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Research Article

Heart Rate Variability Metrics during Sleep in Children with Asperger's Syndrome

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Abstract

Purpose: To describe the characteristics of Heart Rate Variability (HRV) metrics during sleep in children with Asperger Syndrome (AS) and children with Typical Development (TD).

Methods: Children aged 6 to 10 years diagnosed with AS (n = 10) and TD (n = 10) were included in the study. Polysomnographic recordings were performed on two consecutive nights, the first night being the adaptation night and the second being used for the analysis of the characteristics of sleep and HRV metrics.

Results: Inter-subject analysis showed that children with AS had a shorter heart period in all sleep stages, as well as higher REM sleep latency and fewer sleep cycles compared with children with TD. Likewise, measures related to parasympathetic activity were similar between both groups. Intra-subject analysis showed that children with AS had minimal differences between all sleep stages with most measures of the three domain methods of HRV analysis, while the children with TD presented an HRV according to the characteristics of each stage of sleep.

Conclusion: Children with AS showed little autonomic flexibility when moving from one sleep stage to another, evaluated with the three-domain methods of HRV analysis. These results could indicate some degree of immaturity in sleep-related circuits in children with AS, which in turn affects HRV.

Introduction

Asperger Syndrome (AS), a neurodevelopmental disorder, is characterized by deficits in social interaction and stereotypic and repetitive behaviors [1]. Although impairments usually persist throughout life, some patients may live independently in adulthood [2].

Physiological dysregulation involving the Autonomic Nervous System (ANS) is thought to be associated with Asperger syndrome [3]. One of the functions of the ANS is to regulate homeostasis, which is maintained through the combined interchange of the sympathetic and parasympathetic components. The two major divisions of ANS are anatomically distinct and act in a complementary manner to regulate physiological processes such as blood pressure and Heart Rate (HR). The sympathetic nervous system activates the "fight or flight" arousal response during stress or strenuous physical activity by increasing metabolic output, including stimulation of the cardiovascular system and norepinephrine release [4]. The parasympathetic nervous system is associated with the restoration and optimization of organ function and regulates bodily functions including digestion, urination, and cardiovascular activity [5]. When a person is resting, the parasympathetic nervous system induces a calm physiological state that supports the maintenance of homeostasis, such as slowing the HR to conserve energy [6].

The functional interplay between the parasympathetic and sympathetic nervous systems enables the adaptability and health of the individual. When this balance is disturbed, homeostatic mechanisms are disrupted [7] and autonomic

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dysfunction is involved, for example, in the anxiety [8] and social behavior problems [9] observed in autistic patients, which can be manifested as changes in heart rate variability (HRV). In autistic children, heart rate variability can occur in response to anxiety and behavioral issues, leading to autonomic dysfunction. It should be noted that activation or inhibition of either branch of ANS does not imply inhibition or activation of the other. Depending on the context, co-activation or co-inhibition may occur [10].

There are different ways to study the ANS noninvasively, one of which is HRV analysis, which measures the oscillations or variations that exist between heartbeats, known as the interbeat interval (IBI). Mathematical methods for analyzing IBI data are classified by domain (time, frequency) and nonlinear [11]. Time domain methods measure the time that elapses between one beat and another so that the mean, standard deviation, or differences between short and long IBIs can be determined [12]. In the frequency domain, IBIs are represented by oscillations, and analyses are performed to characterize this oscillation, such as power spectral analysis. In the nonlinear domain, analyses are based on chaos theory and complex systems [13]. These analyses allow quantification of the structure and complexity of the IBI [14]. Low variability in HRV is associated with poor health and various diseases [15,16], whereas high variability reflects psychological and physiological flexibility and adaptability, resilience, and good health [17].

Of all the methods available to analyze IBI, only some reflect the autonomic regulation of cardiac activity. In the field of psychophysiological study of cognition or emotion, HRV measurements that relate to ANS function, particularly the parasympathetic or vagal divisions, are most commonly used [18]. Metrics related to autonomic function, especially those in the frequency domain, also predominate in the assessment of HRV during sleep [19,20].

Sleep is a physiological and behavioral state of isolation from environmental stimuli, and the psychophysiological characteristics of each stage of sleep are well-defined. Consequently, sleep offers a good opportunity for the study of HRV [21,22]. Moreover, there are some cardiovascular activities, such as blood pressure, that change from wakefulness to sleep [23]. Similarly, through the various sleep phases, cardiovascular changes occur, for example, the heart rate is usually lower in Non-Rapid Eye Movement (NREM) sleep and increases in rapid eye movement (REM) sleep [24]. This variation permits a complementary understanding of what has been found during wakefulness in children with AS, that is, to discern whether autonomic deficits prevail during sleep or present characteristics similar to children with typical development. However, few investigations have been conducted on HRV during sleep in populations with autism spectrum disorder [25,26], specifically AS. In the case of AS, only a spectral analysis has been conducted by means of a fast Fourier transform.

Initial investigations related to HRV in patients with autism primarily determined that atypical sensory responses that were observed originated from intense physiological reactivity [27,28]. Furthermore, autistic patients exhibited a lower Heart Period (HP) during wakefulness than control individuals of a similar age [29,30], that is, autistic patients have a higher heart rate. However, results have subsequently been contradictory. Under baseline conditions, some studies have observed a higher HR in autistic patients compared to Typically Developing (TD) children of a similar chronological age [31,32]. In contrast, other studies have reported no significant differences in the baseline HR between children with AS and control children [33,34]. These discrepancies may be due to several factors, such as age, the level of functioning, and the general symptom heterogeneity that is characteristic of autistic spectrum disorder.

In this context, it is interesting to evaluate several HRV metrics during sleep in a sample with AS, as well as to determine whether the behavior of these measures differs from a typically developing population. Note that several sleep studies appear on patients with autism, mainly investigating adolescents [33,34] and adults [32,35], which is why we were interested in carrying out this work in the pediatric population (6–10 years). After this age range comes adolescence, which involves biological, physiological, and psychosocial changes that can modify HRV [36] and sleep structure [33,34].

The objective of this study was to describe the characteristics of HRV during sleep in children diagnosed with AS and children with TD. The HRV analysis includes metrics from the time, frequency, and nonlinear methods. It also compared the characteristics of sleep architecture between both groups.

Method

Design

Cross-sectional descriptive.

Ethical Considerations

The Research Ethics Committee of the Faculty of Psychology of the National Autonomous University of Mexico with number FPSI/422/CEIP/582/2018 approved this research.

Participants

The sample consisted of ten TD children and ten children diagnosed with AS according to DSM IV [37]. The inclusion criteria were children between 6 and 10 years, residents of Mexico City, and consent from parents and guardians and the child. AS Children were from the *Caritas de Amistad* Association and had been diagnosed by a specialist at least one year previously. Parents of children with normal development answered a brief interview to rule out health problems.

The exclusion criteria were the diagnosis of a neurological, psychiatric, or sleep disorder or having at least one direct family member who had it, as well as consumption of psychotropic drugs. The elimination criteria were the presence of some sleep disorder identified through Polysomnography (PSG) or that the sleep percentages were not in the ranges considered normal. All participants were briefed on the research procedure and

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subsequently signed an informed consent letter (Appendix 1). The PSG studies were performed in the Neuroscience laboratory of the Faculty of Psychology of the National Autonomous University of Mexico. In addition, the evaluations considered the basic principles set out in the Helsinki Declaration [38].

Procedure

PSG studies were conducted on two consecutive nights during 8 continuous hours, the first PSG was considered an adaptation night and served to detect the presence of some indicator of sleep disorder, and the second night was used for analysis. In the first PSG, the Electroencephalogram (EEG) was recorded with contralateral references to the mastoids according to the following derivations: F3-M2, F4-M1, C3-M2, C4-M1, O1-M2, and O2-M1. It was also recorded the Electrooculogram (EOG), the surface Electromyography (EMG) of the chin and the right and left tibial muscles, Electrocardiogram (ECG) with derivation I, oronasal airflow recorded by a thermistor, respiratory effort measured with thoracoabdominal bands and oxygen saturation recorded with a pulse oximeter. In the second PSG, the EEG, EOG, EMG of the chin, and the ECG with derivation-I were recorded. The sampling frequency of the EEG and EOG was 400 Hz with a 0.05-30 Hz filter; EMG 10-100 Hz; ECG de 0.05-70 Hz; oronasal thermistor and thoracoabdominal bands from 0.1-15 Hz.

The PSGs were recorded using a Cadwell Easy II instrument. The start of recordings (lights out) was adjusted to the usual time of falling asleep for each participant, and 8 hours were allowed until the end of the recording. Sleep stages were classified according to the AASM 2.5 version [39]. For this study, only data obtained during the second PSG were used. It is important to mention that all participants adapted to the placement of the sensors and there were no complications with the equipment.

Measures of HRV

For each child, several ECG signal samples were obtained during the N2, N3, and REM sleep stages. The duration of each sample was five minutes. Samples were omitted that were obtained two minutes before and after stage transitions or in which there were movements or sleep arousal. The ECG signals were exported in European Data Format (EDF). The QRSTool version 1.2.2 [15] was subsequently used to obtain the IBIs. In addition, the QRSTool software was used to verify and correct the presence of artifacts in the IBIs. HRV analysis was conducted using Kubios software [40].

Time domain analysis: The following metrics were calculated: Heart Period (HP), root mean square of the successive differences (RMSSD), and the number of adjacent intervals that varied by more than 50 milliseconds expressed in percentage (pNN50). The latter two are considered indicators of parasympathetic activity [41].

Frequency domain analysis: The power spectrum was calculated using Welch's method. The following bands were considered: Low-Frequency band (LF) 0.04 to 0.15 Hz and High-Frequency (HF) band 0.15 to 0.4 Hz, the power spectral density values of each band were expressed in natural logarithm. The HF band is a metric associated with parasympathetic activity, whereas the LF band is associated with sympathetic and parasympathetic activity [11].

Nonlinear domain analysis: The nonlinear metrics include the Poincaré graph, which allows us to visually identify patterns within a specific period [42,43]. From Poincaré's graph, the standard deviation of the orthogonal points to the graph of the function identity (SD1) and the standard deviation of the distributed points on the graph of the function identity (SD2) were considered. Finally, the approximate entropy (ApEn) quantifies how regular and predictable a system can be. When their values are small, they indicate that the signal is predictable [44].

Statistical analysis

A Shapiro-Wilk normality test was performed, obtaining an alpha value of 0.04, that is, there was no normal distribution and we chose to use non-parametric statistics.

The statistical analyses were divided into two types. The first consisted of inter-subject analyses. Sleep structure variables and HRV metrics were compared between both groups, for which the Mann–Whitney U test was used. Within-subject analyses through Friedman rank tests were applied to compare HRV among N2 (second stage of NREM sleep characterized by the presence of electroencephalographic elements such as sleep spindles and K complexes), N3 (third stage of NREM sleep, where there is high amplitude slow cerebral waves activity) and REM sleep (Rapid Eye Movement sleep). In the case of statistically significant results on the Friedman test, post-hoc analysis of the N2-N3, N2-REM, and N3-REM pairs was added along with the Wilcoxon signed-rank test. For the Mann–Whitney U and Friedman rank tests, a significance value of $p < 0.05$ was considered. In the post-hoc analyses, to avoid the error of multiple comparisons, the p-value was divided by the number of comparisons, which in this case was three, resulting in $p < 0.017$.

Results

The sample of participants was ten children diagnosed with AS with an average age of 8.2 (Standard deviation [SD] = 1.33) years; and ten children with TD with an average age of 8.3 (SD = 1.22) years.

Inter-subject analysis

When comparing HRV metrics for each sleep stage, significant differences were observed in some metrics between both groups (Table 1). In the three-time domain metrics, it was found that in the three sleep phases, the median was smaller in the AS group, though in the HP alone, significant differences appeared between the two groups (Figure 1). The two frequency domain metrics found that HF was lower in the group with AS in the three sleep phases, though these differences did not reach statistical significance.

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In the AS group, the LF metric was lower in REM sleep and greater in the N3 stage. The only significant difference was recorded in stage N2, where there was a significant difference with a lower value in the AS group (Figure 2). In the nonlinear metrics, there were no significant differences between the groups. The two measures associated with the Poincaré graph were lower in the group with AS, while approximate entropy was higher.

In the comparison of sleep structure between the groups (Table 2), significant differences were found in REM sleep latency (Figure 3) and number of sleep cycles (Figure 4) in which the children with AS were found to have higher latency and fewer sleep cycles. Sleep efficiency was similar in both groups with a median of 95%.

Intra-subject analysis

In the AS group, no significant differences were found in the comparison of the values of each HRV metric among the three sleep stages.

In the TD group, most metrics showed significant differences between the three sleep stages (Table 3). All three-time domain metrics had significant differences, with post hoc

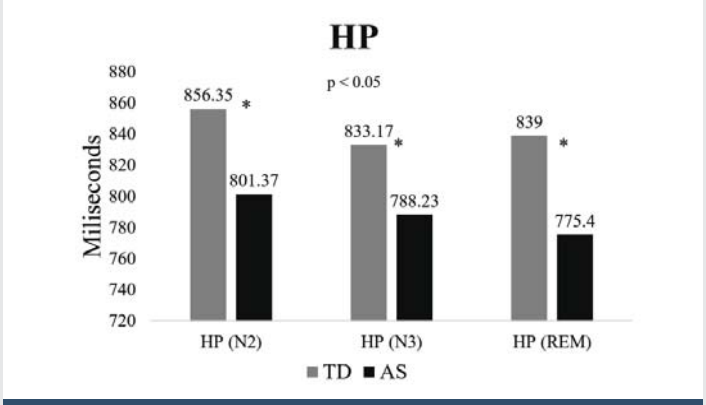

Figure 1: Heart Period: significant differences between the two groups. The Mann-Whitney U test was used. *significant at $p < 0.05$.

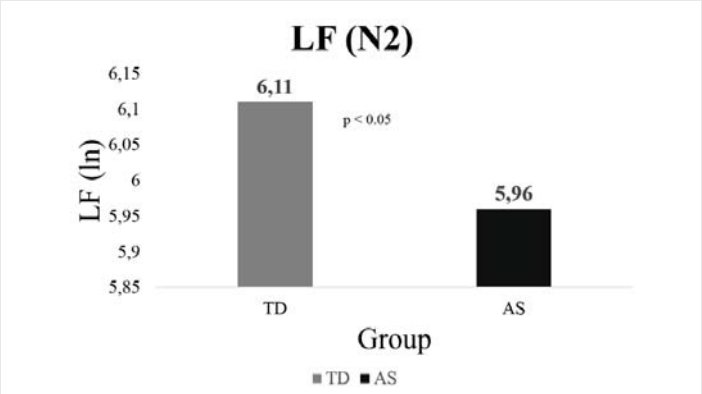

Figure 2: Significant differences in LF between both groups in N2. The Mann-Whitney U test was used. *significant at $p < 0.05$.

Table 1: Comparison of measures of heart rate variability between the TD group and the group with AS.

HRV metrics	Typical development	Asperger syndrome	U	p
N2 HP (ms)	856.35 [810.88-915.55]	801.37 [763.74-860.13]	11	0.003*
N3 HP (ms)	833.17 [772.48-911.55]	788.23 [747.72-831.09]	21	0.028*
REM HP (ms)	839.00 [782.05-875.40]	775.40 [738.71-838.22]	15	0.008*
N2 RMSSD (ms)	72.08 [53.46-112.63]	54.91 [42.24-116.80]	33	0.199
N3 RMSSD (ms)	69.64 [63.84-82.69]	60.82 [38.27-97.74]	41	0.496
REM RMSSD (ms)	79.23 [59.61-93.17]	59.96 [41.82-94.19]	31	0.151
N2 pNN50 (%)	50.68 [36.44-65.33]	36.97 [24.44-59.17]	25	0.059
N3 pNN50 (%)	50.18 [38.01-59.67]	40.70 [19.66-61.52]	34	0.226
REM pNN50 (%)	39.89 [31.58-45.76]	29.64 [18.51-46.89]	28	0.096
N2 LF (ln)	6.11 [5.97-6.89]	5.96 [5.50-7.27]	23	0.041*
N3 LF (ln)	5.54 [5.09-6.28]	5.87 [5.30-6.77]	46	0.762
REM LF (ln)	6.92 [6.57-7.58]	6.65 [6.21-7.27]	34	0.226
N2 HF (ln)	7.70 [7.18-8.20]	7.18 [6.47-8.68]	31	0.151
N3 HF (ln)	7.43 [7.05-8.02]	7.26 [6.34-8.21]	46	0.762
REM HF (ln)	7.75 [7.17-8.09]	7.07 [6.63-8.24]	34	0.226
N2 SD1 (ms)	51.04 [37.85-79.76]	38.88 [29.91-82.71]	33	0.199
N3 SD1 (ms)	49.31 [38.12-58.56]	43.06 [27.09-69.23]	41	0.496
REM SD1 (ms)	56.10 [42.21-65.98]	42.46 [29.61-66.70]	31	0.151
N2 SD2 (ms)	65.76 [54.67-80.73]	55.66 [41.72-113.37]	28	0.096
N3 SD2 (ms)	55.33 [44.10-69.16]	52.79 [37.29-83.78]	43	0.597
REM SD2 (ms)	74.86 [57.89-91.69]	60.95 [50.22-93.52]	30	0.131
N2 ApEn (au)	1.05 [0.98-1.12]	1.09 [1.04-1.17]	27	0.082
N3 ApEn (au)	1.02 [0.98-1.12]	1.11 [1.06-1.16]	29	0.112
REM ApEn (au)	1.13 [1.08-1.16]	1.14 [1.11-1.21]	29	0.112

Note: ms: milliseconds; ln: Natural logarithm; au: arbitrary unit; ApEn: Approximate Entropy. Data are expressed in medians and percentiles [25th -75th] *Significant at $p < 0.05$.

Table 2: Sleep Macrostructure.

Sleep measures	Typical development (n = 10)	Asperger Syndrome (n = 10)	U	p
TTW (min)	21.75 [9.75-32.62]	20.75 [12.75-35.00]	46.5	0.791
TTN1 (min)	23.50 [19.50-29.25]	26.75 [24.00-37.87]	29	0.112
TTN2 (min)	213 [204.37-241.37]	225.75 [200-245.62]	43.5	0.623
TTN3 (min)	125.25 [110.75-133.37]	131.25 [101-147.37]	42	0.545
TTREM (min)	93.25 [77.62-115.62]	85.25 [71.62-103.62]	40.5	0.473
TST (min)	470.25 [447-474]	478.25 [455.50-485.12]	37	0.326
TBT (min)	484 [475.62-494.75]	491.50 [482.62-511]	27.5	0.089
SE (%)	95.61 [93.22-98.26]	95.80 [93.10-97.44]	46.5	0.791
LatN1 (min)	11.50 [3.75-27.75]	17.00 [7.37-19.62]	42	0.545
LatN2 (min)	2.00 [1.50-3.25]	2.00 [1.50-5.00]	48	0.908
LatN3 (min)	10.50 [8.75-11.25]	8.00 [5.75-11]	29	0.118
LatREM (min)	89.00 [61.75-129.75]	178.25 [153.50-204.75]	9	0.002*
WASO (min)	6.75 [3.37-7.75]	4.00 [1.87-10.37]	46	0.761
%N1	5.00 [4.75-6.25]	6.0 [5-8]	32	0.158
%N2	47.00 [43.00-51.25]	48.00 [43.25-55.50]	46	0.762
%N3	26.50 [23.75-30.00]	27.00 [23.50-32]	44	0.648
%MOR	20.00 [17.5-24.50]	18.00 [15.50-21.75]	33	0.210
NREM-REM cycles	5.00 [3.75-5.00]	4.00 [3-4]	21	0.021*

Note: TTW: Total Wake Time; TTN1: Total Time of N1; TTN2: Total Time of N2; TTN3: Total Time of N3; TTREM: Total Time of REM; TST: Total Sleep Time; TBT: Total Bedtime; SE: Sleep Efficiency; LatN1: stage N1 latency; LatN2: stage N2 latency; LatN3: stage N3 latency; LatREM: REM sleep latency; WASO: Wake After Sleep Onset. Data are expressed in medians and percentiles [25th-75th]. *Significant at $p \leq 0.05$.

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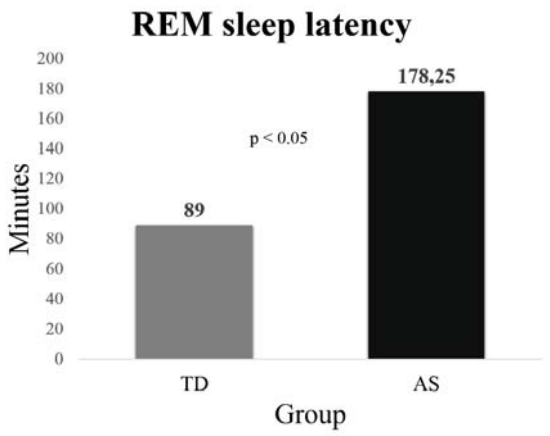

Figure 3: Significant differences in REM sleep latency between both groups. The Mann-Whitney U test was used. *significant at $p < 0.05$.

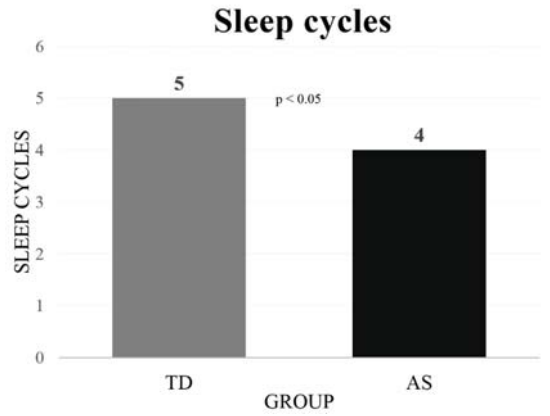

Figure 4: Significant differences in the number of sleep cycles between both groups. Mann-Whitney U test was used. *Significant at $p < 0.05$.

Table 3: HRV metrics comparison among sleep stages in the TD group.

HRV analysis	Chi Square	p	Post hoc comparison		
			N2-REM	N2-N3	N3-REM
HP	6.2	0.045*	0.009**	Ns	ns
RMSSD	8.6	0.014*	ns	Ns	ns
pNN50	8.6	0.014*	ns	Ns	ns
LF	16.8	<0.001*	ns	0.005**	0.005**
HF	5.60	0.090	ns	Ns	ns
SD1	1.40	0.070	ns	Ns	ns
SD2	9.6	0.008*	ns	0.005**	ns
ApEn	7.8	0.020*	ns	Ns	ns

Note: *Significant at $p < 0.05$, **Significant at $p < 0.017$.

analyses identifying that HP was significantly higher in the N2 phase compared to the REM stage. A significant difference was recorded only for the LF metric of the frequency domain. The post-hoc analysis found that LF varied significantly between N2 and N3, as well as between N3 and REM, with a lower LF value in stage N3 and a higher value in the REM stage. In non-linear metrics, the Poincaré graph, only SD2 varied significantly. Post-hoc analysis found a significant difference between stages N2 and N3, with the minimum value of SD2 in stage N3. Finally, ApEn initially showed significant differences between the three sleep stages, although, in the post hoc analysis, no significant differences were found. The ApEn showed the same pattern of a lower value in the N3 phase and a higher value in the REM stage.

Discussion

The main objective of the present study was to compare the characteristics of HRV metrics between AS and TD children during sleep. Two types of analysis were performed, one of inter-subject type in which the HRV metrics were compared between both groups, while the other intra-subject analysis evaluated the behavior of each metric between sleep stages N2, N3, and REM.

The inter-subject comparison found that the HP was significantly lower in the AS group in the three sleep stages. The HP value is the measurement of heartbeat duration, and lower values of HP indicate higher cardiac activity [45]. HP and resting heart rate can be considered to be inverse, although the relationship is not linear. Previous research recorded similar HR values both in the AS and control groups; however, in that study, sleep was not separated into different stages [23]. However, subsequently, results have been contradictory as under baseline conditions, some studies have observed higher HR in autistic patients compared to TD children of a similar chronological age [31,32], whereas other studies observed no significant differences [33,34]. These discrepancies may be due to several factors, such as age, level of functioning, and general symptom heterogeneity that is characteristic of autistic spectrum disorder. In this study the sample was homogeneous since all had the diagnosis of AS and the age range was similar between both groups evaluated.

It has been proposed [6] that higher HR in AS can be an indicator of a delay in autonomic maturation, which can cause abnormalities in some of the branches of the ANS. In this case, the sympathetic branch produces higher cardiac activity [5]. Similarly, elevated HR in all sleep stages may be due to an increase in norepinephrine levels, which are known to be higher in children with AS compared to control children [46]. However, RMSSD, pNN50, and HF metrics are related to parasympathetic activity [11], but these metrics were not significantly different between both groups. In contrast, waking studies have found that children with AS have difficulties related to vagal modulation [47]. For example, it is proposed in polyvagal theory that children with emotional and behavioral regulation disturbances (as in AS) present the dysregulation of parasympathetic activity [48]. However, this symptomatology appears to be exclusively present during the wakefulness state (difficulties in social communication, stereotyped movements, etc.). Autonomic deficits could affect cognitive functions, social engagement, and recognition of faces and voices, among other functions [49-51].

The LF band in stage N2 was significantly different between the groups, with lower values recorded in the AS group. The LF band is related to changes in baroreceptor and vasomotor activities associated with blood pressure [11]. During sleep,

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changes in blood pressure associated with the presence of K complexes occur, which are characteristic of sleep stage N2 [52]. Additionally, children with AS have fewer K complexes in comparison to children with TD [53]. In this study, the number of K complexes was not evaluated, and their relationship should be evaluated in future studies.

With nonlinear metrics, information is obtained about the structure and complexity of IBIs [14]. In these measures, no significant differences were found between the two groups. This result could be because the analyses were carried out on samples of short duration (five minutes of each sleep stage). Perhaps a long-term analysis would show noticeable differences between both groups. Note that these methods consider the nonlinear interaction between multiple systems [54], which causes the complexity of the cardiac signal that interacts with hormonal, molecular, baroreceptor, chemoreceptor systems, and more. These systems were not analyzed in the present study; thus, it would be convenient for future research to analyze the interaction of cardiac activity with other systems and examine samples of longer duration.

In addition, when comparing the macrostructure of sleep, it was found that, in most sleep variables, there were no significant differences between the groups (the methodology used in this study did not affect significantly the sleep characteristics). Sleep efficiency was approximately 90%, which is considered an appropriate value [54]. Although, it has been reported that some sleep parameters may differ between the populations [55], sleep disorders and abnormalities in the sleep macrostructure are common comorbidities in AS patients [56]. We only found significant differences in REM sleep latency and the number of NREM-REM sleep cycles. In the AS group, REM sleep latency was 177 minutes, this value is above the range of 90–120 minutes considered to be normal [57]. Several studies are consistent in finding abnormalities not only in the latency to REM sleep of children with AS but have also described less REM sleep, abnormal twitches, and undifferentiated sleep [58].

Significant differences in the NREM-REM sleep cycles suggest a different pattern in the distribution and sequence of sleep stages that does not involve the time or percentage of each sleep stage. This cycle repeats in periods of approximately 90–120 minutes during the night [58], resulting in approximately five cycles in a night of eight hours of sleep. We found that the AS group had a lower number of non-REM–REM sleep cycles than the group with TD. This is evidence of an alteration in the distribution of non-REM–REM cycles associated with prolonged REM sleep latency.

When analyzing each group independently through intra-subject analysis, a distinct pattern was identified between both groups in the distribution of HRV metrics between the N2, N3, and REM stages of sleep. In the case of the control group, statistically significant differences were found between all sleep stages (N2-REM, N2-N3, and N3-REM) in most HRV measures, except for HF and SD1. The measures that showed significant differences between the different sleep stages in the TD group are described below.

1. **HP (ms):** The differences were observed between N2-REM, which could be due to physiological variances between these two sleep stages. The N2 phase is characterized by a greater predominance of parasympathetic activity, while REM sleep is characterized by fluctuations in the sympathetic and parasympathetic systems. In addition, there is a greater activation of limbic structures, such as the amygdala and hippocampus [58], which could explain why the cardiac period was greater during REM sleep.

2. **LF:** This band is related to changes in baroreceptor and vasomotor activities associated with blood pressure [11]. Differences were observed between N2-N3 and N3-REM. Again, the values decreased when entering the N3 phase and increased in REM sleep, which is expected according to the physiological characteristics of these sleep stages.

3. **SD2:** This nonlinear measure indicates slow changes in IBI related to the regulation of both arms of the ANS [43]. Differences in this measure were found between N2-N3 as well as between N3-REM.

In general, while children with a typical development present an autonomic functioning that goes according to the physiological characteristics of each phase, children with Asperger's present differences between the stages of non-REM and REM sleep, that is, that probably REM sleep is one that marks the autonomic differences in this group since in the parameters of the macrostructure of sleep was also found a higher latency to this phase of sleep.

On the other hand, HRV is an important clinical tool, as several studies have described that individuals with lower HRV are more likely to develop cardiovascular diseases [12] and psychiatric conditions such as anxiety, however, most of these studies have been carried out in wakefulness, so the present work opens the possibility of providing a clinical panorama focused on sleep medicine in the pediatric population, since HRV could detect the risk of suffering from various sleep disorders such as insomnia, sleep apnea, parasomnias, etc., which is vitally important in the early stages of development. However, more studies are needed, not only in the population with AS but with other medical and psychiatric conditions and even in apparently healthy individuals.

Another important consideration is the degree of severity of autistic symptoms, as AS is considered a high-functioning neurodevelopmental disorder, as individuals typically have high cognitive development that may be higher than average. Perhaps conducting this study on individuals with more severe autistic symptoms could show more noticeable differences.

Limitations of the study

One of the limitations of this study is the small sample size, because data collection was affected by the onset of the pandemic, it is recommended that future investigations increase the sample size. Similarly, it would be advisable to

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include the evaluation of sleep microstructure variables such as sleep spindles and K complexes. Given the results in the NREM-REM cycles, it would be advisable to sample cardiac activity considering these cycles. On the other hand, it would be useful to include the recording of cardiac activity in wakefulness to compare the data with those obtained during sleep.

Conclusion

In the sleep of typically developing children, HRV showed changes considered normal when moving from one sleep phase to another, while children with AS had little autonomic flexibility since the values obtained with the three analysis methods were similar between all sleep stages. There were also atypical values in REM sleep latency and the number of sleep cycles in children with AS. These results could indicate some degree of immaturity in sleep-related circuits in children with AS, which at the same time affects HRV, this is consistent with other studies carried out on wakefulness and sleep. These data may have clinical implications whose physiological meaning must be solved for future treatment of patients with Asperger´s syndrome, for example, heart rate variability biofeedback training could be helpful in increasing parasympathetic activity in Asperger's patients, which could decrease their daytime symptoms and improve sleep characteristics.

Data availability

All data are included in the manuscript.

Statements and declarations

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(Appendix)

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