Attenuated responses to sympathoexcitation in individuals with Down syndrome

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Fernhall, Bo, and Mari Otterstetter. Attenuated responses to sympathoexcitation in individuals with Down syndrome. J Appl Physiol 94: 2158–2165, 2003. First published February 7, 2003; 10.1152/japplphysiol.00959.2002.—This study evaluated blood pressure and heart rate responses to exercise and nonexercise tasks as indexes of autonomic function in subjects with and without Down syndrome (DS). Twenty-four subjects (12 with and 12 without DS) completed maximal treadmill exercise, isometric handgrip (30% of maximum), and cold pressor tests, with heart rate and blood pressure measurements. Maximal heart rate and heart rate and blood pressure responses to the isometric handgrip and cold pressor tests were reduced in subjects with DS (P < 0.05). Both early (first 30 s) and late (last 30 s) responses were reduced. Obesity did not appear to influence the results, as both obese and normal-weight subjects with DS exhibited similar responses, and controlling for body mass index did not alter the results between controls and subjects with DS. Individuals with DS, without congenital heart disease, exhibited reduced heart rate and blood pressure responses to isometric handgrip exercise and cold pressor testing, consistent with autonomic dysfunction. Autonomic dysfunction may partially explain chronotropic incompetence observed during maximal treadmill exercise in individuals with DS.

exercise; hemodynamic responses; chronotropic incompetence

Down syndrome (DS), or trisomy 21, is associated with physical and physiological perturbations, which may contribute to the low physical work capacity observed in this population (6, 11). Many individuals with DS have congenital heart disease (30–40%) (6), but physical work capacity is still low in individuals with DS without congenital heart disease (11, 35). Motivation, task understanding, and sedentary lifestyles have been suggested as contributors to low physical work capacity in individuals with DS (5, 42). Recent data suggest that these factors do not explain most of the deficit (10, 11, 34), but reduced heart rate (HR) response to exercise, or chronotropic incompetence, has been identified as a major contributor to reduced physical work capacity in populations with DS (8, 10, 11, 17, 18).

Although chronotropic incompetence has been demonstrated in a variety of other populations, the mechanism of blunted HR response to exercise is still uncertain but may be related to autonomic regulatory dysfunction (17, 25). In most populations with chronotropic incompetence, depressed sympathetic tone or response seems to contribute to a blunted HR response during exercise (25, 29, 32, 41), but incomplete vagal withdrawal has also been implicated (41).

Isometric handgrip exercise and cold pressor testing are two simple, noninvasive, and validated tests of sympathetic activation (21, 23, 40, 46). The HR and blood pressure (BP) responses are used as indicators of global sympathetic activation (cold pressor test) or sympathetic activation during exercise (isometric handgrip test). Preliminary data show that individuals with DS have significantly reduced HR and BP responses to isometric exercise compared with nondisabled control subjects (13), suggesting reduced sympathetic activation in this population during exercise. However, the subjects with DS had much higher body mass index (BMI) than controls; thus it is possible that obesity could explain these findings, because obesity has been related to altered autonomic function (28).

Considering the potential impact of chronotropic incompetence on exercise tolerance, exercise prescription, and cardiovascular risk, investigating the autonomic response to exercise and other sympathoexcitatory tasks will substantially enhance our understanding of possible factors related to chronotropic incompetence in individuals with DS. This study provides more definite insight regarding autonomic control of HR and BP in individuals with DS, by evaluating the autonomic response during both exercise and a nonexercise task and carefully evaluating the impact of obesity on these responses. Thus the purpose of this investigation was to 1) compare the HR and BP responses during isometric handgrip exercise and cold pressor testing between individuals with DS (without congenital heart disease) and a control group of age- and gender-matched healthy controls. We hypothesized that both HR and BP responses would be lower in individuals with DS, indicative of reduced sympathoexcitation. 2) The second purpose was to evaluate if the HR and BP changes during isometric handgrip and cold pressor testing were influenced by obesity in the population. The costs of publication of this article were defrayed in part by the payment of page charges. The article must therefore be hereby marked “advertisement” in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

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METHODS

Subjects

Twenty-four healthy subjects, 12 with DS and 12 without disabilities, between 17 and 39 yr of age, volunteered for the study. There were six men and six women in each group. All subjects were sedentary or moderately active, but none was participating in any extensive exercise training. Subjects were recruited from the local community and from local support groups for individuals with DS. All subjects were free of any overt disease based on medical history. Subjects were excluded from the study if they exhibited any of the following: 1) history of cardiovascular disease or a history of diabetes or any other metabolic disease that may affect the resting and exercise measurements; 2) any HR-altering medications or any other medication that may alter metabolic responses; 3) smoking; 4) any contraindications to exercise; 5) severe or profound mental retardation; 6) asthma or other significant respiratory disorders; 7) congenital heart disease; or 8) atlanto-axial instability. The nature of study participation was explained, and, after initial screening, all subjects signed informed consent. For subjects with DS, their parents also signed informed consent. The study protocol was approved by the University Medical Center Institutional Review Board at the George Washington University Medical Center.

Study Design

All familiarizations and testing sessions were conducted between June 1999 and August 2000. Subjects were tested in a postprandial state (~3 h) on 2 separate days and refrained from exercise 24 h before each test day. Subjects were also asked to refrain from caffeine ingestion on testing days. Both testing sessions were completed within a 3-wk period for each subject. The maximal treadmill test was conducted on a separate day from the handgrip and cold pressor tests. The order of testing was randomized, and subjects rested in a supine position for 15–30 min between tests (handgrip and cold pressor) to ensure that HR and BP had returned to resting levels before commencing the second test.

Familiarization

Subjects with DS were familiarized with all testing protocols before data collection. The number and length of familiarization sessions depended on the response of the individual subject. Data collection started when a subject could satisfactorily conduct each test, including comfortably walking on a motorized treadmill. We have previously shown that, through this familiarization procedure, valid and reliable exercise data can be collected on this population (6, 9, 11, 14). Subjects without DS were familiarized with test procedures on the day of testing before each procedure and demonstrated that they could satisfactorily complete the test tasks before data collection.

Protocol

Treadmill exercise test. Cardiorespiratory fitness and maximal HR were evaluated by using a treadmill protocol individualized to the capabilities of each individual. Subjects started by walking at a comfortable speed for 3 min, followed by a fast walk for 2 min. Thereafter, the grade was increased 2.5% every 2 min until a grade of 12.5% was reached. From this point, treadmill speed was increased 1 mph every minute until exhaustion. Oxygen uptake (\(\dot{V}O_2\)) was measured with a computerized on-line breath-by-breath system (SensorMedics V-max), and the \(\dot{V}O_2\) was averaged over 20 s. HR was measured by using a Polar HR monitor and was continuously monitored throughout the test. The test was terminated when the subject could no longer keep up with the treadmill speed or showed signs of volitional fatigue. The test was considered a valid peak effort if \(\dot{V}O_2\) plateaued (less than a 150 ml/min increase) with an increase in work rate, or if there was a plateau in HR (less than a 2 beat/min increase) with an increase in work rate concomitant with a respiratory exchange ratio of >1.0. This protocol has been shown to yield valid and reliable data in subjects with and without DS (6, 9, 14).

Handgrip testing. Maximal grip strength was determined with the subject in a supine position by using the dominant hand. Grip strength was measured with an electronic handgrip dynamometer (TSD121C, Biopac Systems) interfaced with a personal computer and with visual feedback on the computer monitor. Subjects were given standardized encouragement to produce maximal effort. Maximal voluntary contraction was determined by using the highest of three maximal contractions. This method has yielded valid and reliable strength measures in subjects with DS in our laboratory, with intra-class reliability coefficients >0.93. After several minutes of rest to allow hemodynamic variables to return to rest, the test was started with a 2-min rest period, followed by a 2-min isometric handgrip contraction at 30% of maximal voluntary contraction. We chose a 2-min contraction period to standardize length of contraction, and pilot testing revealed that 2 min was the longest contraction period possible to ensure inclusion of all subjects with DS. During the contraction phase of the test, subjects received visual feedback on the computer monitor to help them produce the correct force required. BP and HR were collected on-line, in real-time mode. Beat-to-beat \(\dot{V}O_2\) was measured noninvasively by using arterial tonometry (CMD 7000, Colins Medical Instruments) in the nondoninant arm, with the arm extended at heart level. The BP monitor was interfaced with a computer (Biopac systems). HR was collected by using a one-lead ECG (CM5), interfaced with a computer (Biopac systems). All HR and \(\dot{V}O_2\) data were collected at 1,000 Hz and stored on the computer and analyzed off-line after completion of testing.

Cold pressor testing. The cold pressor test was performed in the supine position, and the subject’s hand was immersed in cold water up to the wrist for 2 min, followed by a 2-min recovery period. Care was taken to ensure that the subject avoided any isometric contractions, breath holding, or performance of the Valsalva maneuver. HR and BP were continuously collected on-line, at rest and during immersion, in exactly the same manner as described for the handgrip test. Data were stored on the computer and analyzed off-line after completion of testing.

Data Analyses

Descriptive characteristics between groups were compared by using independent t-tests. The HR and BP response to handgrip and cold pressor testing were evaluated by using 30-s averages of beat-to-beat data. The change from resting values was compared with the first 30 s and the last 30 s of handgrip exercise or cold pressor responses, as indicators of early vs. late responses (40, 46), by using a 2 × 2 ANOVA with repeated measures [group (DS vs. non-DS) by time
RESULTS

Subject characteristics and treadmill exercise data are shown in Table 1. Both groups were of similar age, but all other variables were significantly different between groups. During the maximal treadmill testing, seven of the controls and nine of the subjects with DS achieved a plateau in $V_{\dot{O}}_2$. Both maximal HR achieved on the maximal treadmill test and the change in HR from rest to maximal exercise were significantly higher in the control group. The change in HR during the cold pressor test (A) and handgrip test (B) are shown in Fig. 1. There was a significant group-by-time interaction for both tests, showing that the overall change in HR differed between groups during both tests, caused by a lower increase in HR in subjects with DS. Controlling for BMI did not alter these results.

Changes in mean arterial BP (MAP) during the cold pressor (A) and handgrip tests (B) are shown in Fig. 2. There was a significant group-by-time interaction effect for both tests, showing that the comparison group increased MAP significantly more than the group with DS for both time points. Controlling for BMI did not alter these results.

The comparison of the obese and nonobese subjects with DS is shown in Table 2. None of the responses was significantly different between groups. A careful examination of Table 2 reveals that both the HR and BP responses were very similar between groups, with the nonobese subjects exhibiting slightly smaller changes, but this was not significant.

DISCUSSION

The main finding of this study was that both HR and BP responses to cold pressor testing and isometric handgrip exercise were reduced in subjects with DS without congenital heart disease. It appears that this was not a function of the higher BMI observed in the group with DS. Statistically, controlling for BMI did not alter our results. Furthermore, there was no difference in the HR or BP responses to handgrip and cold pressor testing between obese and nonobese subjects with DS. All subjects with DS exhibited markedly reduced hemodynamic responses to all tests, regardless of obesity status, suggesting that obesity status did not influence the responses of subjects with DS. Our data are consistent with the notion that HR responses to sympathetic tasks are reduced in individuals with DS, and this reduced HR response to sympathetic tasks may partially explain chronotropic incompetence during maximal treadmill exercise in individuals with DS.

Table 1. Descriptive characteristics and maximal treadmill performance of individuals with and without Down syndrome

<table>
<thead>
<tr>
<th>Variable</th>
<th>With DS</th>
<th>Without DS</th>
</tr>
</thead>
<tbody>
<tr>
<td>$n$</td>
<td>12</td>
<td>12</td>
</tr>
<tr>
<td>Age, yr</td>
<td>23.8 ± 1.8</td>
<td>26.4 ± 1.0</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>83.6 ± 6.3</td>
<td>67.8 ± 2.3*</td>
</tr>
<tr>
<td>Height, m</td>
<td>1.54 ± 0.02</td>
<td>1.72 ± 0.03*</td>
</tr>
<tr>
<td>BMI</td>
<td>34.8 ± 2.2</td>
<td>22.8 ± 0.73*</td>
</tr>
<tr>
<td>$V_{\dot{O}}_2$ peak, ml·kg$^{-1}$·min$^{-1}$</td>
<td>18.1 ± 1.6</td>
<td>43.8 ± 2.0*</td>
</tr>
<tr>
<td>Maximal heart rate, beats/min</td>
<td>154 ± 4.2</td>
<td>187 ± 2.0*</td>
</tr>
<tr>
<td>$V_{\dot{E}}$peak, 1-min</td>
<td>54.9 ± 4.0</td>
<td>110.8 ± 5.6*</td>
</tr>
<tr>
<td>Heart rate reserve, beats/min</td>
<td>85.6 ± 3.1</td>
<td>129.6 ± 3.1*</td>
</tr>
<tr>
<td>$RER_{peak}$</td>
<td>1.06 ± 0.03</td>
<td>1.26 ± 0.02*</td>
</tr>
<tr>
<td>Peak treadmill speed, mph</td>
<td>3.43 ± 0.18</td>
<td>5.54 ± 0.30*</td>
</tr>
<tr>
<td>Handgrip MVC, kg</td>
<td>10.9 ± 1.4</td>
<td>26.6 ± 2.4*</td>
</tr>
</tbody>
</table>

Values are means ± SE. DS, Down syndrome; BMI, body mass index; $V_{\dot{O}}_2$ peak, peak oxygen consumption; $V_{\dot{E}}$peak, peak minute ventilation; $RER_{peak}$, peak respiratory exchange ratio; MVC, maximal voluntary contraction. *Group difference, $P < 0.05$. 

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because the group with DS had significantly higher BMI compared with controls, it is possible that our observed differences could be attributed to obesity and not to DS per se. However, when we compared obese and nonobese subjects with DS, there was no difference between the groups, and the response trends were nearly identical. We also statistically controlled for BMI when comparing subjects with DS and controls, and this did not alter our findings. Thus it is unlikely that obesity can account for the reduced HR and BP responses in subjects with DS.

**Significance of the Cold Pressor Test**

Cold pressor testing is often used to evaluate the sympathetic influence on circulation in humans (31, 46). HR and BP responses in normal subjects are well characterized (16, 43, 46), and differential responses have been observed in a variety of clinical populations (31, 37, 48). In normal subjects, HR is expected to increase 7–12 beats/min during the first 1–2 min of immersion and may stabilize or decrease with more prolonged immersion (43, 46). Our control group showed the expected change in HR, but the response was greatly diminished in our subjects with DS (Fig. 1). Victor et al. (46) showed that the cold-induced increase in HR was entirely a function of sympathetic activation, because HR changes were completely abolished by β-adrenergic blockade (propranolol). This suggests that our subjects with DS exhibited reduced HR responses as a result of reduced sympathetic activation in response to cold.

MAP is also expected to increase 15–30 mmHg during the first 2 min of cold immersion (16, 43, 46), consistent with our observations in the comparison group. However, our subjects with DS showed virtually no change in MAP (Fig. 2) during the cold pressor test. Studies of muscle sympathetic nerve activity have shown that the increase in MAP is caused by increased sympathetic activation (31, 46), as changes in MAP are closely mirrored by changes in muscle sympathetic nerve activity. Thus the reduced BP responses during cold pressor testing in our subjects with DS are also consistent with reduced sympathetic activation in these subjects.

It is possible that the reduced hemodynamic responses during the cold pressor test in subjects with

**Impact of Obesity**

Obesity impairs autonomic control of HR and BP (28, 36, 49). However, responses to isometric handgrip exercise have been varied. Obese individuals have been shown to exhibit both higher (49) and lower (45) BP responses during isometric handgrip exercise. Obese patients have also been shown to exhibit lower sympathetic response to cold exposure (28). In our study, 

### Table 2. Absolute heart rate, systolic and diastolic blood pressure responses of nonobese (BMI < 30) and obese (BMI > 30) subjects with Down syndrome to 2-minute cold pressor and isometric handgrip (30% MVC) testing

<table>
<thead>
<tr>
<th>Variable</th>
<th>Rest</th>
<th>30 Seconds</th>
<th>120 Seconds</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Nonobese</td>
<td>Obese</td>
<td>Nonobese</td>
</tr>
<tr>
<td>CP heart rate, beats/min</td>
<td>70.6 ± 5.8</td>
<td>74.7 ± 4.1</td>
<td>70.2 ± 5.5</td>
</tr>
<tr>
<td>HG heart rate, beats/min</td>
<td>66.4 ± 4.6</td>
<td>77.7 ± 4.2</td>
<td>66.1 ± 4.2</td>
</tr>
<tr>
<td>CP SBP, mmHg</td>
<td>114.9 ± 7.2</td>
<td>129.4 ± 4.8</td>
<td>110.6 ± 12.2</td>
</tr>
<tr>
<td>HG SBP, mmHg</td>
<td>112.2 ± 6.6</td>
<td>129.9 ± 5.5</td>
<td>111.2 ± 6.7</td>
</tr>
<tr>
<td>CP DBP, mmHg</td>
<td>53.5 ± 4.4</td>
<td>63.1 ± 3.7</td>
<td>48.3 ± 5.3</td>
</tr>
<tr>
<td>HG DBP, mmHg</td>
<td>53.1 ± 6.9</td>
<td>67.3 ± 5.8</td>
<td>49.9 ± 5.0</td>
</tr>
</tbody>
</table>

Values are means ± SE; n = 5 nonobese and 7 obese subjects. CP, cold pressor test; HG, isometric handgrip test; SBP, systolic blood pressure; DBP, diastolic blood pressure. There was not a significant group main effect nor any significant group-by-time interactions.
DS were influenced by impaired peripheral somatosensory function in this population. Recent data showed that both sensory nerve conduction velocity and action potential amplitudes were significantly reduced in individuals with DS compared with controls (1). Furthermore, Hennequin et al. (19) showed that individuals with DS experienced increased pain latency in response to ice placed on the hand and forehead. Thus both sensory nerve and nociceptor function may be altered in persons with DS, which could at least partially explain the reduced hemodynamic response to cold that we observed in this population.

**Significance of the Handgrip Test**

Two minutes of isometric handgrip exercise at 30–35% of maximal voluntary contraction are expected to induce HR increases in the magnitude of 15–20 beats/min (22, 40, 43). Our comparison group exhibited the expected increase in HR, but our subjects with DS showed only 50% of the expected increase (Fig. 1). The increase in HR during the first minute of isometric handgrip exercise at this intensity is mediated primarily by vagal withdrawal, as it is not affected by β-blockade but is either mostly, or completely, abolished by atropine (15, 22, 26). A gradual increase in sympathetic activation, together with vagal withdrawal, accounts for HR changes after the first minute (20, 22, 40, 43). Our data, showing that the subjects with DS exhibited reduced increases in HR at both the 30- and 120-s time periods, suggest that subjects with DS exhibit both increased parasympathetic and decreased sympathetic modulation of HR during isometric handgrip exercise.

MAP increases 25–40 mmHg with 2 min of isometric handgrip exercise at contraction intensities between 30 and 35% of maximal voluntary contraction (21, 22, 40, 43). The BP changes observed in our comparison group are within these expected increases (Fig. 2). Conversely, the BP changes in our group with DS were approximately one-half of the expected response after the 2-min contraction. Furthermore, the initial response (first 30 s) was a slight decrease in both systolic and diastolic pressure in our subjects with DS, which is in the opposite direction of the expected response. Seals et al. (40) showed that the initial increase in arterial BP during isometric contractions >25% of maximum was a function of tachycardia, and the increase after the initial 1–1.5 min was due to increased sympathetic stimulation, as they showed by increases in muscle sympathetic nervous activity. Because the initial increase in HR is due to vagal withdrawal (22), it is likely that the initial increase in arterial BP is a function of increased cardiac output as a function of increased HR, caused by vagal withdrawal. Actual measurements of cardiac output during isometric handgrip support this notion, as stroke volume does not change (43). Consequently, the reduced BP response during isometric handgrip exercise in the subjects with DS was probably a function of reduced vagal withdrawal and reduced sympathetic stimulation.

**Evidence in Support of Blunted Vagal Withdrawal**

The main evidence in support of blunted vagal withdrawal in subjects with DS from our study is the reduced HR response during the first 30 s of the handgrip test. The cold pressor test is primarily a test of global sympathetic activation, as shown by Victor et al. (46); thus the reduced HR response during this test is not an indication of blunted vagal withdrawal. Because Maciel et al. (26, 27) and Flessas and Ryan (15) have shown that β-blockade slightly diminishes, but does not eliminate, the early HR response to isometric handgrip exercise, the contribution of sympathetic stimulation to the early HR increase is minimal. However, atropine almost completely eliminates the early HR response (15, 26, 27); thus this increase appears to be caused by parasympathetic withdrawal. The blunted HR response at 30 s in our subjects with DS is consistent with blunted vagal withdrawal. In support of this notion, we have observed blunted vagal withdrawal, measured by HR variability analysis, during handgrip exercise in a small number of subjects with DS (unpublished observations). We have also observed greater vagal influence at rest, through HR variability analyses (47), in subjects with DS, suggesting that parasympathetic influence is greater in this population. However, Sacks and Smith (39) showed greater pupil dilation in response to an anticholinergic agent in individuals with DS, consistent with enhanced cholinergic sensitivity. Because enhanced receptor sensitivity can be a function of receptor upregulation in response to reduced cholinergic function, they interpreted their findings as reduced cholinergic drive in subjects with DS. This is in contrast to our findings, but studies that simultaneously investigate cholinergic drive and receptor sensitivity in subjects with DS are lacking.

**Evidence in Support of Decreased Sympathetic Modulation**

The data from both the cold pressor and the handgrip test show that sympathetic modulation is reduced in individuals with DS. Both the HR and BP responses to the cold pressor test are primarily caused by sympathetic stimulation (46), and these responses were greatly diminished in our subjects with DS. Furthermore, both the late HR and BP responses during handgrip testing are caused primarily by sympathetic stimulation (40), and these responses were also reduced in our subjects with DS. The notion that individuals with DS have reduced sympathetic responses to stress is supported by Eberhard et al. (4), who showed that circulating catecholamines in response to incremental cycle ergometer exercise were reduced in individuals with DS. Udeschini et al. (44) showed no increase in catecholamines after 1 min of cold pressor testing in individuals with DS, whereas controls showed an increase, but there was no difference between controls and subjects with DS. This study also showed reduced HR and BP responses to cold pressor testing in subjects with DS, but these were also not different from con-
trols. It is likely that these nonsignificant findings were due to the low number of subjects in the study \((n = 5)\), and power analyses on their data show that, with 18–20 subjects per group, the responses of the individuals with DS would be significantly different from those of controls.

It is possible that reduced levels of circulating catecholamines contribute to the lower maximal HRs in individuals with DS, as reduced sympathetic drive or response has been postulated to be the cause of chronotropic incompetence in other populations \((25, 29, 32, 41)\). Consistent with this notion, human skin fibroblasts from individuals with DS were hyperresponsive to \(\beta\)-adrenergic stimulation, suggesting receptor upregulation \((30)\). This would also be consistent with lower levels of plasma dopamine \(\beta\)-hydroxylase activity in individuals with DS, because this enzyme converts dopamine to norepinephrine \((24)\). However, despite the lower levels of \(\beta\)-hydroxylase, resting and standing levels of plasma norepinephrine were higher in subjects with DS compared with healthy controls \((7)\), but neither of these studies \((3, 7)\) reported orthostatic responses between individuals with DS and controls \((24)\). These conflicting findings suggest that more research is needed on the mechanism of the reduced sympathetic response to exercise and cold stress in individuals with DS.

Possible Impact of Impaired Baroreceptor Function

It is possible that abnormal baroreceptor function, manifested through an impaired baroreflex, could alter the HR and BP responses to both static and dynamic exercise. In normal healthy controls, the arterial baroreflex gain is reset during both static and dynamic exercise \((20, 38)\), allowing HR to increase in the presence of increased BP. It is possible that an impaired baroreflex could affect the HR increase during exercise in subjects with DS; however, little evidence exists to support this concept. Anecdotal observations of excessive drops in BP with standing (orthostatic hypotension) have been reported \((2)\), but no systematic studies reporting orthostatic hypotension in subjects with DS exist. The orthostatic index has been shown to be lower in subjects with DS than controls \((3)\), indicating a lesser increase in HR in response to standing. We recently showed lower HR increases in response to a 10-min upright tilt in subjects with DS compared with healthy controls \((7)\), but neither of these studies \((3, 7)\) measured BP. Others have shown no differences in orthostatic responses between individuals with DS and healthy controls. Both HR and BP changes during a sit-to-stand task were slightly lower in subjects with DS \((24)\), but these differences were not significant. Udeschini et al. \((44)\) supported these findings, showing no difference in the HR and BP responses from sitting to standing between subjects with DS and controls. Thus there are conflicting reports regarding the HR response to an orthostatic challenge in individuals with DS, but little evidence for an abnormal baroreflex in this population.

Chronotropic Incompetence

Chronotropic incompetence in response to maximal exercise is well documented in persons with DS \((8, 10–12)\). The low maximal HR in this population is not caused by lack of effort or poor motivation \((10–12)\), but has been speculated to be a physiological consequence of DS \((6, 10)\). The physiological mechanism for the chronotropic incompetence is unknown, but it has been speculated that altered autonomic function plays an important role in populations without DS \((25, 32)\). Our data support the notion that autonomic dysfunction may explain the chronotropic response to exercise in individuals with DS, showing both reduced vagal withdrawal and blunted sympathetic response to isometric exercise and cold stress. Both reduced vagal withdrawal and reduced sympathetic drive have been implicated as possible mechanisms for chronotropic incompetence in populations without DS \((25, 41)\).

Limitations

There are several limitations to this study. First, we did not directly measure sympathetic and parasympathetic modulation of the HR and BP responses but made inferences based on information from prior studies regarding control of these responses during handgrip and cold pressor testing. Thus we can only speculate on possible mechanisms for observed responses. However, the control mechanisms for HR and blood changes during these tasks are well established. Although HR variability analyses may provide additional insight, such analyses require 5-min steady-state data. This was not possible in our study, because both HR and BP changed throughout the 2-min measurement periods. Thus steady state was not achieved, and our measurement periods were too short to yield reliable HR variability results. Second, DS is a genetic disorder with diverse physiological consequences. It is not known if our results are generalizable to other populations of subjects with DS. However, physical work capacity and HR responses to maximal exercise are remarkably consistent in the literature, and our present data are similar to previously reported data. Third, maximal treadmill exercise and handgrip exercise are effort dependent; thus it is possible that our subjects with DS may have produced lower effort than our control subjects. We used validated protocols and accepted criteria for peak effort during the maximal treadmill testing, which were achieved by all of our subjects. During handgrip exercise, several peak efforts were produced, and we used the best response, which is an accepted method for determining peak handgrip strength and is a reliable measure of handgrip strength in subjects with \((\text{intraclass reliability} >0.93 \text{ in our laboratory})\) and without DS \((33)\). During the submaximal 2-min handgrip task, computer feedback was used to aid subjects to maintain the correct effort. The investigators also provided feedback to ensure that the appropriate level of contraction was maintained. The response during cold pressor testing is not effort dependent and yielded similar re-
sults. Thus we do not believe that our data were substantially influenced by lack of effort in our subjects with DS.

In conclusion, we observed blunted HR and BP responses during cold pressor testing and isometric handgrip exercise in individuals with DS. The blunted HR response during these tasks may explain the chronotropic incompetence observed during maximal treadmill exercise in subjects with DS. Our results apply only to individuals with DS without congenital heart disease, because no subjects with congenital heart disease were included in this study.

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