Normal Heart Rate with Tilt, Yet Autonomic Dysfunction in Persons with Down Syndrome

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ABSTRACT

Persons with Down Syndrome (DS) exhibit altered autonomic function at rest and in response to adrenergic stimuli. It is unknown if a subset of persons with DS that have similar heart rate responses to a task would have similar responses in heart rate variability (HRV). **PURPOSE:** To compare cardiac autonomic function during upright tilt using HRV analysis in persons with and without DS when persons with and without DS were matched for the change in HR. **METHODS:** Persons with (25 ± 2 yrs; 30.4 ± 1.9 kg/m^2, n=15) and without DS (27 ± 2 yrs; 24.7 ± 1.1 kg/m^2, n=15) were matched on their HR response to a 5 min tilt at 80°, whereas a subset of persons with DS (28 ± 3 yrs; 33.5 ± 2.0 kg/m^2, n=11) were not matched for the change in HR. HRV was assessed in both the frequency (natural log transformation (Ln) of low frequency (LF), high frequency (HF), LF/HF ratio, and total power (TP)) and time domains (Root mean square of successive differences (RMSSD)). **RESULTS:** Changes in HR were similar in DS-Matched and control, but lower in DS-Not Matched. Tilt effects were observed for LnHF, LnTP, and RMSSD in all groups (*P<0.05). Both groups of persons with DS exhibited a reduction in LnLF with no change in the control group (†P<0.05). The increase in LF/HF was greater in the group without DS when compared to DS-Not Matched (8.71 ± 2.38 vs. 2.34 ± 1.39, P<0.05), but not when compared to DS-Matched (3.59 ± 1.10, P=0.075). **CONCLUSION:** Despite similar heart rate response to passive upright tilt in the DS-matched, we still observed reduced sympathetic dominance in response to upright tilt in persons with DS.

KEY WORDS: HEART RATE, AUTONOMIC FUNCTION, UPRIGHT TILT, DOWN SYNDROME.

INTRODUCTION

Paragraph Number 1 Reduced aerobic capacity is common in persons with Down syndrome (DS), even in the absence of congenital heart defects (4, 14, 18, 28, 33). One of the primary contributors to this lower work capacity is reduced peak heart rates (HR) in response to aerobic exercise (11, 20). It has been suggested that cardiac autonomic dysfunction may partially explain the blunted HR response in this population (12, 13). Indeed, several studies investigating cardiac autonomic function using heart rate variability (HRV) analysis have reported altered autonomic function in persons with DS (3, 15, 19, 34). Persons with DS exhibit reduced changes in parasympathetic modulation, coupled with lower sympathetic modulation in response to sympatho-excitatory perturbations, such as isometric handgrip exercise, and submaximal exercise (13, 16, 29). However, such perturbations are largely influenced by central command, which could mask intrinsic levels of autonomic function. Other perturbations that lead to less stimulation via central command, such as passive upright tilt, may yield insightful information regarding underlying autonomic control in this population.

Paragraph Number 2 Passive upright tilt is a procedure that minimizes central command (32) and adrenal catecholamines (5) when assessing autonomic regulation of HR. Only a few studies have investigated cardiac autonomic function during passive upright tilt in persons with DS (1, 2, 10). During passive upright tilt, a blunted HR response, another indicator of autonomic dysfunction, was reported in persons with DS, suggesting reduced sympatho-excitation (10). Using HRV analyses, attenuated parasympathetic withdrawal and sympatho-excitation has been reported in persons with DS when compared to persons without DS during passive upright tilt (2, 3). However, it is not clear if autonomic dysfunction is present in all persons with DS and if this autonomic dysfunction is the cause of the lower HR response to passive upright tilt in this population. It is also unclear if there is a subset of persons with DS who have normal changes in

HR and who do not exhibit autonomic dysfunction. To date, there are no studies that have compared the HR responses to passive upright tilt in a DS population, which groups them into the responders and non-responders. Since underlying autonomic dysfunction is associated with reduced work capacity and quality of life in persons with DS (12), it would be important to understand if a subset of persons with DS who have normal HR responses to sympathetic stressor also have normal autonomic function. This is especially important in population with DS, as autonomic function impacts functional capacity, activity levels, and quality of life (12). It is still unclear whether persons with DS who exhibit normal HR responses to sympathoexcitation have normal autonomic function, or if DS per se causes autonomic dysfunction regardless of the HR response to a sympathoexcitatory task. This warrants further investigation that compares autonomic function to a task that removes most of the influence of central command (e.g. tilt), whereby HR responses are matched between groups with and without DS.

Paragraph Number 3 Therefore, the purpose of this study was to compare cardiac autonomic modulation during passive upright tilt using HRV analysis in persons with and without DS matched for the change in HR. Our design included three different groups: persons with DS matched on HR response to passive upright tilt (DS-Matched) with controls without DS, persons without DS matched on HR response (control), and persons with DS that were not matched on the HR response (DS-Not Matched). It was hypothesized that DS-Matched would not exhibit altered cardiac modulation when compared to control. In contrast, we hypothesized the DS-Not Matched group would exhibit a reduced parasympathetic withdrawal and sympatho-excitation versus the two matched groups.

METHODS

Participants

Paragraph Number 4 A total of 49 persons aged 16 to 40 yrs participated in the study, 34 persons with DS and 15 without DS. Eight persons with DS were excluded because of missing HRV data; therefore, data on a total of 41 persons (26 persons with DS and 15 without DS) were used for analysis. Fifteen persons with and 15 without DS (total of 30, control) were matched for HR change (mean of 16 bpm) to passive head-up tilt. The participants with DS matched for HR were individually matched with the controls. The group with DS-Not Matched consisted of 11 persons. Participants with DS were recruited from local organizations and community support groups. Participants without DS were recruited from the local and university communities. All participants were in sinus rhythm and had a normal ECG. All participants with DS were sedentary, and the participants without DS were either sedentary or recreationally active (e.g. participating in less than 1.5 hr/wk of regular exercise). None of the participants had evidence or history of cardiovascular disease based on medical history. Participants were excluded from the study if they exhibited any form of cardiovascular disease including congenital heart disease, as were those with any medication that may alter cardiovascular responses. Other exclusion criteria included smoking, severe or profound intellectual disability, any pulmonary disorders, hypertension, and diabetes. All participants, as well as, the parent(s) and/or guardian(s) of the participants with DS signed informed consent forms prior to study participation. The protocol was approved by the Institutional Review Board.

Study Design

Paragraph Number 5 All participants were familiarized with tests (treadmill exercise test and passive upright tilt) prior to data collection. One to two additional familiarization sessions

were conducted for participants with DS to ensure satisfactory performance. Participants were 4 h post-prandial and refrained from caffeine and exercise for 24 h prior to data collection on each testing days, more than 1 but less than 21 days apart. The first day of testing consisted of a maximal exercise test on a motorized treadmill (Quinton, Bothell, WA) to confirm the presence of chronotropic incompetence in participants with and without DS. The passive upright tilt was performed on the second day in the morning at ambient temperature (22-24 C°) and consisted of a 10-min supine rest, followed by a 5 min head-up tilt at 80°. Body mass index (BMI) was calculated (kg/m^2).

Peak Aerobic Capacity

Paragraph Number 6 Detailed information on the protocols can be found elsewhere (4). In brief, participants with DS underwent an individualized graded protocol, and participants without DS underwent the same protocol, except at higher speeds. The initial stage consisted of comfortable walking for 3 min, followed by a 2-min stage of fast walking. From this point, treadmill grade was increased by 2.5% every 2 min until 12.5% grade was reached. Thereafter, the speed was increased every min until exhaustion. Oxygen uptake (VO_2) was measured using an on-line breath-by-breath system (Quark B^2, Cosmed, Rome, Italy), and the data were expressed in 20-sec averages.

Passive Upright Tilt

Paragraph Number 7 After being secured on an electrically controlled tilt table with straps located at the torso and thighs, participants rested in a supine position for 10 min before head-up tilt was initiated. Resting data were collected during the last 5 min of the 10-min period.

Participants were then tilted to 80° for 5 min. HR was collected using a single lead electrocardiogram (modified CM5) interfaced with a computer data collection system (BIOPAC, Santa Barbara, CA) at a sampling rate of 1,000 Hz. HRV was analyzed off-line.

Heart Rate Variability Analysis

Paragraph Number 8 HRV was analyzed in the frequency and time domains. As previously described (2, 3), the ECG data were automatically and visually analyzed and edited for arrhythmias and artifacts, and converted to a tachogram of the R-R interval. The harmonic components of R-R interval variability were evaluated from segments of 500 beats by the autoregressive method (model order 10) using the Heart Signal software (Oulu, Finland). The 2 primary components of the frequency domain analysis included low frequency (LF, 0.04-0.15 Hz) and high frequency (HF, 0.15-0.40 Hz) spectra (35). LF reflects both sympathetic and parasympathetic influences, although LF may be indicative of baroreflex sensitivity (17, 35). HF is a marker of parasympathetic modulation of HR, thus the LF/HF ratio is indicative of sympathovagal balance (35). The root mean square of successive differences (RMSSD), an additional indicator of parasympathetic modulation of HR (35), was analyzed in the time domain.

Data Analysis

Paragraph Number 9 Descriptive characteristics and treadmill exercise responses were compared between groups using one-way analysis of variance (ANOVA). Data were checked for normality of distribution using Shapiro-Wilk tests. Data that were skewed were either analyzed using a non-parametric test or were naturally log transformed (Ln) and analyzed using

parametric tests. A 3 x 2 ANOVA with repeated measures [group (DS-Not Matched, DS-Matched, and Control) by condition (rest vs. tilt)] was conducted on all dependent variables to compare differences between groups in response to tilt. When a significant group-by-condition interaction was detected, between-group differences at each level were examined using appropriate *post-hoc* analyses. To examine potential group differences in the change in HR with passive upright tilt we used Kolmogorov-Smirnov test of distributions between groups because the change in HR was not normally distributed. To examine the effect of differences in BMI and VO_{2peak} between groups, we repeated the analyses using BMI or VO_{2peak} as a covariate. Values are mean ± SE. The alpha level was set at 0.05. All data analysis was carried out using Statistical Package for the Social Sciences (SPSS, v 19.0, IBM SPSS, Inc., Armonk, NY).

RESULTS

Paragraph Number 10 Descriptive characteristics and treadmill exercise responses are shown in Table 1. Height, VO_{2peak} and HRpeak were higher, whereas BMI was lower in the control group when compared to DS-Matched and DS-Not Matched groups (P <0.05). No differences were found between groups in age and weight.

Paragraph Number 11 Resting HR was 70±3 bpm in the DS-Not Matched, 68±2 bpm in the DS-Matched, and 62±3 bpm in the control groups, respectively, with no group differences (P=0.06). HR change data are presented in Figure 1. HR change was lower in the DS-Not Matched group when compared to the DS-Matched and control groups (P< 0.05).

Paragraph Number 12 Raw HRV data in the frequency domain are shown in Table 2. No group differences at rest were found in any variable. In response to passive upright tilt, HF decreased similarly in all groups (P < 0.05). A significant interaction was found for LF/HF (P <

0.05). LF/HF increased during tilt in the DS-Matched and control groups. In Figure 2, the change in LF/HF was greater in the control group when compared to the DS-Not Matched group ($P<$ 0.05), but not when compared to the DS-Matched group ($P = 0.075$). No difference in LF/HF changes was found between the two DS groups.

Paragraph Number 13 Log transformations of HRV data in the frequency domain are shown in Figure 3. No group differences at rest were found in any of the frequency domain log transformed data, nor for RMSSD (Figure 4). In response to passive upright tilt, LnHF (Figure 3) and RMSSD (Figure 4) decreased in all groups ($P < 0.05$). A tilt effect was also observed for LnTP ($P < 0.05$), with an overall decrease in LnTP. There was a group-by-time interaction for LnLF ($P < 0.05$), in that only the DS–Matched group exhibited a reduced LnLF ($P < 0.05$; Figure 3). The power calculated for this interaction equals 0.74. No effect of tilt was observed in the control group, whereas the reduction in LnLF for the DS-Not Matched group approached significance ($P = 0.075$). Controlling for BMI or VO_{2peak} did not change the results of the present study.

DISCUSSION

Paragraph Number 14 This study examined whether cardiac autonomic modulation during passive upright tilt differs between persons with and without DS, when persons with DS were matched for the change in HR to persons without DS. The main finding was despite similar HR responses, persons with DS that were matched for changes in HR exhibited similar alterations in HRV during passive upright tilt compared to persons with DS with significantly lower HR responses. Furthermore, the changes in HRV in individuals with DS matched for HR response with controls were still significantly different than controls. This reduction in LnLF was

comparable to persons with DS whose HR response was not matched. Furthermore, the change in LF/HF was reduced in persons with DS whether or not the change in HR was matched. These results are consistent with the notion of altered HRV to perturbations in persons with DS, suggestive of autonomic dysfunction, regardless of the HR response (2, 13, 22).

Resting Autonomic Function

Paragraph Number 15 HRV analysis provides information largely on the parasympathetic modulation of the sinoatrial node at rest and during steady-state tasks (3, 25, 26, 35), with some parameters inferring a combination of parasympathetic and sympathetic (e.g. LF) modulation. At rest, several studies have found similar HR and cardiac autonomic modulation between persons with and without DS (2, 16). Mendonca et al. (30) compared HRV in adults with and without DS found that both groups exhibited similar resting HR and HRV parameters. Consistent with prior data, we also observed no differences in resting HRV measures and HR between groups, suggesting similar resting autonomic control of HR in persons with DS. In persons with intellectual disabilities with or without DS, Baynard et al. (3) reported a greater parasympathetic modulation at rest only in persons with intellectual disabilities with DS, suggesting DS is associated with increased parasympathetic modulation of the SA node at rest. In support of our data, Figueroa et al. (16) also observed similar resting HR and HRV in persons with DS when compared with persons without DS. Our results are supported by previous data that have shown that DS did not appear to be associated with altered autonomic modulation of HR at rest (2, 16, 30).

Tilt Response

Paragraph Number 16 Chronotropic incompetence, characterized by an inappropriate HR response to sympatho-excitatory perturbations, has been reported in persons with DS (13, 20). In the present study, HR increased similarly in response to passive upright tilt in persons without DS and persons with DS whose HR change was matched. However, the HR increase was approximately 30% lower in the non-matched group, suggesting an abnormal HR response to passive upright tilt in this group of persons with DS (20). Consistent with our data, Agiovlasitis et al. (2) also reported that despite similar HR responses to passive upright tilt, persons with DS exhibited depressed sympathetic modulation in response to passive upright tilt when compared to persons without DS. In the present study, we observed altered autonomic modulation to passive upright tilt, evidenced by the reduced LnLF power and LF/HF ratio, in both groups of persons with DS. Fernhall et al. (10) reported a blunted HR response to passive upright tilt in persons with DS, consistent with reduced sympatho-excitation. Together, those studies and ours are consistent in reporting reduced sympathetic dominance in persons with DS irrespective of their HR response to a perturbation with little central command such as passive upright tilt.

Paragraph Number 17 Consistent with passive upright tilt studies, altered cardiac autonomic dysfunction in persons with DS has been demonstrated during other sympatho-excitatory perturbations (16, 19). Fernhall et al.(13) has shown an attenuated rise in HR in response to isometric handgrip exercise and cold pressor testing in persons with DS, suggesting an attenuated response to sympatho-excitation. In contrast, one study reported similar parasympathetic withdrawal, but heightened sympathetic modulation during submaximal treadmill exercise in persons with DS (29). These studies employed perturbations that largely involve central command, which could contribute to inconclusive findings in sympatho-excitatory studies. These perturbations could potentially mask intrinsic levels of autonomic

function. Hence, in this study, we employed passive upright tilt, which minimizes central command (32) and adrenal catecholamines (5), while some degree of central command may be involved in the autonomic modulation of HR, possibly due to increased muscle tension and mental trepidation in anticipation to and during passive upright tilt (36), we still found altered cardiac autonomic function in persons with DS, despite normal HR changes.

Paragraph Number 18 Mechanisms explaining cardiac autonomic dysfunction in persons with DS are unclear. The interpretation of LF is controversial, with evidence suggesting that LF represents sympathetic outflow as well as a combination of both sympathetic and parasympathetic modulations (8, 27, 35). Several studies suggest that altered autonomic function could result from lower baroreflex sensitivity (21) or a blunted metaboreflex-induced pressor response (6) in persons with DS. Recently, a review study by Goldstein et al. (17) and a study by Moak et al. (31) reported that LF reflects baroreflex sensitivity instead of sympathetic modulation. It is possible that persons with DS exhibit reduced baroreceptor sensitivity; however, this was not assessed in the present study. Obesity is associated with autonomic dysfunction and reduced baroreflex sensitivity (23, 24). Our persons with DS were obese (BMI of >30 kg/m^2); however, controlling for BMI did not change the results of the present study. Our finding is consistent with other studies that report altered autonomic function in persons with DS that was independent of obesity (13, 16). Cardiorespiratory fitness is associated with autonomic function (12), but there was no difference in VO_{2peak} between the two groups with DS. Furthermore, controlling for VO_{2peak} did not alter our findings. Thus, differences between the two groups with DS cannot be explained by differences in cardiorespiratory fitness. Two studies have reported reduced catecholamine responses to exercise perturbations in persons in DS (7, 9). Even though this was not measured in the present study, it is possible that altered autonomic

function may partially be mediated by the attenuated catecholamine concentrations in persons with DS.

Paragraph Number 19 Our findings may have substantial clinical implications for persons with DS. Our data suggest that even in normal HR response to sympathetic stressor, like passive upright tilt, this does not indicate that persons with DS have normal autonomic function. In fact, both groups with DS exhibited similar VO_{2peak} and HR_{peak}. This suggests that HR responses to sympathetic tasks, other than maximal exercise, do not necessarily provide useful information regarding autonomic function or functional capacity in this population.

Limitations

Paragraph Number 20 Limitations of the present study warrant consideration. First, the present study is a retrospective study that matched persons with DS on changes in HR response to tilt, which led to a smaller sample size. Second, we did not control breathing rate, which can potentially affect measures of HRV (35); however, controlled breathing is not feasible in persons with DS. In addition, it is possible that some degree of central command may be involved due to possible muscle tension and mental trepidation in anticipation to and during passive upright tilt (36); however, persons with and without DS underwent the same challenge in the current study, yet autonomic dysfunction is still present in persons with DS, despite normal HR changes, and each person with DS was familiarized with testing several times. It is also plausible that autonomic dysfunction in the DS-Matched group may be partly due to sex differences within this group; however, this aspect cannot be explored in the current study due to small sample size. Finally, we used HRV, which is an indirect method, to assess cardiac autonomic function; however, this method has been validated (35).

Conclusion

Paragraph Number 21 We investigated cardiac autonomic function in persons with and without DS when matched for HR change to passive upright tilt and observed reduced sympathetic dominance in response to passive upright tilt in persons with DS despite similar HR responses.

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Figure Captions

Figure 1: Heart rate changes in response to passive upright tilt in persons with DS (DS-Matched), persons without DS (control), and persons with DS (DS-Not Matched). Values are means ± SE. *significantly different than the other groups ($P < 0.05$).

Figure 2: Low frequency: high frequency ratio changes in response to passive upright tilt in persons with DS (DS-Matched), persons without DS (control), and persons with DS (DS-Not Matched). Values are means ± SE. *significantly different than DS-Not Matched ($P < 0.05$).

Figure 3: The natural logarithms (Ln) of low frequency (LF), high frequency (HF), and total power at (TP) rest and during passive upright tilt in persons with DS (DS-Matched), persons without DS (control), and persons with DS (DS-Not Matched). Values are means ± SE. †interaction ($P < 0.05$). $^{\#}$significantly different from rest only in persons with DS (DS-Matched) ($P < 0.05$). ¶significantly different than in both groups of persons with DS (DS-Matched and DS-Not Matched) during tilt ($P < 0.05$). *tilt effect ($P < 0.05$).

Figure 4: The root mean square of successive differences (RMSSD) at rest and during passive upright tilt in persons with DS (DS-Matched), persons without DS (control), and persons with DS (DS-Not Matched). Values are means ± SE. *tilt effect ($P < 0.05$).

Table 1: Descriptive Characteristics

	DS Not Matched (n=11)	DS Matched (n=15)	Control (n=15)
Males/Females (n)	6/5	8/7	5/10
Age (yrs)	28 ± 3	25 ± 2	27 ± 2
Height (cm)	153.1 ± 2.7	152.2 ± 2.1	168.3 ± 2.1 *
Weight (kg)	78.5 ± 4.9	70.3 ± 4.1	70.2 ± 3.7
BMI (kg/m^2)	33.5 ± 2.0	30.4 ± 1.9	24.7 ± 1.1 *
VO_{2peak} (ml/kg/min)	22.5 ± 2.3	25.3 ± 1.7	39.1 ± 2.1 *
HR_{peak} (bpm)	164 ± 3	168 ± 4	187 ± 3 *
V_{Epeak} (L/min)	60.9 ± 5.0	67.5 ± 5.3	111.8 ± 5.5 *
RER_{peak}	1.08 ± 0.03	1.14 ± 0.02	1.24 ± 0.02 *

NOTE: Values are mean ± SE.BMI, body mass index; VO_{2peak}, peak oxygen consumption; HR_{peak}, peak exercise heart rate; V_{Epeak}, peak exercise ventilation; RER_{peak}, peak exercise respiratory exchange ratio. *significantly different than the two DS groups ($P < 0.05$).

Table 2: Raw Heart Rate Variability Data in the Frequency Domain in Response to Tilt

	DS Not Matched		DS Matched		Control	
	Rest	*Upright Tilt*	*Rest*	*Upright Tilt*	*Rest*	*Upright Tilt*
LF (ms^2)	1948 ± 755	1637 ± 934	1304 ± 178	770 ± 154	1466 ± 289	1830 ± 377
HF (ms^2) *	1155 ± 419	890 ± 364	1308 ± 359	272 ± 312	1555 ± 359	825 ± 312
LF/HF †	1.76 ± 0.49	4.10 ± 2.13	2.27 ± 0.45	5.87 ± 1.96 #	1.69 ± 0.42	10.41 ± 1.82 #
TP (ms^2)	6435 ± 1789	6188 ± 2243	3995 ± 1646	2321 ± 2063	4461 ± 1532	4921 ± 1921

NOTE: Values are mean ± SE. LF, low frequency; HF, high frequency; LF/HF, low frequency to high frequency ratio;

TP, total power. †interaction ($P < 0.05$). *tilt effect ($P < 0.05$). #significantly different from rest ($P < 0.05$).

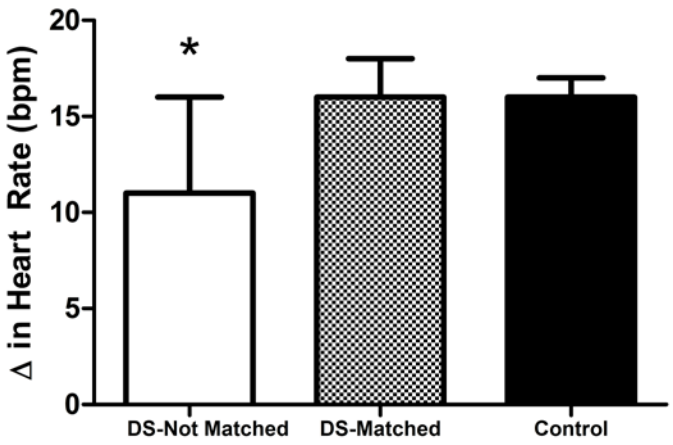
20
15
10
5
0
Δ in Heart Rate (bpm)
*
DS-Not Matched
DS-Matched
Control

Figure 1

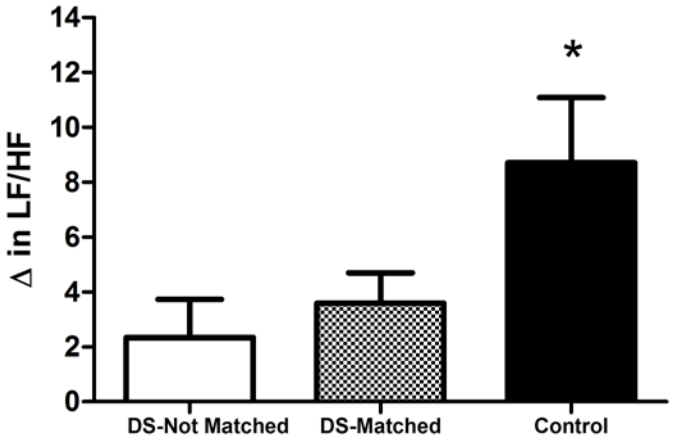

Figure 2

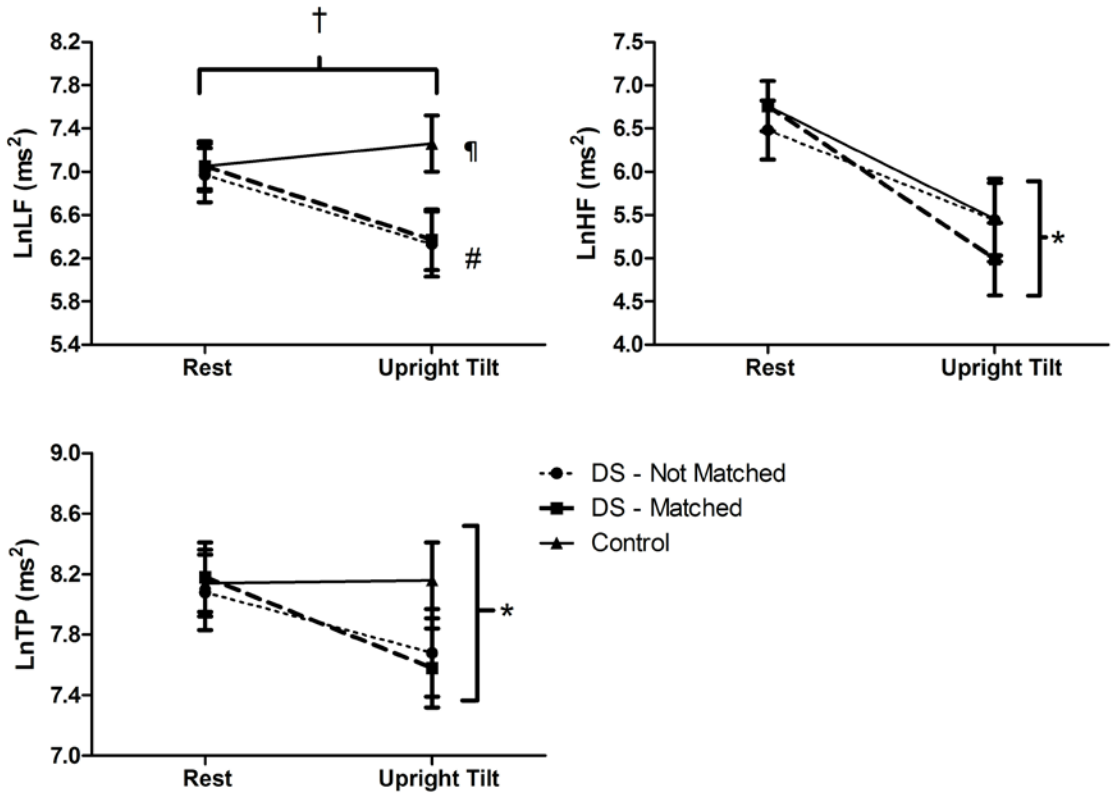

Figure 3

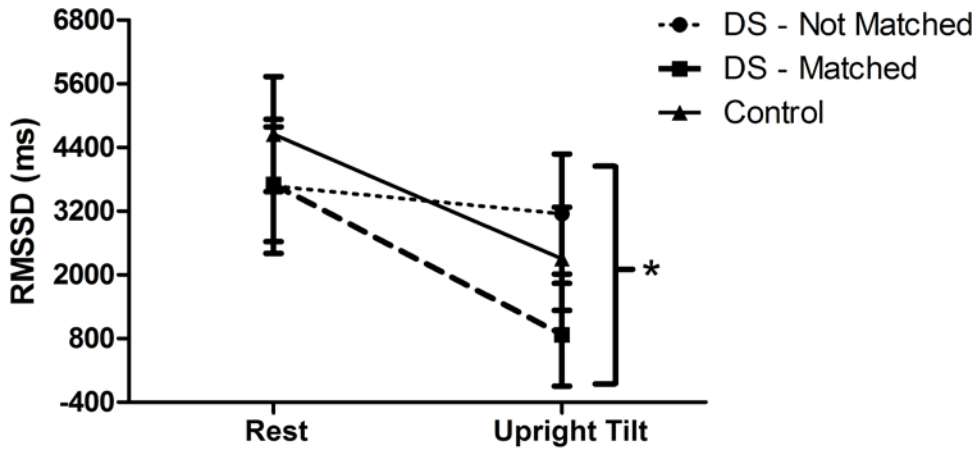
6800
5600
4400
3200
2000
800
-400
RMSSD (ms)
Rest
Upright Tilt
DS - Not Matched
DS - Matched
Control
*

Figure 4