Altered autonomic cardiac regulation in individuals with Down syndrome

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Altered autonomic cardiac regulation in individuals with Down syndrome. Am J Physiol Heart Circ Physiol 289: H2387–H2391, 2005. First published July 15, 2005; doi:10.1152/ajpheart.00560.2005.—We tested the hypothesis that individuals with Down syndrome, but without congenital heart disease, exhibit altered autonomic cardiac regulation. Ten subjects with Down syndrome (DS) and ten gender- and age-matched healthy control subjects were studied at rest and during active orthostatism, which induces reciprocal changes in sympathetic and parasympathetic traffic to the heart. Autoregressive power spectral analysis was used to investigate R-R interval variability. Baroreflex modulation of sinus node was assessed by the spontaneous baroreflex sequences method. No significant differences between DS and control subjects were observed in arterial blood pressure at rest or in response to standing. Also, R-R interval did not differ at rest. R-R interval decreased significantly less during standing in DS vs. control subjects. Low-frequency (LFnu) and high-frequency (HFnu) (both expressed in normalized units) components of R-R interval variability did not differ between DS and control subjects at rest. During standing, significant increase in LFnu and decrease in HFnu were observed in control subjects but not in DS subjects. Baroreflex sensitivity (BRS) did not differ between DS and control subjects at rest and underwent significant decrease on going from supine to upright in both groups. However, BRS was greater in DS vs. control subjects during standing. These data indicate that subjects with DS exhibit reduced HR response to orthostatic stress associated with blunted sympathetic activation and vagal withdrawal and with a lesser reduction in BRS in response to active orthostasis. These findings suggest overall impairment in autonomic cardiac regulation in DS and may help to explain the chronotropic incompetence typically reported during exercise in subjects with DS without congenital heart disease.

Autonomic nervous system; arterial baroreflex; heart rate variability; orthostatic stress

IT HAS RECENTLY BEEN SUGGESTED that subjects with Down syndrome (DS) not suffering from concomitant congenital heart disease may exhibit a dysfunction in autonomic cardiac regulation, which would manifest mainly with a reduced heart rate (HR) response to excitatory stimuli (4). Specifically, studies dealing with work capacity in subjects with DS reported a reduced HR response to exercise (5–7, 13, 14), which was tentatively explained by a blunted sympathetic activation. Recently, Fernhall and Otterstetter (4) reported reduced blood pressure (BP) and HR responses to cold pressor test and static handgrip in adults with DS without congenital heart defects. On the basis of these hemodynamic responses, the authors speculated that subjects with DS have reduced sympathetic activation associated with reduced vagal withdrawal. In contrast, Udeschini et al. (39) observed no significant differences in BP and HR responses to cold pressor test between subjects with DS and control subjects. Similarly, whereas one recent study (8) observed a reduced HR response to head-up tilt, other studies have shown no differences in response to active orthostasis between individuals with DS and healthy control subjects (39). Hence, although there is some evidence of impaired autonomic cardiac regulation in response to excitatory stimuli in subjects with DS, the data are still conflicting. In addition, the more subtle mechanisms of this impairment have received less attention. In fact, studies performed so far have made inferences based on the target organ response, that is, HR. Only a few studies have directly assessed sympathetic and vagal cardiac modulation in awake subjects with DS, reporting no differences in autonomic cardiac modulation at rest and a reduced vagal withdrawal in response to brief isometric handgrip (10) and submaximal dynamic exercise (1), without differences in cardiac sympathetic activation in these patients compared with healthy individuals (10) or people with mental retardation without DS (1). Finally, there is no information on the baroreflex control of the sinoatrial node, which is a key component of cardiovascular homeostasis to challenging stimuli and carries relevant pathophysiological and prognostic information (23, 29). A more thorough understanding of autonomic cardiac regulation in subjects with DS might have important clinical implications, because life expectancy is greatly enhanced in this patient population (3) and alterations in autonomic cardiac regulation are associated with an increased cardiovascular risk (16). Therefore, in this study we investigated the HR response to active standing, a stimulus known to induce reciprocal changes in sympathetic and vagal outflow, in subjects with DS to test the hypothesis that all the mechanisms of neural cardiac regulation are impaired in this patient population.

METHODS

Subjects. We studied 10 subjects with DS (6 women and 4 men; mean age 26.3 ± 2.3 yr, body mass index 26.2 ± 1.1) and 10 healthy volunteers (6 women and 4 men; mean age 26.1 ± 4.0 yr, body mass index 23.9 ± 0.3; P = 0.064 vs. DS). Subjects with DS were recruited from the Developmental Disability program of the Pediatric Neurorehabilitation Division of the Istituto di Ricovero e Cura a Carattere Scientifico (IRCCS) San Raffaele, where they had been screened for cardiovascular disease through physical examination, resting ECG, and echocardiographic examination. Patients were also free from any diseases that could influence the autonomic nervous system, e.g., diabetes or other metabolic diseases and asthma or other respiratory illnesses.

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disorders. No subjects had severe mental retardation. No subjects were involved in regular physical activity.

All control subjects were normotensive, took no medication, and were free from any disease based on medical history and physical examination. All subjects were nonsmokers and were not involved in regular physical activity. All participants gave informed consent to the study after the nature of the study was explained. For subjects with DS, their parents gave informed consent. The protocol was approved by the Ethics Committee of the IRCCS San Raffaele Pisana.

Recorded variables. The electrocardiographic signal was recorded from a precordial chest lead. Arterial BP was continuously and noninvasively measured from the third finger of the hand with the plethysmographic method of the unloaded arterial wall (Finapres, Ohmeda 2300 NIBP monitor). Respiratory signal was recorded by means of a thoracic belt (Biopac). The three analog signals were sampled at 300 Hz/channel (Biopac Systems) and stored on a hard disk for subsequent analyses.

Protocol. The experiments were performed in the morning in a laboratory at ambient temperature (22–24°C). The subjects were required not to eat or drink coffee for at least 2 h. After instrumentation, the subjects lay supine for 15 min before experiments to relax in a room made dark and noiseless. The experiments consisted of 10 min of supine rest followed by 10 min of active orthostasis. With the subject supine, the arm with the instrumented finger was held extended in the midaxillary position. The elbow was also held by a padded support, whereas the forearm was free. In the standing posture, the arm with the instrumented finger was held extended by an adaptable support with the hand at heart level, taken as the fourth intercostal space (19).

Power spectral analysis. The methodology for spectral analysis was described in detail previously (17). Briefly, a derivative-threshold algorithm provided the continuous series of R-R intervals (tachogram) from the ECG signal. The harmonic components of R-R interval variability were evaluated by the autoregressive method (model order 8–12). Components in the frequency band from 0.03 to 0.15 Hz were considered as low frequency (LF) and those in the range from 0.15 to 0.4 Hz, which are synchronous with respiration, as high frequency (HF). Oscillations slower than 0.03 Hz were considered very low-frequency components. The power density of each spectral component was calculated both in absolute values and in normalized units (31, 38), the latter obtained by dividing the absolute power of each spectral component by total power after having subtracted from it the power of the direct current (DC) component, if present, and multiplying this value by 100. The normalization procedure is particularly helpful in allowing comparisons between subjects or experimental conditions characterized by differences in total power or in DC noise (31). LF and HF components of R-R interval variability, in normalized units, are considered an expression of sympathetic and vagal modulation of the sinoatrial node, respectively (18, 26, 31, 32, 38). Spectral analysis of the respiratory signal was performed on the signal sampled once for every cardiac cycle, using a procedure similar to that described for R-R interval. Respiratory spectra were used to assess the main respiratory frequency and to locate the respiratory component of the power spectral analysis of R-R interval variability.

Spontaneous baroreflex analysis. Details of this analysis were described previously (17–19). Briefly, the beat-by-beat time series of systolic blood pressure (SBP) and R-R interval were scanned by a computer to identify sequences of three or more consecutive beats in which SBP and R-R interval changed in the same direction, either increasing (+R-R/+SBP) or decreasing (−R-R−SBP). A linear regression was applied to each individual sequence, and only regressions with linear $r^2$ values $>0.85$ were accepted. The mean individual slope of the SBP-R-R interval relationship, obtained by averaging all slopes computed within a given test period, was then calculated and taken as a measure of the integrated baroreceptor reflex sensitivity for that period (2, 33). This method has provided reproducible results during many laboratory tests, including active orthostatism (19).

Statistics. Each variable was checked for normality of distribution by the Kolmogorov-Smirnov test. When the normality test was passed, parametric statistical analyses, which included Student’s paired and unpaired t-tests, were used. When the test was failed, nonparametric statistical analyses, which included the Wilcoxon test and the Mann-Whitney rank-sum test were used. Because the major part of autonomic variables had distributions that were significantly different from normal, nonparametric statistical tests were used for these variables. Values are presented as means ± SE or as median and interquartile range, as appropriate. Differences were considered statistically significant when $P < 0.05$.

RESULTS

Cardiovascular responses to standing. Arterial pressure (AP) was not significantly different in the supine posture between DS and control subjects (Table 1). During standing, AP did not change significantly from supine level in both groups. Supine R-R interval was not significantly different between DS and control subjects. In both groups, R-R interval decreased significantly during standing; however, R-R interval was significantly less in control subjects than in subjects with DS, and the magnitude of the R-R interval decrease was significantly greater in controls than in subjects with DS (199.3 ± 82 vs. 130.5 ± 56 ms; $P = 0.04$).

Power spectral and spontaneous baroreflex analyses. R-R interval variance did not differ significantly between DS and control subjects at rest and underwent a significant decrease during standing in both groups (Table 2). The tendency toward a greater variance in DS subjects was due to two subjects showing a very large variance. At rest, the HF and LF components of R-R interval variability were not significantly different between the two groups. During standing, control subjects showed significant increases and decreases in LF and HF R-R interval oscillations (in normalized units), respectively, whereas in subjects with DS no significant changes in either LF or HF oscillations (in normalized units) were detected. Baroreflex sensitivity (BRS) did not differ significantly between DS and control subjects in the supine posture and underwent a significant decrease during standing in both groups; however, BRS was significantly less in control subjects than in subjects with DS during standing. No significant

### Table 1. Cardiovascular responses to active orthostatism

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<tr>
<th></th>
<th>Down Syndrome</th>
<th>Control</th>
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<tbody>
<tr>
<td></td>
<td>Rest</td>
<td>Stand</td>
<td>Rest</td>
</tr>
<tr>
<td>R-R interval, ms</td>
<td>1,062.6±61.8</td>
<td>932.1±67.5*</td>
<td>925.1±40.7</td>
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<tr>
<td>Systolic blood pressure, mmHg</td>
<td>116.1±2.7</td>
<td>115.0±5.5</td>
<td>118.7±2.8</td>
</tr>
<tr>
<td>Diastolic blood pressure, mmHg</td>
<td>73.5±2.3</td>
<td>74.5±3.4</td>
<td>71.7±2.0</td>
</tr>
</tbody>
</table>

Values are means ± SE. Rest, resting in supine position; Stand, active orthostatism. *$P < 0.01$ vs. Rest; †$P < 0.05$ vs. Down syndrome.
difference was detected in BRS between increasing (+RR/+SBP) and decreasing (−RR/−SBP) BP ramps during either supine posture or standing in both experimental groups. Respiratory rate was not significantly different between DS and control subjects both in the supine posture (0.27 ± 0.02 vs. 0.28 ± 0.02 Hz) and while standing (0.29 ± 0.03 vs. 0.29 ± 0.02 Hz), with no significant changes on going from supine to standing in both groups.

**DISCUSSION**

The novel finding of the present study is that neural cardiac regulation in response to a physiological excitatory stimulus is impaired in patients with DS without overt cardiovascular diseases and involves alterations in both branches of the autonomic nervous system and baroreflex cardiac modulation. During supine rest, no significant differences were observed in AP, R-R interval, and neural cardiac modulation between subjects with DS and control subjects. As expected (19, 20, 28, 31), in healthy subjects active orthostatism, with the attendant sympathetic activation and decrease in vagal activity, induced a significant decrease in R-R interval, associated with a decrease in the HF and an increase in the LF components (in normalized units) of R-R interval variability, respectively, and a concomitant decrease in BRS. In contrast, in subjects with DS no significant changes in either LF or HF components of R-R interval variability were observed in response to standing and the decrease in R-R interval was significantly less than in controls; in addition, BRS, although reduced compared with the supine posture, underwent a lesser decrease in patients with DS compared with healthy subjects.

These findings clearly point toward an impaired autonomic cardiac regulation in patients with DS, which would not be evident at rest but would be manifested in response to a task like standing affecting the overall autonomic nervous system. The observed results would indicate both a blunted sympathetic activation and a reduced vagal withdrawal in response to orthostatic stress in patients with DS, both of which would contribute to the reduced tachycardic response to standing. The relatively lesser reduction in baroreflex opposition to HR changes at the current, similar AP levels, as suggested by the significantly greater BRS values during standing in DS compared with control subjects, might have also contributed to the reduced HR response.

To our knowledge, this is the first study to provide direct experimental evidence of an impairment of all the mechanisms regulating HR in patients with DS. This finding could provide a clue to explain, in part, the lower HR response to exercise and the low physical work capacity typically observed in patients with DS (4–7, 10, 13, 14), because HR increase during exercise is due to both vagal withdrawal and sympathetic activation, with a relevant contribution provided by a lessened baroreflex opposition to HR increase, i.e., a decreased BRS (17, 21). This study confirms recent data by Fernhall et al. (8) of a blunted HR response to upright tilt in DS but also extends them in that it provides direct experimental evidence as to the neural mechanisms involved in the blunted HR response to orthostatic stress. In this context, it should be pointed out that steady-state HR responses to upright tilt and active standing do not differ (40). The present investigation also confirms previous findings by Figueroa et al. (10) of the lack of significant differences between individuals with DS and healthy subjects in HR variability parameters at rest. Apparently at variance with the above findings, Baynard et al. (1) reported a significantly greater HF power at rest in patients with DS compared with individuals with mental retardation without DS. Although that study cannot be directly compared with the present study because of the lack of a nondisabled control group (1), it is of note that the difference in resting HF power in the study by Baynard et al. (1) was not significant when expressed in normalized units.

In contrast with the present study, Udeschini et al. (39) reported no significant difference in HR response to standing between individuals with DS and healthy individuals. However, their results were obtained in a very small sample size (n = 5), and no data were provided as to the autonomic mechanisms regulating the sinus node rate, making a comparison with our results difficult. In addition, the increase in HR on going from supine to standing in their control group was inappropriate (5 beats/min) for healthy people (40), raising some doubts about subject selection.

The present investigation, by its design, cannot define the mechanism(s) responsible for the impairment of autonomic cardiac regulation in DS. However, the consistent findings of abnormalities in brain stem auditory evoked potentials (9, 11), failure of growth and maturation in the brain from an early age, with loss of neurons (41, 42) and dendrites (37), and damage to the neurotransmitter system (27, 43) would provide the anatomic substrate for the autonomic dysfunction occurring at a central, brain stem, site as a result of the genetic disorder.
Our findings carry potential clinical implications. It has been suggested that chronotropic incompetence could help to explain the higher levels of cardiovascular disease among individuals with DS (34), inasmuch as chronotropic incompetence is associated with increased cardiovascular risk (22, 24, 25) even before heart disease develops (24, 35) in nondisabled populations, but the mechanism(s) of chronotropic incompetence is still to be clearly elucidated (24, 30, 36). The alteration in sympathetic, parasympathetic, and baroreflex cardiac modulation observed in the present investigation could provide the physiological basis for the chronotropic incompetence of DS patients, and this may be related to the increased risk of developing heart disease in subjects with DS who exhibit chronotropic incompetence. However, at present, it is not known whether chronotropic incompetence and impairment in autonomic cardiac regulation, separately or in relation with one another, have an impact on health outcome in people with DS. Individuals with DS are living longer than in the past (3, 15), with a median age of survival that is now over 60 yr (12). Given the longer life expectancy in this population, longitudinal studies may be warranted to evaluate the impact of impaired autonomic cardiac regulation on health outcome in DS patients.

Limitations of the study include the small sample size, which decreases the statistical power of the study. However, the consistency of several reports showing autonomic dysfunction in individuals with DS with the findings of the present study would support our conclusion of an impairment of autonomic control of HR in DS and suggests that our findings are not unique to the DS subjects in the present investigation. The possibility that caffeine ingestion could have influenced our results cannot be totally ruled out. However, not all subjects, either controls or persons with DS, were used to drinking coffee as a part of their breakfast, and often experiments were conducted in the morning more than 2 h after breakfast. In addition, there was no significant difference in BP, HR, or any autonomic variable at rest between control subjects and subjects with DS. Hence, we believe it very unlikely that our findings were substantially influenced by caffeine ingestion.

A final potential limitation of this study includes the indirect method used to assess changes in autonomic function. However, the issue of the validity of this approach to assess changes in autonomic regulation was recently addressed by experiments in humans (32). Direct recordings of muscle sympathetic nerve activity were performed during various states of autonomic regulation, as produced by graded infusions of vasodilators and vasoconstrictors. The presence of similar, coherent oscillations at low and high frequencies in nerve activity and R-R interval (as well as in BP) variability at various levels of induced pressure changes provided support for the use of LF and HF R-R variability components to obtain information on the changing state of sympathetic and vagal modulation of the sinoatrial node, respectively.

In conclusion, we investigated autonomic mechanisms of cardiac regulation in response to standing in patients with DS and observed blunted sympathetic activation and vagal withdrawal associated with a lesser reduction in baroreflex opposition to HR changes in response to active orthostatism in this patient population. These findings may help to explain the chronotropic incompetence typically reported in subjects with DS without congenital heart disease.

GRANTS

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REFERENCES


