Effects of Exercise Training on Heart-Rate-Variability Indices in Individuals With Down Syndrome

Fani Giagkoudaki, Eleftherios Dimitros, Evangelia Kouidi, and Asterios Deligiannis

Objective: To investigate the effects of an exercise-training program on heart-rate-variability (HRV) indices in individuals with Down syndrome (DS). Design: Controlled clinical trial. Participants: 10 people with DS, age 24.2 ± 5.1 y (group A), and 10 age-matched healthy sedentary individuals (group B). Method: At baseline all subjects underwent a clinical examination and an ambulatory 24-h Holter monitoring for the evaluation of cardiac autonomic-nervous-system (ANS) activity by time- and frequency-domain analysis. Intervention: After initial evaluation, group A followed a 6-mo exercise-training program and thereafter underwent the same HRV analysis. Results: At the beginning of the study, group A showed a higher LF:HF ratio than group B, indicating impaired sympathovagal balance, likely because of lesser vagal modulation. Moreover, both time- and frequency-domain indices in group A were significantly lower than in group B. At the end of the study, exercise training was found to improve the sympathovagal balance, mainly by increasing vagal activity, in group A. Conclusion: The results indicate that individuals with DS have ANS dysfunction that can be improved by exercise’s increasing the parasympathetic modulation.

Keywords: autonomic-nervous-system dysfunction

Individuals with Down syndrome (DS) usually exhibit cardiovascular abnormalities, even in the absence of congenital heart disease.1,2 Obesity, diabetes mellitus, and physical inactivity, which are primary risk factors for cardiovascular disease, are common in those with DS.3,4 Cardiac autonomic-nervous-system (ANS) dysfunction occurs often in people with DS, and there is evidence that individuals with DS exhibit sympathovagal imbalance, reduced sympathoexcitation, or blunted vagal withdrawal.5,6 They are found to have increased vagal tone at rest and reduced sympathoactivation during exercise.7 It is well known that cardiac ANS dysfunction, measured using heart-rate-variability (HRV) analysis, is associated with malignant arrhythmias and has been linked to increased risk of cardiovascular morbidity and mortality in various patient groups, especially in those with coronary heart disease.8,9

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However, there is no study linking HRV analysis to risk of cardiovascular problems in people with DS. Moreover, chronotropic incompetence in individuals with DS is suggested to contribute to their reduced exercise capacity.10–12

HRV analysis is a common, reliable, noninvasive method of evaluating ANS activity.13 Decreased HRV indices reflect enhanced sympathetic and depressed vagal activity.8 Patients with diabetes mellitus, end-stage renal disease, and coronary artery disease heart failure and patients after heart transplant are found to have severely reduced variability, indicating poor prognosis.14,15

Exercise training is thought to be capable of modifying the autonomic balance.8 It is already known that aerobic exercise training causes enhanced vagal activity at rest and increased HRV in healthy individuals in comparison with sedentary controls.16,17 Furthermore, several studies have reported the beneficial effects of mainly aerobic-training programs on cardiac autonomic activity in cardiac, dialysis, and diabetic patients, as well as in sedentary individuals.8,17 Exercise training is recommended for individuals with DS to improve cardiovascular fitness.18–20 However, the effects of training on cardiac autonomic outflow in individuals with DS are still unknown. Therefore, the aim of this study was to investigate whether an exercise program is effective in improving the HRV indices in people with DS.

Methods

Participants

Subjects with DS were recruited from the Down Syndrome Association of Greece. From a pool of 45 subjects with DS, 23 met the criteria for inclusion. Seventeen DS subjects with mild to moderate intellectual disabilities volunteered to participate in this study and underwent a baseline interview. Seven of them withdrew from the study because of severe health disorders or behavioral problems. Finally, the intervention group contained 10 adults with DS (6 women, 4 men, group A), age 24.2 ± 5.1 years, and another 10 healthy sedentary individuals (5 women, 5 men, group B), age 23.3 ± 4.6 years, served as controls. All individuals with DS lived with their parents; none was institutionalized. Inclusion criteria were being over 18–30 and having no known cardiovascular disease or contraindication to exercise. None of the subjects smoked or was taking any medication that may affect ANS activity, such as β-blockers. Informed consent was obtained from all participants and from their parents before the study began. The study protocol was approved by the Ethics Committee of the Aristotle University of Thessaloniki.

Study Design

Assessments were made at baseline and after 6 months. Before data collection, each subject was familiarized with the laboratory and screening settings. All subjects were tested on 2 consecutive days. The first day of testing consisted of noninvasive cardiovascular screening, after which the participants were outfitted with an ambulatory ECG Holter recorder for 24 hours. The second day of
testing consisted of analysis of the Holter-monitoring data. All analyses were performed by the same cardiologist, who was blinded to the identity of trained subjects and controls. After the baseline assessments were conducted, subjects with DS who were included in the study followed a 6-month, 3-d/wk exercise-training intervention.

**Procedure**

All subjects underwent a noninvasive cardiovascular screening that included physical examination, blood pressure measurement, resting ECG, and an echocardiographic study to ensure the absence of contraindications to exercise. In addition, body weight and height were measured, and body-mass index (BMI) was calculated from the following formula: $\text{BMI} = \frac{\text{weight (kg)}}{\text{height}^2 (\text{m}^2)}$.

**Time- and Frequency-Domain Analysis of HRV**

All subjects underwent a 24-hour ambulatory ECG Holter monitoring, which was repeated at the end of the study only for the individuals with DS at least 2 days after their last exercise training session. A 3-channel digital ambulatory ECG Holter recorder (GBI-3S) with electronic RAM memory was used for time- and frequency-domain analysis. WinTer Holter Analyzer software (Galix Biomedical) was used for the analysis. This software has been tested and approved by the U.S. Food and Drug Administration. Moreover, both ectopic beats and artifacts were automatically and manually discarded by a blinded investigator. The frequency analysis was based on applying the fast Fourier transform. The data were neither resampled nor interpolated. The subjects were asked to avoid caffeine and alcoholic beverages, as well as any activity other than their daily activities that could affect heart rhythm, during the recording. All participants were asked to abstain from exercise when HRV data were collected both at the beginning of the study and after the 6-month exercise-training program.

From the time-domain analysis the following indices were evaluated: the standard deviation of normal-to-normal intervals (SDNN); the standard deviation of the average interbeat (RR) interval calculated over short periods, usually 5 minutes (SDANN); the mean of the 5-minute standard deviation of the RR interval calculated over 24 hours (SDNN index); the square root of the mean squared differences of successive RR intervals (rMSSD); and the proportion derived by dividing the number of interval differences of successive RR intervals greater than 50 milliseconds by the total number of RR intervals (pNN50). From the frequency-domain analysis the following indices were evaluated: low-frequency (LF; range 0.04–0.15 Hz) and high-frequency (HF; frequencies with range 0.15–0.4 Hz) components during the 24 hours, day, and night and the LF:HF ratio. Most researchers consider the LF component a parameter that includes both sympathetic and vagal influences and the HF component a marker of vagal activity. Finally, the LF:HF ratio is a marker of sympathovagal balance. These components were expressed both in meters squared and in normal units (NU), which represent the relative value of each power component in proportion to the total power minus the very-LF component. 


Exercise Protocol

After initial evaluation, group A participated in a 6-month exercise-training program, which included mainly aerobic exercises such as walking, jogging, traditional dancing, and simple basketball exercises for men and rhythmic gymnastics with balls and ribbons for women. Three expert exercise trainers were responsible for the training sessions. Training sessions were conducted 3 times per week and lasted 60 minutes. Training intensity was initially 60% and progressed to 80% of maximal heart rate, which according to Fernhall et al. is 170–180 beats/min. Subjects of group A were wearing sport testers during training sessions to ensure the intensity of exercise. During the first 2 weeks, apart from the simple aerobic exercises, subjects of group A were taught how to use the basketballs and ribbons safely and were asked to inform the trainers in case of any unusual symptoms.

Statistical Analysis

Statistical analyses were performed using SPSS version 12.0 for Windows (Statistical Package for Social Sciences, Chicago, IL, USA). Descriptive statistics were calculated for all variables. A Mann–Whitney U test was used to compare the results between the groups both at the beginning and at the end of the study. A Wilcoxon test was used to compare the results within the 2 measurements in people with DS. Spearman correlation was used to obtain the relationships between body-weight changes, BMI changes, and HRV changes in group A. A 2-tailed P value of less than .05 was considered statistically significant.

Results

The characteristics of the participants are presented in Table 1. Participants in group A were statistically significantly shorter than those in group B. At the end of the exercise-training program body weight was found to be significantly decreased by 4.8% (P < .05) in group A, unlike BMI, which was not statistically significantly decreased. There was no cardiovascular or other complication that developed as a consequence of exercise training during the 6-month study. None of the subjects appeared in the Holter monitoring study to have malignant arrhythmias either at the beginning or at the end of the study. Group A had a statistically significantly higher resting heart rate (78.3 ± 7.7 beats/min in group A vs 70.5 ± 7.1 beats/min in group B). After training, resting heart rate was decreased by 2.2% (NS) in Group A, which was not significantly different from group B.

Table 1  Subject Characteristics (Mean ± SD)

<table>
<thead>
<tr>
<th></th>
<th>Group A</th>
<th>Group B</th>
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<tbody>
<tr>
<td>Age (y)</td>
<td>24.2 ± 5.1</td>
<td>21.3 ± 6.4</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>157.0 ± 0.1*</td>
<td>173.3 ± 0.1</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>58.4 ± 7.5</td>
<td>69.5 ± 19.1</td>
</tr>
<tr>
<td>Body-mass index (kg/m²)</td>
<td>23.6 ± 2.0</td>
<td>22.8 ± 4.2</td>
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</table>

*P < .05 A vs B.
Time- and frequency-domain-analysis results are shown in Tables 2 and 3, respectively. At the beginning of the study, group A had lower SDNN by 16.1% ($P < .05$), SDANN index by 17.9% ($P < .05$), SDNN index by 17.0% ($P < .05$), rMSSD by 26.6% ($P < .05$), and pNN50 by 40.4% ($P < .05$) compared with group B. From the frequency-domain analysis, LF components during 24 hours, day, and night in group A were decreased by 20.7% ($P < .05$), 19.8% ($P < .05$), and 17.7% ($P < .05$), respectively, compared with group B, as well as HF during 24 hours, day, and night, by 35.8%, 33.2%, and 41.1% ($P < .05$).

After training, only pNN50 was found to be significantly increased, by 41.2% ($P < .05$), and the LF:HF ratio decreased by 29.8% ($P < .05$, Figure 1) in group A. There were nonsignificant changes in all the other time- and frequency-domain indices. Specifically, HF components increased during 24 hours and day by 19.2% and 23.2%, respectively, but LF components only by 3.4% and 2.9%, respectively. HF was also increased during night by 30.6%, in contrast with LF, which decreased by 2.4%. However, when HF and LF components were expressed in NU, only HF significantly increased, by 30.7% ($P < .05$), after the 6-month training in group A (Figure 2). There was no significant difference between any of the posttraining values of group A and baseline values of group B. Moreover, there were no significant relationships between changes in HRV indices and changes in body weight or BMI in subjects with DS.

**Discussion**

The results of the study confirm earlier work showing that individuals with DS have ANS dysfunction, characterized by an imbalance between sympathetic and vagal systems. The novel finding of the current study is that a 6-month exercise-training program can restore the cardiac ANS modulation in individuals with DS. Specifically, exercise training was found to increase HF, which, based on results of other studies, is interpreted as an increase in vagal tone, and also led to an improvement in sympathovagal balance.

![Figure 1](image-url) — Low-frequency to high-frequency ratio (LF/HF) results. *$P < .05$ between baseline and final values in group A.
### Table 2  Time-Domain-Analysis Results (Mean ± SD)

<table>
<thead>
<tr>
<th></th>
<th>Before</th>
<th>After</th>
<th>( P ), before vs after</th>
<th>B</th>
<th>( P ), A before vs B</th>
<th>( P ), A after vs B</th>
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<tbody>
<tr>
<td>SDNN (ms)</td>
<td>152.8 ± 33.8</td>
<td>152.6 ± 33.7</td>
<td>.8</td>
<td>182.1 ± 27.5</td>
<td>.05</td>
<td>.06</td>
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<tr>
<td>SDANN index (ms)</td>
<td>134.6 ± 30.8</td>
<td>137.5 ± 29.9</td>
<td>.7</td>
<td>163.9 ± 27.8</td>
<td>.02</td>
<td>.06</td>
</tr>
<tr>
<td>SDNN index (ms)</td>
<td>69.9 ± 12.7</td>
<td>72.5 ± 12.5</td>
<td>.4</td>
<td>84.2 ± 15.4</td>
<td>.04</td>
<td>.1</td>
</tr>
<tr>
<td>rMSSD (ms)</td>
<td>40.8 ± 12.0</td>
<td>44.7 ± 10.6</td>
<td>.6</td>
<td>55.6 ± 16.6</td>
<td>.02</td>
<td>.07</td>
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<tr>
<td>pNN50 (ms)</td>
<td>17.0 ± 10.1</td>
<td>24.0 ± 9.0</td>
<td>.04</td>
<td>28.5 ± 12.2</td>
<td>.05</td>
<td>.2</td>
</tr>
</tbody>
</table>

Abbreviations: SDNN, SD of normal-to-normal intervals; SDANN, SD of the average interbeat (RR) interval calculated over short periods, usually 5 min; rMSSD, square root of the mean squared differences of successive RR intervals; pNN50, proportion derived by dividing the number of interval differences of successive RR intervals greater than 50 ms by the total number of RR intervals.

### Table 3  Frequency-Domain-Analysis Results (Mean ± SD)

<table>
<thead>
<tr>
<th></th>
<th>Before</th>
<th>After</th>
<th>( P ), before vs after</th>
<th>B</th>
<th>( P ), A before vs B</th>
<th>( P ), A after vs B</th>
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<tbody>
<tr>
<td>Low frequency (ms²)</td>
<td></td>
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<tr>
<td>24 h</td>
<td>1126.6 ± 289.1</td>
<td>1164.8 ± 289.8</td>
<td>.3</td>
<td>1421.4 ± 276.3</td>
<td>.04</td>
<td>.3</td>
</tr>
<tr>
<td>day</td>
<td>1123.6 ± 281.7</td>
<td>1156.0 ± 284.5</td>
<td>.7</td>
<td>1400.5 ± 326.7</td>
<td>.04</td>
<td>.2</td>
</tr>
<tr>
<td>night</td>
<td>1142.0 ± 267.4</td>
<td>1114.1 ± 339.4</td>
<td>.6</td>
<td>1387.0 ± 230.7</td>
<td>.03</td>
<td>.1</td>
</tr>
<tr>
<td>High frequency (ms²)</td>
<td></td>
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<tr>
<td>24 h</td>
<td>575.5 ± 321.9</td>
<td>685.8 ± 96.1</td>
<td>.6</td>
<td>896.5 ± 279.0</td>
<td>.04</td>
<td>.09</td>
</tr>
<tr>
<td>day</td>
<td>478.6 ± 270.8</td>
<td>589.5 ± 178.1</td>
<td>.2</td>
<td>716.1 ± 159.4</td>
<td>.05</td>
<td>.4</td>
</tr>
<tr>
<td>night</td>
<td>790.1 ± 5.9</td>
<td>1031.7 ± 119.5</td>
<td>.09</td>
<td>1342.5 ± 479.3</td>
<td>.03</td>
<td>.2</td>
</tr>
</tbody>
</table>
At the beginning of the study, subjects with DS had higher resting heart rate than the healthy subjects. Similarly, Guerra et al\textsuperscript{11} noted that individuals with DS have higher heart rate at rest than controls, as well as chronotropic incompetence, which expressed with decreased cardiovascular responses during exercise. Lake et al\textsuperscript{24} have reported higher levels of noradrenalin at rest and upright position in individuals with DS than in controls. In contrast with the current study, Iellamo et al\textsuperscript{25} reported no significant difference in resting heart rate in the supine posture between individuals with DS and healthy controls but lower heart rate during standing, indicating impaired autonomic cardiac regulation in patients with DS.

In addition, individuals with DS at the beginning of the study had more LF than HF components during both day and night. Sacks and Smith\textsuperscript{26} have also reported increased cholinergic sensitivity and reduced cholinergic activity in DS. On the contrary, Fernhall et al\textsuperscript{27} suggested that vagal modulation, measured by HRV at
rest, is greater in those with DS. It is reported that DS appears to be associated with increased parasympathetic modulation\textsuperscript{13} and a reduced sympathoactivation in response to exercise.\textsuperscript{28}

The sedentary lifestyle of people with DS is believed to be among the main factors contributing to their cardiovascular morbidity and decreased levels of physical fitness. Training programs may improve these parameters. Moreover, it is important to increase participation in physical activity patterns, to prevent obesity and promote psychosocial health. There was no adverse effect of exercise training during the study. In a meta-analysis, Dodd and Shields\textsuperscript{29} reported that no unexplained withdrawals or negative effects were reported in any of the studies, suggesting that cardiovascular exercise programs are safe for people with DS.

The current study showed that exercise training was able to improve the sympathovagal balance in people with DS and “normalize” HRV indices, because posttraining values were similar to values of sedentary healthy individuals. This is mainly demonstrated by the significant increase of pNN50 and HF and the decrease of LF:HF after training. There was also a small and nonsignificant increase in the LF components, which can be attributed to the duration of the exercise program. Similar effects of exercise training on HRV indices were detected in other patients with sympathovagal imbalance, such as patients with coronary artery disease, heart failure, end-stage renal disease on dialysis, and diabetes mellitus.\textsuperscript{17,30,31} In these patients, the depression of sympathetic and augmentation of vagal activity at rest and during submaximal effort after training were associated with reduced incidence of cardiac arrhythmias and better hemodynamic stability. In addition, the HRV index was found to be significantly correlated with aerobic capacity.\textsuperscript{17,30}

This beneficial effect of exercise training on sympathovagal balance was associated with a reduction in the resting heart rate of our subjects with DS. Lewis and Fragala-Pinkham\textsuperscript{13} reported that a 6-week exercise program in subjects with DS caused decreased heart rate both at rest and during a submaximal stress test. Similar findings are reported by Dyer,\textsuperscript{3} whose subjects with DS demonstrated a lower resting heart rate and blood pressure after a 13-week strength-training program. It is already known that vagal modulation of the sinoatrial node is the dominating control factor of heart rate at rest.\textsuperscript{34} Many studies have also noted the reduced intrinsic rate of the sinoatrial node in modulating bradycardia in athletes.\textsuperscript{35} Moreover, changes in heart rate from exercise training may result from a training-induced change in stroke volume or left-ventricular anatomical adaptations,\textsuperscript{36} which unfortunately were not examined in this study.

It has been suggested that obesity influences cardiac ANS activity. Specifically, there is evidence that obesity is associated with sympathovagal imbalance, characterized by depressed parasympathetic tone and increased sympathetic activity.\textsuperscript{37,38} On the other hand, Peterson et al\textsuperscript{39} demonstrated a relationship between increased body fat and sympathetic- and parasympathetic-nervous-system hypoactivity. In this study, exercise training caused a significant decrease in body weight. However, our results showed that neither body weight nor BMI affected cardiac autonomic control in subjects with DS. These results are consistent with previous findings showing that autonomic dysfunction is independent of obesity in subjects with DS.\textsuperscript{12,40}
Limitations

Limitations of the study include the small sample size. It was extremely difficult to persuade individuals with DS to attend an exercise program and to achieve compliance to exercise for 6 months. In addition, the control group was only tested once, at baseline, and its data were used as reference values for healthy sedentary age- and sex-matched individuals. Our intention was to examine whether individuals with DS before and after the intervention achieved the values of healthy controls. Moreover, we assumed that HRV values would have been stable after 6 months in healthy sedentary individuals who did not undergo any kind of intervention. Another potential limitation of this study is the lack of estimation of our subjects’ aerobic capacity. Most of the individuals with DS at baseline could not cooperate and accomplish a maximum exercise test wearing a facemask for the collection of expired air. Therefore, we cannot prove that the exercise-training program improved their aerobic fitness. Finally, this is not a retrospective study, and the effects of exercise training on cardiovascular morbidity and long-term survival were not assessed.

Conclusion

The results of the current study provide evidence that exercise can benefit the autonomic dysfunction of people with DS by altering the 2 branches of the ANS. Specifically, exercise training was able to restore vagal modulation and improve sympathovagal balance to levels seen in healthy persons without DS. Thus, exercise training appears to be a useful lifestyle intervention to improve cardiac autonomic modulation in people with DS. However, future research should be conducted to investigate whether these beneficial effects of exercise training on HRV indices lead to better cardiovascular prognosis in individuals with DS.

References


