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PII: S1389-9457(17)30413-6

DOI: 10.1016/j.sleep.2017.09.036

Reference: SLEEP 3550

To appear in: *Sleep Medicine*

Received Date: 5 May 2017

Revised Date: 27 September 2017

Accepted Date: 27 September 2017

Please cite this article as: Kakar E, Corel LJA, Tasker RC, de Goederen R, Wolvius EB, Mathijssen IMJ, Joosten KFM, Electrocardiographic variables in children with syndromic craniosynostosis and primary snoring to mild obstructive sleep apnea: significance of identifying respiratory arrhythmia during sleep, *Sleep Medicine* (2017), doi: 10.1016/j.sleep.2017.09.036.

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# Electrocardiographic variables in children with syndromic craniosynostosis and primary snoring to mild obstructive sleep apnea: significance of identifying respiratory arrhythmia during sleep

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**ABBREVIATIONS**

| | |
|---|---|
| AASM | american academy of sleep medicine |
| ECG | echocardiogram |
| HF | high frequency |
| HRV | heart rate variability |
| ICP | intracranial pressure |
| IH | intracranial hypertension |
| IQR | interquartile range |
| LF | low frequency |
| LF/HF ratio | low frequency/high frequency ratio |
| LR | likelihood ratio |
| LR+ | positive likelihood ratio |
| NREM | non-rapid eye movement |
| oAHI | obstructive apnea-hypopnea index |
| OCT | optical coherence tomography |
| ODI | oxygen desaturation index |
| OSA | obstructive sleep apnea |
| OSAS | obstructive sleep apnea syndrome |
| PSG | polysomnography |
| RA | respiratory arrhythmia |
| REM | rapid eye movement |
| RERA | respiratory effort related arousal |
| $SpO_2$ | oxygen-hemoglobin desaturations on pulse oximetry |
| SWS | slow wave sleep |
| TST | total sleep time |

UARS upper airway resistance syndrome

**ABSTRACT**

**Background** In the spectrum of children with symptomatic sleep disordered breathing (SDB), some individuals – such as those with upper airway resistance syndrome (UARS) – do not have abnormalities on polysomnography (PSG). In this study we have assessed whether assessment of respiratory arrhythmia (RA) and heart rate variability (HRV) analysis helps in management of children with syndromic craniosynostosis and none-to-mild obstructive sleep apnea (OSA).

**Methods** Prospective cohort study in children aged 1 to 18 years old with syndromic craniosynostosis. Children were selected for HRV analysis from the ECG if their obstructive apnea-hypopnea index (oAHI) was between zero and five per hour (i.e., oAHI ≤5/hour). Subjects were divided into groups based on the presence or absence of respiratory arrhythmia (with or without RA respectively) using the electrocardiogram (ECG). The main analysis included studying the relationship between RA and HRV, symptoms, interventions, and sleep architecture.

**Results** We identified 42 patients with, at worst, mild OSA. We found higher parasympathetic control and higher total power in children with RA during the non-rapid eye movement (non-REM) sleep. Children with RA also have a relatively higher percentage of paradoxical breathing non-REM sleep (p=0.042). Intracranial hypertension was distributed equally between groups. Last, RA patients showed increased parasympathetic activity that further increased in non-REM sleep.

**Conclusion** In syndromic craniosynostosis cases with SDB and PSG showing oAHI ≤5/hour, the presence of RA may indicate subsequent need for treatment interventions, and a trend toward higher occurrence of clinical symptoms. ECG analyses of HRV variables in subjects with RA demonstrate increased parasympathetic activity and total power. Such findings may add to the diagnosis of apparently asymptomatic children.

**KEYWORDS**

Sleep disordered breathing; Obstructive sleep apnea; Polysomnography; Respiratory arrhythmia; Heart rate variability; Craniosynostosis

## INTRODUCTION

Craniosynostosis is a congenital disorder characterized by premature fusion of skull sutures which can be part of a syndrome such as Apert, Crouzon, Muenke or Saethre-Chotzen syndrome.(1) Two-thirds of these children have sleep disordered breathing (SDB), particularly obstructive sleep apnea (OSA).(2) In such children OSA is mainly caused by a combination of anatomical abnormalities of the upper airway at the level of the tongue base and palate, as well as decreased pharyngeal muscular tone during sleep. Symptoms include sleep-associated apnea, snoring, frequent awakenings, sweating, enuresis, and daytime sleepiness. Of note, apnea and oxygen-hemoglobin desaturations on pulse oximetry ($SpO_2$) induce tonic activation of chemoreflex activity, and an increase in sympathetic nerve activity, which causes sympathetic predominance.(3-7) In the daytime, there may be headaches, behavioral changes and daytime tiredness, which can lead to physical, functional and social impairment.(8)

Within the spectrum of sleep-disordered breathing (SDB) in children with craniosynostosis severe OSA necessitates treatment, whereas the consequences of mild OSA are less clear. Moderate forms of SDB, like the upper airway resistance syndrome (UARS),(9) are considered when there are symptoms of OSA, yet no abnormality on polysomnography (PSG). These children suffer from a partially obstructed upper airway, but recognizable obstructive events or abnormal respiratory gas exchange is not observed.(10) Common symptoms are snoring, increased respiratory effort, and frequent arousals. Together, these problems may cause tiredness during the day and excessive sleepiness. Given that UARS is more common than OSA(10, 11), the use of OSA indicators to assess severity may underestimate UARS in children.(9, 11, 12)

Since there is a need for refining the clinical evaluation in cases of craniosynostosis with milder forms of SDB, we reasoned that an indirect, non-invasive approach to diagnosis using changes in respiratory arrhythmia (RA) and changes in the heart rate variability (HRV) may be of value. RA shows the absolute difference in heart rate above or below baseline heart rate. HRV describes the variations between consecutive heartbeats and is decreased in patients with OSA.(13-16) Currently, HRV is only used as a warning sign for myocardial infarction and diabetic neuropathy, but it can be used to assess autonomic balance(17-19), which may be important in understanding the pathophysiology of SDB.(14, 20-24) As a secondary outcome we assessed interventions and intracranial hypertension in this sample. We hypothesize that children with RA are more likely to undergo interventions and acquire intracranial hypertension.

**METHODS**

Patients

The Ethics Committee of the Erasmus Medical Center (MEC-2005-273) approved this human subjects study of *post hoc* analysis of data collected from a prospective, observational cohort (enrollment period March 2012 to March 2016) at the Dutch Craniofacial Center (Sophia Children's Hospital – Erasmus University Medical Center, Rotterdam, The Netherlands). We included children aged between 1 and 18 years with syndromic (i.e., Apert, Crouzon, Muenke, Saethre-Chotzen syndromes, based on genetic analysis), or complex craniosynostosis (defined as multiple suture synostoses in which no genetic cause is found yet), or unicoronal craniosynostosis.

Polysomnography

All patients had undergone overnight, in-hospital, level 1 PSG that included assessment of the following cardiorespiratory and neurophysiologic variables: nasal airflow (thermistor), chest and abdominal wall motion, $SpO_2$, transcutaneous partial pressure of carbon dioxide, and electrocardiogram (ECG). PSG data were analyzed using Shell+ BrainRT Software (Suite Version 2.0;O.S.G. Rumst, Belgium), using ECG frequency of 250Hz for sampling. A study was considered suitable for analysis if it provided a total sleep time (TST) of at least 360 minutes, free of artifact. Respiratory events were scored using the *American Academy of Sleep Medicine* (AASM) criteria.(25)

An ***obstructive event*** was defined as a reduction in nasal airflow of ≥90% (apnea) or 30-90% (hypopnea), for at least two breaths, in the presence of thoracic and abdominal breathing movement. Hypopnea was only included in the analysis if it was associated with a subsequent $SpO_2$-desaturation of at least 3% from baseline, or with

an arousal. Central apnea/hypopnea meets the same criteria as the above *obstructive event* definition, but without the presence of thoracic and abdominal breathing movement. A mixed apnea had to meet the central apnea criteria and be associated with absence, in one part, and presence, in the other part, of thoracic and abdominal breathing movement. The oxygen desaturation index (ODI) was assessed by dividing the total number of $SpO_2$ desaturations by the TST in hours.(25) A respiratory effort related arousal (RERA) was defined as the sequence of breaths lasting at least 10 seconds which did not meet criteria for an apnea or hypopnea and was characterized by increasing respiratory effort leading to an arousal from sleep. Sleep quality (i.e., sum of rapid eye movement [REM] sleep and slow wave sleep [SWS or N3] divided by the TST) and sleep efficiency (i.e., TST divided by the time in bed [TIB]) were also evaluated. EEG is performed to score the sleep stage.(25, 26) In the current report, children were selected for HRV analysis from the ECG if their obstructive apnea-hypopnea index (oAHI) was between zero and five per hour (i.e., oAHI ≤5/hour).

***Paradoxical breathing*** is present when the child's thoracic and abdominal movements are not synchronous. It is considered a sensitive indicator for increased airway resistance.(27) Even though it may be normal physiology, in children with breathing problems the percentage of paradoxical breathing is higher. Respiration was assessed as paradoxical if the lowest peak of the chest motion was synchronous with the highest peak of the abdominal motion, and *vice versa*. The percentage of paradoxical breathing was calculated using the duration of paradoxical breathing divided by the TST, and multiplied by 100.

***Respiratory arrhythmia (RA)*** was defined as an absolute difference in heart rate of more than 10 beats per minute change above or below baseline heart rate.

Outcome variables

***Clinical evaluations*** comprised of the five symptoms assessed from patient records, divided into two main groups; breathing and sleep abnormalities, at the time of PSG. These were assesses as followed: breathing abnormalities; snoring, audible breathing, and oral breathing, and sleep abnormalities; restless sleep and tiredness. Subjects were categorized as having symptoms if at least one of the above was present, no difference was made in the total number of symptoms with which the child was presenting. Any intervention, or treatment, in relation to timing of OSA and PSG was also recorded. These interventions included surgical interventions (i.e., adenotonsillectomy , midface advancement [monobloc, facial bipartition, or Le Fort III] mandibular advancement, nasal septum correction, and maxillary widening), and non-surgical interventions (i.e., nasal corticosteroid spray)(28). We also assessed whether these children suffered from intracranial hypertension. In our protocol(29-33), all patients were routinely screened for the presence of symptoms/signs related to possible intracranial hypertension, including: downward deflection of the occipital-frontal head circumference growth trajectory; and, papilledema diagnosed by a pediatric ophthalmologist with a funduscopic examination or optical coherence tomography (OCT). In some cases, invasive intracranial pressure (ICP) monitoring was carried out. The determination of “intracranial hypertension” used in the current report was based on assessments made near the time of the PSG (± 3 months) and follow-up at 1 year after PSG (± 3 months).

Assessment of HRV

HRV was determined by measuring the RR-interval of the ECG-signal using Kubios HRV software (Biosignal Analysis and Medical Imaging Group (BSAMIG), Department of Applied Physics, University of Eastern Finland, Kuopio, FINLAND) (17) HRV variables were analyzed using the time and frequency domains, as well as by using non-linear analysis (Table 1). For the frequency domain analysis the frequency bands were set as followed: LF; 0.04−0.15 Hz, and HF (0.15−0.4 Hz).

In order to analyze the HRV data, we divided the PSG dataset into 2 minute epochs, that were artifact-free during both REM and non-REM (NREM) sleep stages.(16) This approach allowed evaluation of persistent changes in HRV after respiratory events, without other events potentially influencing heart rate.(13, 17, 34-36) Artifacts were defined as respiratory events (i.e., apnea, hypopnea, arousals, $SpO_2$ desaturation ≥3%), sighs, and movements during sleep.

Statistical analysis

Non-parametric statistical methods were used based on the small sample size in each group and the not normally distribution of the RA-groups. Occurrence of symptoms was compared to the occurrence of RA. Variables were subsequently compared between groups, using either a chi-square test (expected value above 5) or fisher's exact test (expected value below 5). The Mann Whitney U test was used for comparing continuous variables between two categorical variables. Variables with a P-value <0.05 was considered statistically significant. Results are presented as median (range) or median

(interquartile range [IQR]). Power calculation was not feasible without prior information. Hence, in the exploratory analyses of the impact of RA and HRV variables we describe sensitivity, specificity, likelihood ratio of a positive result (LR+), and changes from pre- to post-test probability of the outcome of interest.

## RESULTS

We identified 42 craniosynostosis patients with oAHI ≤ 5/hour (30 cases with oAHI <1/hour; and, 12 cases with oAHI ≥1/hour). Their diagnoses were: Apert (n=5), Crouzon (n=14), Muenke (n=2), Saethre Chotzen (n=4), complex craniosynostosis (n=9), and unicoronal synostosis (n=8). The mean age at time of PSG was 6.8 years (range: 1.0 – 18.0 years) and 45% (19/42) of cases were male.

### RA, clinical evaluation, and interventions

On comparing those with and without RA, we found that RA was present in 22/42 patients, and those with and without this phenomenon were similar in age (6.4 [IQR, 3.5-9.3] versus 5.5 [1.7-10.5] years, P=0.80), and had similar baseline respiratory rate (17.0 [15.0-21.0] versus 18.0 [16.0-21.5] breaths/minute, P=0.21), see Table 2.

Overall 31/42 (74% pre-test probability) had one or more symptoms. 86.4%(19/22) of the RA+ group had one or more symptoms compared with 60% (12/20) of the RA- group (P=0.052), see Table 3. On exploratory analysis, when considering the presence of RA as a “diagnostic test” of presence of one or more symptoms we found with a

sensitivity of 0.61, a specificity of 0.73, and a LR+ of 2.26, that the post-test probability of one or more symptoms was 86.4%. In regard to interventions, 21/42 (50% pre-test probability) underwent one or more interventions. 54.5% (12/22) of the RA+ group underwent one or more interventions, compared with 45.0% (9/20) of the RA- group (P=0.54), see Table 4. On exploratory analysis, when considering the presence of RA as a “diagnostic test” of subsequent interventions we found with a sensitivity of 0.57, a specificity of 0.48 and a LR+ of 1.1, that the post-test probability of subsequent intervention was 52,3%. Last, the occurrence of intracranial hypertension in the RA+ and RA- groups, at the time of the PSG (18% vs. 15%) and 1 year later (0.0% vs. 0.0%), was no different (p=0.56 and 0.52, respectively)(see Table 5).

HRV analysis

In the HRV analysis (using time domain and non-linear analysis variables), there were significantly higher values for a range of variables during both NREM and REM sleep (Tables 6 and 7). In the frequency domain, high frequency (HF) was significantly higher and the low-to-high frequency ratio (LF/HF) was significantly lower in the RA+ group, during both sleep states. Also, in the frequency domain, the total power of the frequency bands during the NREM sleep was significantly higher in the RA+ group (4970.0 vs. 1334.0, p=0.011)(Table 6). A higher percentage of paradoxical breathing during NREM sleep was found in the RA+ group, compared with the RA- group (19.0% versus 9.2%, P=0.042) (see Table 2). There was no difference in sleep characteristics between both groups (see Table 2).

## DISCUSSION

In this pilot study of children with syndromic craniosynostosis and primary snoring to mild OSA (oAHI ≤5/hour) we have made two significant observations. First, in about one-half of the patients in our practice, RA was evident in the PSG test. Second, the presence of RA+ in non-to-mild OSA may be indicative of higher parasympathetic activity, particularly during NREM sleep. Taken together, these data provide important insight into the pathophysiology of SDB during NREM sleep in patients with syndromic craniosynostosis.

In our study we found that children with RA had a trend toward more clinical symptoms. It was remarkable that we did not find any differences in sleep architecture, as we have reported in more severe cases of SDB in craniosynostosis.(2, 8, 37) It could be argued that symptoms were not severe enough to alter sleep architecture. Also, we did not find a difference in rate of finding IH. However, on closer inspection of HRV we did make some key observations.

In the analyses of different HRV variables we found that the RA+ group had higher HF and a lower LF/HF ratio, which means that there was increased parasympathetic activity compared to the RA- group. This finding makes sense since the HF power is driven by the parasympathetic activity, which in turn is associated with respiratory activity. This physiology may account for have overriding or possible limitation in increased sympathetic activity associated with OSA.(38, 39) Comparing this finding to previous studies of children who actually have OSA, a higher level of sympathetic activity is the usual finding. Liao et al.(14) compared children with none-or-

mild SDB with children with moderate-or-worse SDB and found that the more severe cases exhibited impaired HRV with excess sympathetic and weaker parasympathetic activity. Muzumdar et al.(13) showed increased sympathetic activity in children with OSA before adenotonsillectomy; after adenotonsillectomy there was an improvement in SDB and the level of sympathetic activity decreased. The most important difference between these studies and our current report is that study participants were children without a chronic condition, and our subjects all had syndromic craniosynostosis. However, we have not excluded the possibility that our subjects had some explanation for impairment of cardiac autonomic modulation as part of their underlying syndrome.

During two different states (NREM versus REM) we found that NREM disclosed a further shift to parasympathetic activity in the RA+ group. Liao et al.(16) reported a shift in cardiac autonomic modulation across sleep stages in children without SDB: a shift towards parasympathetic control from wake-to-NREM sleep, and a shift towards sympathetic control on entering REM sleep. Also, in cases of mild SDB, there was a similar pattern across sleep stages.(16) Therefore, in common with our study, during REM sleep there is less parasympathetic control. Also we found that in NREM sleep total power is significantly higher in children with RA; by implication, this group has to put significantly more effort in maintaining hemodynamic stability during NREM sleep. In addition, in children with RA we have identified a higher percentage of paradoxical breathing during NREM sleep. We speculate that this finding may, therefore, be caused by relatively higher parasympathetic activity in NREM sleep.

A possible explanation for the fact that the RA+ group had increased parasympathetic activity compared to the RA- group might be that the severity and the duration of the

RA+ group may not yet be sufficient enough to impact autonomic modulation in the RA+ group.(16) This may therefore be a predictive finding for OSA in the clinical evaluation.

Another explanation can be found in the normal physiology of healthy subjects.(40) Intense or acute activation of the autonomic nervous system in combination with acute changes in blood pressure lead to higher risk for arrhythmias and SDB.(40-42) This is caused by changes in impulse generation and oxygen metabolism of the heart or in the baroreflex function.(40, 42) Therefore, RA might be caused by the interactions in the sympathetic and parasympathetic system. Adrenergic stimulation will increase automaticity of Purkinje fibers and when the vagal nerve is activated on a background of enhanced automaticity sinus rate is reduced.(40) A question remains, however; whether changes in sympathetic and parasympathetic activity in the RA+ group are related to changes in blood pressure in different sleep stages or to a difference in autonomic modulation, which might be specifically different in these children.

Our study is not without limitations. First, in an ideal physiological assessment we should compare HRV analyses with esophageal pressure monitoring, so as to quantify airway flow-limitation.(43) This technique is too invasive for our clinical subjects and protocol.(43) Therefore, we are unable to identify cases of UARS (i.e., moderate SDB with symptoms of OSA and no abnormality on PSG). However, we have used the oAHI index as a biomarker of severity in airflow limitation and identified a subgroup in which interventions for OSA are more likely – that may be likened to UARS, albeit with the circuitous definition of those with RA. Second, we have not carried out systematic assessment of patient symptoms, but rather used the report of clinical symptoms recorded in the clinical notes. Third, our study group encompasses a wide age range (1

to 18 years) and, as such, we may have missed some relationship between symptom severity and significance, and the evolution of airway development. Fourth, we have not compared our data with a control group but rather studied graded-severity within a subset of cases with craniosynostosis. A control group might have given us reference values for the HRV variables. Last, due to the small sample size we were obligated to use non-parametric statistical testing which is less reliable to detect a real effect.

In conclusion, in patients with syndromic craniosynostosis, SDB and PSG showing oAHI ≤5/hour, the presence of RA may indicate a trend toward higher occurrence of clinical symptoms. Furthermore analysis of HRV variables in subjects with RA demonstrates an increase in parasympathetic activity that changes more during NREM sleep. Therefore, ECG analyses for RA and HRV variables may be a potentially useful aid in the present diagnostic work-up of apparently asymptomatic children with syndromic craniosynostosis screened for SDB.

## ACKNOWLEDGMENTS

EK had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis, including and especially any adverse effects. LJAC, RCT, RDG, EBW, IMJM, and KFMJ contributed substantially to the study design, data analysis and interpretation, and the writing of the manuscript

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## TABLES

**Table 1 HRV measures Non-linear analysis (Poincare plot): the Poincare HRV plot is a graph in which each RR interval (X-axis) is plotted against the next RR interval (Y-axis) as a type of "delay map"**

| Analysis | Variable | Definition |
|---|---|---|
| Time domain analysis | SDNN | The standard deviation (SD) of the normal-to-normal [NN] intervals, i.e., all intervals between adjacent QRS complexes resulting from sinus node depolarization. The SDNN reflects both short and long term variation within the RR interval series, and is an estimate of overall HRV |
| | RMSSD | The square root of the mean squared differences of successive NN intervals, which is a measure of short-term variability |
| | RRti | HRV triangular index which is the integral of the density distribution divided by the maximum of the density distribution, and is an estimate of overall HRV |
| Frequency domain analysis | LF | Low frequency components, which are mainly from sympathetic origin, but may also arise from parasympathetic activity |
| | HF | High frequency components (arising from respiratory sinus arrhythmia [RSA] and breathing), which are of parasympathetic origin |
| | LF/HF ratio | The ratio of low-to-high frequency power components, which reflects autonomic balance |
| | TP | Total power, a measure of the total power of all frequency components |
| Non-linear analysis[a] | SD1 | SD1 is the dispersion (standard deviation) of points *perpendicular* to the axis of line-of-identity and gives a measure of short-term variability |
| | SD2 | SD2 is the dispersion (standard deviation) of points *along* the axis of line-of identity and gives a measure of long-term |

| | | |
|---|---|---|
| | | variability |

**Table 2 Demographics**

| Variable | With RA(mean(IQR)) | Without RA(median(IQR)) | P-value |
|---|---|---|---|
| Age (years) | 6.4(3.5-9.3) | 5.5(1.7-10.5) | 0.80 |
| Respiratory rate (/min) | 17.0(15.0-21.0) | 18.0(16.0-21.5) | 0.21 |
| Mean heart rate (/min) | 81.5(73.7-90.3) | 83.9(72.0-106.2) | 0.47 |
| ODI (events/h) | 1.8(0.6-5.4) | 1.4(0.9-2.7) | 0.49 |
| Sleepquality(%) | 47.3(39.0-53.1) | 44.9(36.0-51.7) | 0.45 |
| Sleepefficiency(%) | 85.4(77.7-91.6) | 79.2(68.3-86.3) | 0.09 |
| Arousalindex | 0.0(0.0-1.2) | 0.0(0.0-4.2) | 0.46 |
| Awakenings(n) | 6.5(4.0-9.8) | 8.0(5.5-16.5) | 0.12 |
| RERA/TST(n) | 5.5(1.8-8.5) | 6.5(2.3-10.8) | 0.40 |
| Paradoxical breathing(%) | 14.5(6.5-33.8) | 11.0(3.3-19.3) | 0.26 |
| Paradoxical breathing, NREM(%) | 12.5(4.8-25.8) | 2.0(0.0-14.8) | 0.042 |
| Paradoxical breathing, REM(%) | 26.0(8.0-35.0) | 30.5(0.3-48.5) | 0.31 |

RA, respiratory arrhythmia; ODI, oxygen desaturation index; RERA; respiratory effort related arousal, IQR; interquartile range

**Table 3 Symptom assessment**

| Symptom assessment | With RA(n=22) | Without RA(n=20) | Symptoms | With RA(n=22) | Without RA(n=20) |
|---|---|---|---|---|---|
| Breathing abnormalities(%) | 86.4(19/22) | 55.0(11/20) | Snoring(%) | 68.1(15/22) | 45.0(9/20) |
| | | | Audible breathing(%) | 54.5(12/22) | 20.0(4/20) |
| | | | Oral breathing(%) | 22.7(5/22) | 0.0(0/20) |
| Sleep abnormalities(%) | 45.5(10/22) | 35.0(7/20) | Restless sleep(%) | 45.5(10/22) | 30.0(6/20) |

| | | | | | |
|---|---|---|---|---|---|
| Symptoms total(%) | 86.4(19/22) | 60.0(12/20) | Tiredness(%) | 27.3(6/22) | 25.0(5/20) |

RA, respiratory arrhythmia; n, group size

**Table 4 Intervention assessment**

| *Intervention | With RA(n=22) | Without RA(n=20) | P-value (chi-square) |
|---|---|---|---|
| Surgical(%) | 40.9(9/22) | 35.0(7/20) | |
| Non-surgical(%) | 22.7(5/22) | 20.0(4/20) | |
| Total(%) | 54.5(12/22) | 45.0(9/20) | 0.54 |

RA, respiratory arrhythmia; n, group size

*One child can be scored more than once, because of a combination treatment of surgical and non-surgical interventions

**Table 5 Intracranial hypertension occurrence at time of PSG and 1 years post PSG**

| Variable | With RA | Without RA | P-value (Fisher's exact) |
|---|---|---|---|
| IH at time of PSG(%) | 18 | 15 | 0.56 |
| IH 1 year post PSG(%) | 0.05 | 0 | 0.52 |

RA, respiratory arrhythmia; IH, intracranial hypertension; PSG, polysomnography

**Table 6 HRV variables in the time domain, non-linear, and frequency domain analyses during NREM sleep**

| Variable | With RA (median(IQR)) | Without RA (median(IQR)) | P-value |
|---|---|---|---|
| SDNN | 73.8(45.3-94.0) | 37.75 (23.8-62.4) | 0.013 |
| RMSSD | 87.6(45.7-120.0) | 44.3(25.2-74.3) | 0.017 |
| RRti | 19.1(11.9-26.4) | 9.8(5.9-17.3) | 0.00 |
| SD1 | 62.2(32.5-85.1) | 31.4(18.0-52.8) | 0.02 |
| SD2 | 106.8(75.8-135.1) | 69.7(56.5-112.6) | 0.09 |
| LF | 915.5(343.0-1831.5) | 490.5(213.5-1294.5) | 0.18 |
| HF | 3680.0(1196.8-6475.8) | 793.5(281.5-2492.5) | 0.00 |
| LF/HF ratio | 0.3(0.2-0.3) | 0.6(0.4-1.1) | 0.00 |
| TP | 4970.0(1763.5-8488.0) | 1334.0(493.3-3916.5) | 0.011 |

RA, respiratory arrhythmia; SDNN, standard deviation of the normal to normal intervals; RMSSD, square root of the mean squared differences of successive NN intervals; RRti, HRV triangular index; LF, low frequency; HF, high frequency, IQR; interquartile range, TP; total power

**Table 7 HRV variables in the time domain, non-linear, and frequency domain analyses during REM sleep**

| Variable | With RA (median(IQR)) | Without RA (median(IQR)) | P-value |
|---|---|---|---|
| SDNN | 55.0(34.9-80.2) | 40.0(24.2-50.4) | 0.039 |
| RMSSD | 62.5(39.1-104.5) | 41.5(22.1-55.3) | 0.023 |
| RRti | 12.1(8.4-17.8) | 7.9(5.1-12.1) | 0.045 |
| SD1 | 44.5(27.8-74.3) | 29.6(15.7-39.4) | 0.025 |
| SD2 | 98.0(66.6-129.4) | 72.1(50.9-105.5) | 0.096 |
| LF | 903.0(407.8-1616.5) | 564.0(246.5-996.8) | 0.212 |
| HF | 1675.5(668.3-4297.3) | 600.0(180.5-1377.3) | 0.019 |
| LF/HF ratio | 0.5(0.3-0.6) | 0.9(0.6-1.3) | 0.002 |
| TP | 2977.5(1052.8-6443.3) | 1211.0(478.5-2428.5) | 0.060 |

RA, respiratory arrhythmia; SDNN, standard deviation of the normal to normal intervals; RMSSD, square root of the mean squared differences of successive NN intervals; RRti, HRV triangular index; LF, low frequency; HF, high frequency, IQR; interquartile range, TP; total power

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**Electrocardiographic variables in children with syndromic craniosynostosis and none-to-mild obstructive sleep apnea: significance of identifying respiratory arrhythmia during sleep**

Highlights

- Increased parasympathetic activity and total power is shown in children with respiratory arrhythmia in the non-rapid eye movement sleep.
- Among children with respiratory arrhythmia there is a higher percentage of paradoxical breathing during the non-rapid eye movement sleep.
- Intracranial hypertension is distributed equally between children with and without respiratory arrhythmia.

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