholamine concentration as indices of sympathetic nervous system activity have ranged from low through normal to high\(^{[4,24,25]}\). Sympathetic nerve activity in skeletal muscle was increased in obese subjects\(^{[22]}\). Skin sympathetic nerve activity was not significantly different in obese
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Fig. 1 Representative tachogram and spectrogram findings obtained from study subjects. The left half of the figure was obtained from a nonobese male subject with a body mass index of 14.6 kg/m². The right half of the figure was obtained from an obese male subject with a body mass index of 22.4 kg/m².

Table 1 Anthropometric measurements, blood pressure, and heart rate of nonobese and obese male children

<table>
<thead>
<tr>
<th></th>
<th>Nonobese (n=9)</th>
<th>Obese (n=7)</th>
<th>P value</th>
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<tbody>
<tr>
<td>Age (years)</td>
<td>9.11 ± 0.29</td>
<td>9.21 ± 0.33</td>
<td>NS</td>
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<tr>
<td>Height (cm)</td>
<td>128.8 ± 4.39</td>
<td>135.0 ± 5.87</td>
<td>P&lt;0.05</td>
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<td>Weight (kg)</td>
<td>26.9 ± 3.63</td>
<td>39.4 ± 3.37</td>
<td>P&lt;0.001</td>
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<tr>
<td>BMI (kg/m²)</td>
<td>16.2 ± 1.32</td>
<td>21.6 ± 0.75</td>
<td>P&lt;0.001</td>
</tr>
<tr>
<td>Triceps (mm)</td>
<td>9.1 ± 2.69</td>
<td>19.6 ± 0.98</td>
<td>P&lt;0.001</td>
</tr>
<tr>
<td>Subscapular (mm)</td>
<td>5.8 ± 1.55</td>
<td>18.0 ± 3.84</td>
<td>P&lt;0.001</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>108.3 ± 6.71</td>
<td>113.8 ± 4.25</td>
<td>P&lt;0.1</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>61.1 ± 6.33</td>
<td>63.9 ± 4.38</td>
<td>NS</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>79.4 ± 6.38</td>
<td>86.4 ± 3.78</td>
<td>P&lt;0.05</td>
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</tbody>
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Abbreviations: BMI, body mass index; Triceps, triceps skinfold; Subscapular, subscapular skinfold; SBP, systolic blood pressure; DBP, diastolic blood pressure.

Table 2 Comparisons of time domain indices between nonobese and obese male children

<table>
<thead>
<tr>
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<th>Nonobese (n=9)</th>
<th>Obese (n=7)</th>
<th>P value</th>
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<tbody>
<tr>
<td>Mean RR (msec)</td>
<td>760.2 ± 60.5</td>
<td>695.2 ± 30.4</td>
<td>P&lt;0.05</td>
</tr>
<tr>
<td>SD (msec)</td>
<td>67.1 ± 36.3</td>
<td>50.6 ± 18.2</td>
<td>NS</td>
</tr>
<tr>
<td>CV&lt;sub&gt;RR&lt;/sub&gt;</td>
<td>8.68 ± 4.27</td>
<td>7.21 ± 2.39</td>
<td>NS</td>
</tr>
<tr>
<td>rMSSD (msec)</td>
<td>74.6 ± 52.2</td>
<td>41.2 ± 17.8</td>
<td>NS</td>
</tr>
</tbody>
</table>

Abbreviations: Mean RR, mean RR interval; SD, standard deviation of RR interval; CV<sub>RR</sub>, coefficient of variance; rMSSD, root mean square of successive difference.

Table 3 Comparisons of frequency domain indices between nonobese and obese male children

<table>
<thead>
<tr>
<th></th>
<th>Nonobese (n=9)</th>
<th>Obese (n=7)</th>
<th>P value</th>
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<tbody>
<tr>
<td>TP ln (msec&lt;sup&gt;2&lt;/sup&gt;)</td>
<td>17.49 ± 0.20</td>
<td>17.25 ± 0.18</td>
<td>P&lt;0.05</td>
</tr>
<tr>
<td>VLF ln (msec&lt;sup&gt;2&lt;/sup&gt;)</td>
<td>17.47 ± 0.19</td>
<td>17.23 ± 0.17</td>
<td>P&lt;0.05</td>
</tr>
<tr>
<td>LF ln (msec&lt;sup&gt;2&lt;/sup&gt;)</td>
<td>11.88 ± 1.19</td>
<td>11.83 ± 0.83</td>
<td>NS</td>
</tr>
<tr>
<td>Lfnu (%)</td>
<td>30.23 ± 11.36</td>
<td>45.77 ± 9.63</td>
<td>P&lt;0.05</td>
</tr>
<tr>
<td>HF ln (msec&lt;sup&gt;2&lt;/sup&gt;)</td>
<td>12.79 ± 1.28</td>
<td>12.01 ± 1.09</td>
<td>NS</td>
</tr>
<tr>
<td>Hfnu (%)</td>
<td>69.77 ± 11.36</td>
<td>54.22 ± 9.63</td>
<td>P&lt;0.05</td>
</tr>
<tr>
<td>LHR (LF/HF)</td>
<td>0.47 ± 0.23</td>
<td>0.90 ± 0.35</td>
<td>P&lt;0.05</td>
</tr>
</tbody>
</table>

Abbreviations: TP ln, natural logarithm of TP; VLF ln, natural logarithm of VLF; LF ln, natural logarithm of LF; LFnu, normalized units of LF; HF ln, natural logarithm of HF; Hfnu, normalized units of HF; LHR, Low/high-frequency ratio (LF divided by HF).

subjects<sup>26</sup>. Previous studies concerning cardiac autonomic nerve activity in obese adults have demonstrated that obese adults have lower parasympathetic nerve activity<sup>12,15</sup>. However, with respect to sympathetic nerve activity, both lower<sup>14,15</sup> and higher<sup>13</sup> activities have been observed. The present findings showed higher sympathetic nerve activity and lower parasympathetic nerve activity in obese children. The reason for these discrepant findings could be attributable to the limitations imposed by the methodology because LF and LHR are not pure indices of sympathetic nerve activity<sup>10,12</sup>.  

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The present results have several limitations. Firstly, we were unable to measure the tidal volume of subjects. However, the controlled ventilation at the frequency of 15 breaths/min we selected could minimize tidal volume effects on respiratory sinus arrhythmia, although lower and higher tidal volumes and a respiratory rate produces pronounced variability in respiratory sinus arrhythmia. Second, the effects of acute and chronic exercise on heart rate variability may not have been excluded. Despite the exclusion of children with regular exercise habits in the present study, the chronic effects of exercise on heart rate variability may be included because all the schoolchildren including the study subjects were scheduled to take physical education. Therefore, further studies will be required to confirm the relationship between the degree of obesity and cardiac autonomic nerve activity in healthy children.

In summary, the present findings suggest that healthy obese children have higher cardiac sympathetic nerve activity and lower parasympathetic nerve activity than nonobese children. The altered autonomic nerve activities shown in obese adults were already present in obese children. The high blood pressure, hyperinsulinemia, impaired glucose tolerance, and hyperlipidemia commonly demonstrated in obese children could be associated with altered autonomic nerve activities. Therefore, it is important to maintain normal weight from childhood. Moreover, because it is known that diet therapy and physical training could reduce the level of sympathetic nerve activity in obesity, these lifestyle modifications might be beneficial for preventing obese children from future morbidity and mortality.

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Acknowledgements

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