

Original article

Reduced cardiac parasympathetic activity in children with autism

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Abstract

Many of the clinical symptoms of autism suggest autonomic dysfunction. The aim of this study was to measure baseline cardiovascular autonomic function in children with autism using the NeuroScope, a device that can measure this brainstem function in real-time. Resting cardiac vagal tone (CVT), cardiac sensitivity to baroreflex (CSB), mean arterial blood pressure (MAP), diastolic blood pressure (DBP), systolic blood pressure (SBP) and heart rate (HR) were recorded in three different groups of children. The symptomatic group ($n=15$) consisted of those with autism who exhibited symptoms or signs of autonomic dysfunction. The asymptomatic group ($n=13$) consisted of children with autism but without symptoms or signs of autonomic dysfunction and the healthy children were in the control group ($n=117$). The CVT and CSB were significantly lower in association with a significant elevation in HR, MAP and DBP in all children with autism compared with the healthy controls. Further more, the levels of CVT and CSB were lower in the symptomatic than in the asymptomatic group. The levels of CVT and CSB were not related to age in all the three groups. These results suggest that there is low baseline cardiac parasympathetic activity with evidence of elevated sympathetic tone in children with autism whether or not they have symptoms or signs of autonomic abnormalities.

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Autism is a complex neurodevelopmental disorder affecting multiple organs and systems of the body. Abnormal structures of the amygdala, limbic system, prefrontal lobes, basal forebrain, brainstem and cerebellum have been found in post mortem studies of patients with autism [1–3]. Abnormal levels of neurotransmitters including norepinephrine, dopamine, acetylcholine, serotonin and neuropeptides have been found in children with autism [4,5]. Animal models with altered neurotransmission of serotonin, oxytocin and GABA exhibit behavioral disorders resembling autism in some features [6–8]. All these brain

structures and neurotransmitters can affect autonomic function.

Many individuals with autism exhibit symptoms in multiple organ systems that are associated with autonomic dysfunction. Up to 80% of children with autism have sleep disorders by parental report [9], and polysomnographic studies have shown disordered sleep in autism [10,11]. Gastroenterological symptoms such as chronic constipation and diarrhea, and psychiatric disorders such as anxiety and other mood disorders have been reported in autism as well [5,12].

Studies of the peripheral autonomic nervous system in autism have demonstrated the following abnormal functions. Skin conductance response (SCR) studies in autistic children have shown a lack of the normal habituation in the magnitudes of SCR to the same stimulus over time [13,14]. Palkovitz and Wiesenfeld [15] did not, however, find differences in electrodermal responses to auditory stimuli compared to normal control, although they noted that the autistic group had a higher baseline electrodermal level.

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Children with autism had blunted autonomic arousal to visual or auditory social stimuli, for example, heart rate and Galvanic skin responses to such stimuli [15,16]. However, these autistic children had hyper-responsive sympathetic system, the fight or flight response [16]. Hutt and Hutt [17] had speculated previously that autism involves chronically high arousal levels, and Barry and James [14] also observed larger tonic electrodermal activity as well as larger responses to sounds in autistic children compared to controls. All these are indications of increased sympathetic tone in autism.

A study of the anti-epileptic effect of vagal nerve (parasympathetic) stimulator in four patients who had autism and medically refractory epilepsy showed striking improvements in both the autistic behaviors and seizure activity in all four patients during treatment with intermittent left vagal nerve stimulation [18]. The improvement of autistic behaviors during stimulation of the parasympathetic nervous system could be due to the suppression of the sympathetic activity, which may suggest that chronic hyperactivity of the sympathetic nervous system may be a factor in some of the autistic behaviors. However, it remains to be established whether the improvement in autistic behaviors during intermittent left vagal nerve stimulation was the result of a better seizure control other than the suppression of sympathetic activity.

The aim of this study was to evaluate the brainstem autonomic function in children with autism at a pre-determined steady state we shall now refer to as the baseline. No previous study has measured baseline function of the brainstem in autism to our knowledge. It has only recently been made possible to measure the baseline cardiovascular autonomic function that is controlled by the brainstem using a continuous, real-time and non-invasive method. A digital device called the NeuroScope (MediFit Diagnostics Ltd, London) can now derive a continuous index of cardiac vagal tone (CVT) [19]. It can also provide a continuous method of monitoring and quantifying the cardiac component of the baroreflex gain in real-time in humans [20]. The validity of this method has been confirmed recently during cardiovascular surgery in human subjects [21]. Therefore, we now have the means for continuous monitoring of indices of cardiac baroreflex sensitivity and cardiac vagal tone, both of which are regulated in the brainstem. We used this technique to study brainstem autonomic function in children with autism and compare it with healthy children of a similar age group.

2. Methods

2.1. Subjects

Children with autism were recruited from The Autism Center, and control healthy children were recruited from the Pediatric Ambulatory Service, both at the University of

Medicine and Dentistry of New Jersey-New Jersey Medical School, Newark, NJ. Children who were autistic due to known syndromes (double syndrome) [5] were excluded from the study. The diagnosis of autism was verified by criteria of Diagnostic and Statistical Manual of Mental Disorders IV, and Autism Diagnostic Observational Schedule-Generic or Autism Diagnostic Interview-Revised.

The subjects in this study were divided into three groups of children as follows. *The symptomatic group*: consisted of 15 children with autism who exhibited at least two of the following signs or symptoms of autonomic dysfunction that had persisted for at least 1 year as reported by parents and confirmed by a physician during a history and/or physical examination. They include unexplained chronic constipation or diarrhea, unexplained urinary retention or dysuria, a history of syncope or documented unexplained orthostatic hypotension, chronic cold and clammy extremities at rest irrespective of ambient temperature, a chronic daily abnormal pattern of breathing, and daily sleep disorder manifested by a prolonged latency in sleep initiation and/or frequent nocturnal arousals. The pediatric neurologist (XM) followed all our subjects for at least one year and these symptoms or signs persisted for a minimum of 1-year prior to this study. Many subjects had these signs and symptoms for many years, however, the duration of symptoms was not recorded for each subject because the data was based on parents' recollections in two thirds of the patients, and the reliability of these recollections was unknown. *The asymptomatic group*: consisted of 14 children with autism who had no clinical evidence of the autonomic signs or symptoms listed above. *The control group*: consisted of 17 healthy children who did not have personal or family history of autonomic symptoms and signs listed above, chronic illnesses or developmental disorders. *Exclusion criteria*: children who took medicines known to affect the autonomic nervous system within 48 h of the study were excluded from the final data analysis. These included medicines such as clonidine, resperidone, amphetamines and other psychostimulants. All the subjects were screened on the day of the study for acute illnesses such as upper respiratory infection, physical and emotional stress and sleep disturbances the night before the study. Those subjects with any of the above confounding factors had their studies rescheduled for another suitable day. Medication use was carefully recorded. The summaries of subjects' profiles in the three groups are shown in Table 1.

All the subjects with autism were patients attending The Autism Clinic and all racial and ethnic backgrounds were represented. There was, however, a skewed representation of male subjects, which reflects the male predominance in this disorder. Effort was made to control the skewed male representation in the healthy control group. Subjects who were taking anti-epileptic medications were asked not to discontinue their treatment.

Table 1
Characteristics of the subjects

Group	Age (years)	Sex	Medication ^a
Autism with symptoms (1)	9.4 ± 4.9	12 M, 3 F	Topiramate (2), Phenytoin (1), Oxycarbamazepine (1), Valproate (3), Montelukast (2)
Autism without symptoms (2)	9.3 ± 3.3	12M, 2F	Topiramate (1), Valproate (1)
Healthy children (3)	8.3 ± 4.7	11M, 6 F	None

^a Medicines taken within 24 h of the study. The numbers in the parentheses indicate the number of subjects taking the respective medicines.

The study protocol was approved by the Institutional Review Board of University of Medicine and Dentistry of New Jersey-New Jersey Medical School.

2.2. Measurement of the cardiac sensitivity to baroreflex (CSB)

The non-invasive index CSB was measured using the NeuroScope (MediFit Diagnostics Ltd, London, UK) as previously described [20,22]. The index is defined as the increase in pulse interval per unit increase in systolic blood pressure. The CSB is calculated according to the formula published previously [23]. The method allows detection of rapid changes in CSB within a continuous measurement.

2.3. Measurement of cardiac vagal tone (CVT)

The non-invasive index CVT was measured on a continuous beat-to-beat basis using the NeuroScope as described previously [19]. The index is defined as ‘pulse-synchronized phase shifts in consecutive cardiac cycles’. It is essentially a form of pulse interval variability that is quantified continuously from the ECG [19]. The index CVT is measured and quantified in arbitrary units of a linear vagal scale (LVS). The least value in this scale is zero, equivalent to full atropinization of human subjects [24].

2.4. Study protocol

The test was performed in a quiet room in the presence of the subjects’ parents. Favorite music or videos known to relax the patients were played during the test when necessary. The parents had free access to the subjects during the entire study period. All the subjects rested in a reclined bed or chair with the head of the bed/chair elevated at 30° in order to support the head to minimize the contraction of neck muscles. The temperature of the room was controlled within 25–28 °C. All the subjects were studied between 10:30 AM and 3:30 PM. The subjects were allowed to rest for at least 10–15 min prior to the start of instrumentation. Recording was done during the best possible resting states of the subjects but data analysis was done during baseline state.

2.5. Definition of baseline state

The subjects would have reached a baseline state if there was no contraction of neck muscles and breathing was smooth and quiet (sinusoid breathing curve) with less than 10% fluctuations about the means in both blood pressure and heart rate from their peaks to troughs.

All the subjects in the symptomatic group and six children in the asymptomatic group had simultaneous EEG monitoring during the study. The EEGs were recorded using the paperless digital video EEG machine (Nicolet Biomedical, Madison, Wisconsin) and electrode caps (Electro-Cap International Inc, Eaton, Ohio).

The ECG was monitored continuously by placing three electrodes on the chest, which were then connected to the NeuroScope in Eithoven’s Lead II configuration. A small finger cuff with infrared sensor was placed on one of the digits of the less used hand, which was then held steadily by the subject’s parent to keep the digit extended when necessary. The finger cuff was connected to a Portapres (Finapres Inc, Belgium), which fed the arterial blood pressure data into the NeuroScope. Arterial blood pressure (BP) was monitored continuously during the study using this arrangement of instruments.

Breathing movements were continuously monitored using a stretch sensitive plethysmograph placed around the chest at the level of the xiphisternum. The plethysmograph was connected to the NeuroScope. Breathing movement was recorded continuously during the study.

Continuous records of BP, heart rate, breathing movements, CVT and CSB were generated and stored by the NeuroScope using VaguSoft software (MediFit Diagnostics Ltd, London, UK) with the subjects resting in supine positions, reclining, or standing.

2.6. Statistics

Data from autonomic function studies for all the groups was analysed for group differences, looking at both overall and pairwise differences. The following comparisons were made using Student’s *t*-test for each autonomic index: between the symptomatic group and controls groups, asymptomatic group and controls and between symptomatic and asymptomatic groups. Probability values (*P*) less than 0.05 were regarded as statistically significant. Data was also

examined for potential age effect among each group for each autonomic index using one-way ANOVA.

3. Results

3.1. Subjects

Sixty subjects were initially studied, 14 of whom were later excluded because they were unable to achieve the defined baseline state or because their medications had known effects on autonomic function and could not be discontinued before the study. One girl who had significant autonomic dysfunction clinically, had to be excluded from the final analysis due to very frequent epileptiform discharges in her EEG at baseline that could have possible effects on autonomic function. Two subjects did not complete the test due to anxiety and intolerance of the ECG pads and/or BP cuff. Blood pressure was unobtainable in the youngest subject (three year old) due to incompatibility of the BP cuff with her small fingers. A 19-year old girl could not keep her digit extended and we were unable to record her BP. A total of 46 subjects had data that was finally analyzed.

Three subjects had repeat studies for the following reasons. One had an occult respiratory infection during the day of the initial study, which was discovered retrospectively. Another subject had poor sleep the night before the initial study and the third subject had a seizure that affected autonomic function during the first study as indicated by pupillary dilatation, bradycardia and hypotension during the recording, there were also clinical and EEG evidence of seizure activity. The EEG recording during repeat study showed no abnormal findings.

The simultaneous awake EEG results of the subjects whose autonomic study were analyzed in this study were normal. Likewise, all the single lead ECG results analyzed were also normal.

Table 2a
Autonomic indices in the three groups

Indices	Autism with symptoms (N, Mean $\pm$ SD)	Autism without symptoms (N, Mean $\pm$ SD)	Healthy children (N, Mean $\pm$ SD)
CVT	15; 4.30 $\pm$ 1.70	14; 6.87 $\pm$ 3.95	17; 12.51 $\pm$ 4.94
CSB	13; 3.43 $\pm$ 1.63	12; 4.86 $\pm$ 3.45	17; 11.48 $\pm$ 4.98
HR	15; 102.5 $\pm$ 16.0	14; 92.9 $\pm$ 11.9	17; 84.9 $\pm$ 10.2
SBP	13; 124.09 $\pm$ 31.14	12; 117.52 $\pm$ 17.63	17; 108.38 $\pm$ 19.40
DBP	81.81 $\pm$ 24.57	76.69 $\pm$ 13.48	61.91 $\pm$ 12.80
MAP	95.90 $\pm$ 26.55	90.19 $\pm$ 13.76	77.40 $\pm$ 14.29

CVT: cardiac vagal tone (units of LVS); CSB: cardiac sensitivity to baroreceptor (ms mmHg⁻¹); HR: heart rate (beats/min); SBP: systolic blood pressure (mmHg); DBP: diastolic blood pressure (mmHg); MAP: mean arterial blood pressure (mmHg).

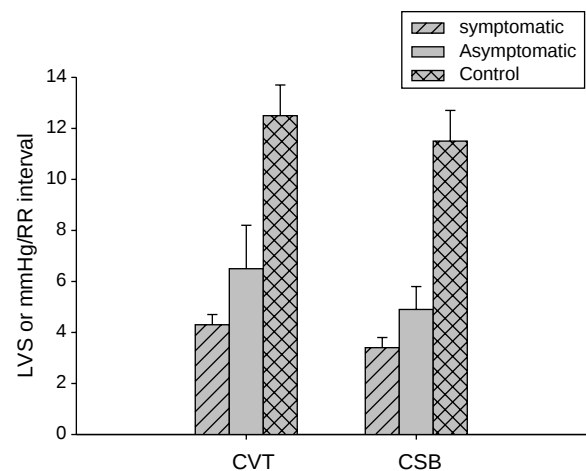


Fig. 1. Resting CVT and CSB in symptomatic, asymptomatic and control groups. CVT is measured as linear vagal scale and CSB is measured as change in mmHg of SBP per change of R–R interval. Values represent means $\pm$ S.E. See Table 2b statistical analysis.

3.2. Cardiac parasympathetic activity

Baseline levels of CVT and CSB are given in Table 2a and Fig. 1. The levels of CVT and CSB were significantly lower in autistic children with or without symptoms compared to those in controls ($P < 0.001$, Student *t*-tests for both CVT and CSB). There was also significantly lower CVT in the symptomatic group as compared with the asymptomatic group ($P < 0.05$, Student *t*-test). However, there was no difference in CSB between autistic subjects with symptoms and those without symptoms (Table 2b).

There was no significant correlation of age with both CVT (Correlation coefficient = -0.26 , $P = 0.34$) and CSB (correlation coefficient = -0.30 , $P = 0.32$). Approximately 93% (14/15) of the symptomatic autistic children and 53% (7/13) of the asymptomatic autistic children had CVT values below the lowest CVT value of 6.49 units in the LVS observed among the healthy control group. Based on this small study, the sensitivity of the index CVT for detecting autonomic dysfunction in this study was 93% and its specificity for the identification of autistic patients with clinically symptomatic autonomic dysfunction was 50% (14/28). The lowest CSB value in the healthy control group was 4.9 ms/mmHg. Eighty percent (12/14) of the autistic

Table 2b
Summary of pairwise comparisons (*t* statistic, *P*-value, degrees of freedom)

Variable	Symptomatic vs. controls	Asymptomatic vs. controls	Symptomatic vs. asymptomatic
HR	3.63, 0.001, 23	NS	NS
CVT	−6.42, 0.001, 20	3.52, 0.001, 28	−2.25, 0.038, 17
CSB	−6.24, 0.001, 20	4.23, 0.001, 26	NS
SBP	NS	NS	NS
DBP	−3.11, 0.004, 27	NS	NS
MBP	−2.53, 0.017, 28	NS	NS

NS: not significant. Student *t*-test.

children with symptoms had levels of their CSB below 4.9 ms/mmHg and 53% (7/13) of the autistic children without symptoms had levels of their CSB below 4.9 ms/mmHg. The sensitivity of CSB for detecting symptomatic autonomic dysfunction was 85% and the specificity for identification of autistic patients with clinical symptoms of dysautonomia was 44%.

3.3. Sympathetic activity

Diastolic (DBP) and mean arterial blood pressures (MAP) were significantly higher in the symptomatic group of autistic subjects compared to healthy children ($P < 0.01$ for DBP, $P < 0.05$ for MAP). Although the averages of DBP and MAP were slightly higher in autistic subjects with symptoms than those without symptoms of autonomic dysfunction, they were not statistically significant. Likewise, there was no significant difference in either DBP or MAP when comparing the asymptomatic group with control. Systolic blood pressures (SBP) were slightly higher in both autism groups compared to healthy children but the difference did not reach statistical significance (Table 2b and Fig. 2).

The resting heart rate was significantly higher in autistic subjects with symptoms compared with controls ($P = 0.001$, Table 2b, Fig. 3). However, there was no significant difference in the mean heart rate of the asymptomatic group compared to that of the control group. The HR in the control group is representative of the HR of national norms for children in the USA [25].

There was a significant age effect on HR when age was added as a covariate to the one-way ANOVA analysis ($F = 4.12$, $P = 0.001$). There were no consistent relationships among HR and either DBP or MAP within individual groups. The SBP, MAP and DBP of the control group are representative of national normal values for children in the USA [26].

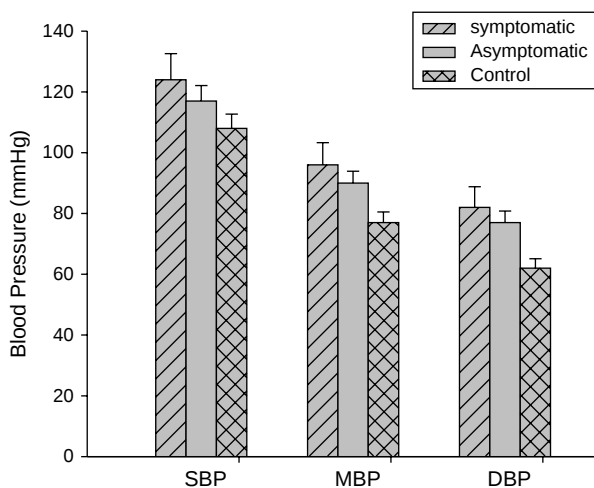


Fig. 2. Resting SBP, MAP and DBP of the three groups. Values represent means $\pm$ S.E. See Table 2b statistical analysis.

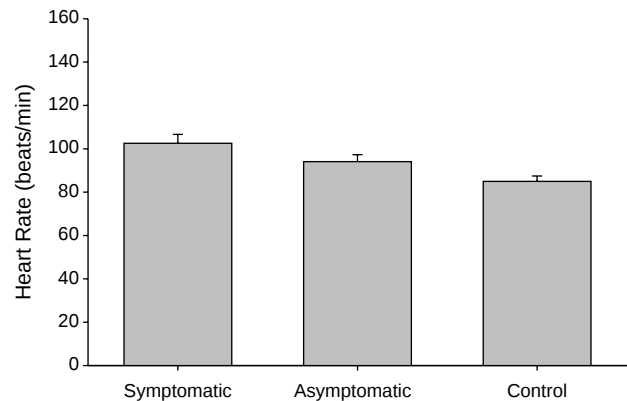


Fig. 3. Resting heart rate of symptomatic, asymptomatic and control groups. Values represent means $\pm$ S.E. See Table 2b statistical analysis.

4. Discussion

4.1. Suitability of our methods

To our knowledge, this is the first study of resting cardiac parasympathetic activity in autism. We investigated the baseline autonomic function in autistic children, with or without clinical evidence of autonomic dysfunction and did not provoke any further autonomic response in this study. Previous studies used provoked autonomic responses to social emotional stimuli [15,16]. These methods may not be appropriate stimuli for autonomic arousal in autistic children, and may have given false negative results. The symptoms and signs of autonomic dysfunction exhibited by the autistic subjects we have studied are consistent with chronic autonomic deficiency and not with intermittent abnormalities due to episodic autonomic arousals. This type of chronic autonomic dysfunctions can be elicited by examination of baseline functions without recourse to provoked autonomic responses. Another problem with provoked autonomic responses is that they require standard stimuli strengths, which are difficult to achieve in uncooperative patients such as autistic children. We have used reliable indices of baseline brainstem autonomic function in this present study as follows.

4.2. CVT

It is now well established that the amount of efferent vagal activity to the heart (cardiac vagal tone) is largely dependent on the degree of stimulation to arterial baroreceptors [27–29]. At a mean arterial pressure above 45 mmHg, ejection pressures of the heart are sufficient to stimulate the arterial baroreceptors at every heartbeat [30]. Because of the very short latency of this baroreflex [31], changes in arterial pressure induce changes in cardiac cycle intervals on a beat-to-beat basis. It is this baroreceptor-induced variability in cardiac cycle intervals that is used by the NeuroScope as a measure of CVT. Cardiac vagal tone is regulated in

the brainstem by yet unknown nuclei in humans, of which nucleus ambiguus probably has a vital role. Disorders affecting baroreceptors, their afferent nerves, brainstem nuclei and the efferent cardiac vagal nerves can all modify CVT. For example, diabetes mellitus or cranial neuropathy affecting the 9th and 10th cranial nerves may affect baroreceptor afferent or efferent cardiac vagal nerves leading to very low CVT. On the other hand, the low CVT in Rett syndrome or neonates are best explained by the immature brainstems [32].

4.3. CSB

Our index CSB only quantifies the beat-to-beat negative feedback control of the cardiovascular system when increases in SBP are immediately followed by increases in the R-R interval indicating the slowing down of heart rate [20]. This type of cardiovascular regulation is tonically regulated at the level of the nucleus of tractus solitarius in the brainstem [33]. When the CSB is found concurrently low with CVT, it is an indication that the deficits originate from the brainstem, most probably at the level of the nucleus of tractus solitarius as explained above.

4.4. Comparison with Rett syndrome

The low baseline values of CVT and CSB in autistic children suggest impaired cardiac parasympathetic activity at the level of the brainstem. Sympathetic activity may be unrestrained as a result and there is evidence of its hyperactivity in the HR and BP results in this study. This provides an interesting comparison between these autistic patients and previous observations in Rett syndrome. It was reported that the dysautonomia in Rett syndrome is due to brainstem immaturity, a finding that is used as evidence of a developmental rather than a degenerative cause of the disease [32]. Neuropathological studies also show evidence of brain immaturity in Rett syndrome [34] supporting the developmental hypothesis of the pathophysiology of Rett syndrome. The identification of mutations in the MECP2 gene [35] has now confirmed the genetic origin and therefore the developmental nature of Rett syndrome.

The dysautonomia in Rett syndrome consists of very low cardiovascular parasympathetic activity causing dysinhibition of a normal sympathetic tone, which in turn result in sympatho-vagal imbalance [36]. There is no evidence of increased baseline sympathetic activity in Rett syndrome compared to a control population at similar ages, judging from the levels of the resting blood pressures DBP, SBP and MAP [36]. We have shown in this study a reduced baseline cardiovascular parasympathetic activity in autism similar to what was reported in Rett syndrome, except that in autism, there is additional evidence of increased baseline sympathetic tone, indicated by the increased levels of blood pressures (see further discussion of the changes in blood pressure in this study below). The dysautonomia caused by

global developmental immaturity of the brain in Rett syndrome appears to be different from what we have shown in autistic children. What could be the possible causes of increased sympathetic tone in autism?

4.5. Possible mechanisms of the autonomic dysfunction

The low baseline CVT and CSB shown in this study may contribute to increased sympathetic tone in autism, but cannot be the only explanation as discussed above in the comparison with Rett syndrome. Increased sympathetic tone in our autistic patients is consistent with previous reports mentioned in our Introduction. However, we also would like to draw attention to the interesting work by Connors and colleagues [37] who reported an increase in relative risk and concordance rate for autism spectrum disorders in dizygotic twins whose mothers were exposed to Terbutaline, a selective β_2 -adrenergic receptor agonist, as treatment for preterm labor. β_2 -adrenergic receptors antagonize the central cardiovascular sympathetic system. Therefore, a β_2 -adrenergic agonist may artificially subdue the central sympathetic activity enough to cause up-regulation of central cardiovascular sympathetic receptors. The up-regulation would be an attempt to compensate for the antagonism. Exposure to the drug terbutaline may have changed receptor functions in the central sympathetic system in the twins [37] as has been documented in studies of lower animals [38]. In addition, the same authors found a significantly increased prevalence of polymorphisms of the β_2 -adrenergic receptors themselves (substitutions with glycine and glutamic acid at codons 16 and 27, respectively) in autistic patients compared to the general population (Connors, personal communication). Could such aberrations of receptors in the central sympathetic system be responsible for the dysautonomia in autism?

4.6. Possible causes of the changes in blood pressure

The elevated resting HR, DBP and MAP were seen in the majority of children with autism, with or without symptoms or signs of autonomic dysfunction, and in all age groups. An increase in HR alone, from any cause, can lead to a proportional increase in the DBP. This would result from the relative shortening of the time period in diastole for arterial blood to escape (run off) through the arterioles, which would be offering the same total peripheral vascular resistance as that prior to the increase in HR. Since less blood would leave arteries during diastole (due to less time), the diastolic pressure will rise and subsequently the MAP will also increase. Our results show that the HR in autistic children with symptoms was 21% higher, but the DBP was 32% higher than that in healthy children. The elevation of DBP was proportionally higher than the increase in HR. It is therefore unlikely that the total peripheral vascular resistance is similar in the autistic and normal healthy children in this study. Increased total peripheral vascular resistance due to increased vasoconstriction as a result of a higher than

normal sympathetic activity is a more likely explanation for the elevated levels of both DBP and MAP in the autistic children, but this would require confirmation by direct measurement of arterial vascular resistance in the two groups. This can now be done non-invasively using ultrasound [23]. Increased arterial vascular resistance due to vasoconstriction can also explain the restrained increase in SBP that did not reach statistical significance because vasoconstriction would reduce venous return causing the stroke volume to fall and preventing any significant increase in SBP. Therefore, our blood pressure results offer some valuable evidence in favor of increased baseline sympathetic activity in autistic children compared with healthy controls, but this requires confirmation by direct measurement of arterial vascular resistance.

4.7. Autonomic responses to provocations

While our results suggest impaired baseline resting cardiac parasympathetic activity associated with increased sympathetic tone, there appears to be normal autonomic arousals in the subjects with autism as indicated by changes in levels of HR and BP in response to agitation and changes in body postures as observed in some of our patients. An example of the tracing is shown in Fig. 4. However, the provocations in autistic subjects were not standardized nor controlled due to the inability to cooperate with commands. The autonomic response to agitation seen in this study was more or less exaggerated. This is consistent with the clinical observation that many children with autism are readily excitable and supported by the skin galvanic testing by Palkovitz and Wiesenfeld [15] showing a super responsive sympathetic system in autism. A better and more controlled study is required for better understanding of brainstem cardiovascular regulation during provocations in autism.

4.8. Shortcomings

We were not able to correlate the degree of autonomic impairment as measured by the NeuroScope system with the

clinical severity of dysautonomia because at present, we do not have a clinical scale for measuring the severity of dysautonomia. We also do not have reliable data on the duration of the symptoms of autonomic dysfunction in every subject we have studied, so we were unable to correlate our results with the duration of symptoms.

This is a preliminary study and it has some limitations. About 4% (2/46) of the subjects could not tolerate the test procedure and they were excluded from the study. One principal investigator measured all the autonomic indices during the resting states and the spontaneous autonomic arousals during such measurements such as agitations, contraction of the neck muscles and changes in the body postures were used to study autonomic responses to arousals. We did not use standardized maneuvers such as Valsalva's maneuver or isometric muscle exercise to measure autonomic arousals because this was either too difficult or impossible in the autistic children. These standard maneuvers were used in control children who could comply with the required commands but the data was not used in this study. Another shortcoming is that a large number of healthy children are yet to be tested to provide a reliable database of normal values as has already been done in adults [32].

Although this study did not perform multiple tests in all subjects, there were subjects tested repeatedly, at request of parents for monitoring the progression of the autonomic dysfunctions or for other reasons stated in Section 3. Four children with autism had tests done on two separate days. All the results in these children were reproducible. Nevertheless, reproducibility of the test was not determined systematically in this study and should be addressed in future study.

4.9. Outlook

Further studies should be extended to a large population of autistic subjects, if possible with training by their behavioral therapists to perform standard maneuvers that can be used for autonomic function testing. This will allow a better study of autonomic arousals in autistic children. A careful clinical analysis of the medical disorders and birth history is necessary in order to correlate them with the autonomic dysfunctions. We feel that therapeutic interventions in autonomic dysfunctions and monitoring of autonomic functions with the NeuroScope system will provide a new avenue for both the understanding and treatment of autism.

4.10. Conclusion

Our results show evidence of reduced baseline cardiac parasympathetic activity in autistic children in association with evidence of increased baseline sympathetic tone. This is distinctively different from previously reported findings in Rett syndrome in which the same NeuroScope system

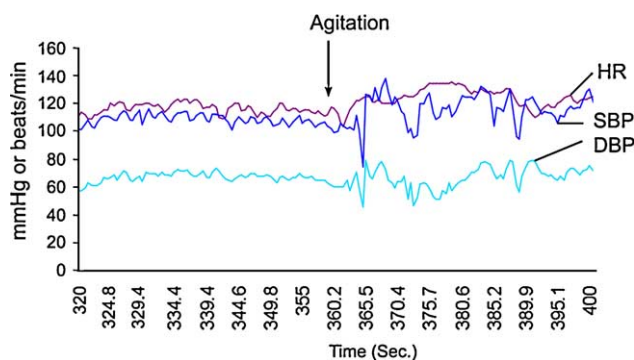


Fig. 4. An example of autonomic response to agitation in a child with autism and autonomic dysfunction. SBP: systolic blood pressure, DBP: diastolic blood pressure, HR: heart rate.

was used to obtain the autonomic measurements and no evidence of increased sympathetic tone was found despite a low parasympathetic activity. The significance of the finding of poorly restrained and yet elevated baseline sympathetic tone in autism remains to be defined.

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