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Original Article

# The nocturnal-polysomnogram and "non-hypoxic sleep-disordered-breathing" in children

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ABSTRACT

*Objective:* To characterize sleep-disordered breathing patterns not related to hypoxia resulting in fragmented sleep in children.
*Methods:* We reviewed the polysomnogram (PSG) data of children with sleep complaints who were being evaluated for sleep-disordered breathing and had an apnea-hypopnea-index $\leq 3$. These data were compared to the recordings of the same children with nasal CPAP administered for one night and to 60 control subjects (children without any sleep complaints). A subgroup of children was monitored with esophageal manometry, but nasal cannula flow data was recorded in all cases.
*Results:* Abnormal breathing patterns, particularly flow limitation, could be seen with more severity and frequency compared to apnea or hypopnea. The observed abnormal breathing patterns were associated with EEG disturbances.
*Conclusions:* Patterns such as flow-limitation, mouth-breathing, changes in inspiratory and expiratory time, rib-cage and expiratory muscle activity, transcutaneous CO2 electrode changes and snoring noises are all variables that should be systematically reviewed when analyzing nocturnal PSG. Current scoring guidelines emphasizes apnea-hypopnea and hypoxic-sleep disordered breathing and therefore treatment is often much delayed in this population of children with evidence of abnormal breathing patterns. Analysis of the various patterns of abnormal breathing noted above allows recognition of "non-hypoxic" sleep-disordered-breathing (SDB).



## 1. Introduction

Often, patients are not diagnosed with sleep-disordered breathing or obstructive sleep apnea until 40 years of age. This is unfortunate as a diagnosis of sleep-disordered breathing at this age is accompanied by various comorbidities, including excessive daytime sleepiness, increased risk of traffic and industrial accidents and cardiovascular complications. Each year, new epidemiological studies have shown associations between sleep apnea and metabolic dysfunction, psychiatric and neurological disorders, ophthalmologic syndromes, and pregnancy complications. Part of the witnessed increase in the prevalence of sleep apnea can be attributed to the rising occurrence of obesity in many countries. There is a long known association between the prevalence of obstructive sleep apnea and obesity. This phenomenon has been seen in both adults and children [1,2]. Studies have shown that the structure and size of the anatomic airway in conjunction with the fatty infiltration seen in obesity can help us determine how quickly OSA symptoms and signs emerge [3].

Our continuous investigation of children and their adult family members has given us extensive insight regarding the long-term progression with age as well how we might potentially act upon the earliest signs to recognize the development of the syndrome and decrease its frequency and its comorbidities.

This report is based on review of 2000 children who were investigated either at the Stanford University Sleep Disorders Clinic or the Taiwan Chang Gung Pediatric Sleep Laboratory over time. The studies reviewed include both prospective and retrospective investigations that were approved by IRBs at the time. Historically, pediatric sleep-disordered breathing was investigated in our clinic with measurement of respiratory effort using esophageal manometry (Pes), nasal and mouth thermistors, variable types of abdominal and thoracic bands, finger-pulse-oximetry, neck

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microphone, and body position, in association with the monitoring of sleep variables (EEG, chin and leg EMGs, eye movements) and one ECG lead. Such recording montage was changed in many places with the introduction of the nasal cannula-pressure transducer near 2000 [4], as it was felt that usage of nasal cannula would be easier to tolerate during total nocturnal sleep time despite the loss of valuable information obtained with use of Pes. Without Pes, quantification of the amount of effort made against any increase in upper-airway (UA) resistance was lost, and monitoring of flow was limited to inspiration. We have used Pes in association with nasal cannula-pressure transducer in some of the recordings discussed here; and we have tried finding variables which replace the information lost without Pes monitoring.

The fact that sleep-apnea-hypopnea was not the only pattern of sleep-disordered-breathing (SDB) leading to disturbed sleep was already well described in 1982 [5]· Also, the notion that the an "EEG arousal" had to last a minimum of 3 s to be scored was very much challenged by the publications of Terzano et al. who finally published an atlas on how to recognize and score "cyclic-alternating-pattern (CAP)" in NREM sleep in 2001 [6]. And we published in 2005 and 2006 usage of CAP scoring in children to recognize disturbance of sleep induced by abnormal breathing without calling upon the American-Academy of Sleep-Medicine (AASM) definition of an "EEG arousal" [7]. We have reported in different articles alternate forms of abnormal breathing patterns during sleep, different from the apnea-hypopnea-index (AHI) such as presence of mouth breathing during sleep [8]. Despite these diverse publications by different investigators [8,9], the term SDB is evoked only when AHI is considered to be abnormally high despite the fact that the polysomnogram-PSG-may show other abnormal findings that should lead to the diagnosis of abnormal breathing during sleep independent of the presence or absence of an abnormal AHI. Also the AHI does not emphasize the severity of other patterns indicative of persistent SDB, while some other matrix may indicate that the abnormal breathing during sleep occurred for much more time than the AHI would indicate. When treating children, the AHI should not be the only variable looked at, but other patterns should be also considered before indicating presence of improvement [10]· Our report presents alternate abnormal breathing patterns observed in the nocturnal PSG in the setting of abnormal breathing during sleep which should be systematically reviewed when investigating abnormal breathing during sleep in children. It is not meant to be an exhaustive list and other patterns may be added over time.

## 2. The study: subjects

This retrospective study investigated polysomnographic patterns related to breathing during sleep observed in pediatric nocturnal PSGs in our clinics. It focused on the relationship between termination of the patterns associated with SDB and EEG changes indicative of sleep-disruption in children with daytime complaints. To be included, nocturnal PSGs must have shown an apnea-hypopnea-index (AHI) $\leq$3 events/hours using standard analysis of the PSG [7]. This retrospective study performed on anonymized data was approved by both the Stanford University and Chang Gung Hospital IRBs. The recordings of 2000 children were reviewed to find-out breathing patterns noted to be associated with sleep-disruption without 3% oxygen saturation drop and without 3 s EEG arousals. Five hundred children, ranging from age 5–14 years of age, with a clinical history suggestive of SDB, were monitored with one PSG night using our standard recording montage (see below), and PSGs were scored for sleep and breathing following the AASM guidelines. As mentioned above, all recordings demonstrated evidence of low AHI during sleep, and were identified with "flow limitation" by nasal cannula [11]. The studied breathing patterns were compared to PSGs obtained on 60 children without complaints or abnormal AHIs (control group). As all 500 children had been placed on nasal CPAP for one night following nocturnal diagnostic PSG, the breathing patterns thought to be abnormal on baseline night were again evaluated for during the titration. Eighty-five of these children had simultaneous monitoring with both Pes and nasal cannula while 415 had only monitoring with nasal cannula.

### 2.1. Recording montage

With the exception of Pes monitoring used only on a subset of patients, our recordings were always performed using the same montage: 4 monopolar EEG leads (EEG electrodes: F1, C3, C4,O1) monitoring sleep-stages and states; 2 [right-R- and left-L-] eye movement leads, 2 chin EMGs, and 2 [R and L] anterior tibialis EMG electrodes, 1 ECG derivation, finger-pulse oximetry from which were derived not only oxygen saturation but also finger-plethysmography (indicative particularly of sympathetic activation). Breathing was monitored with nasal-cannula-pressure-transducer, mouth thermistor (in a scoop), thoracic and abdominal plethysmography bands, 3 rib-cage-diaphragm EMG surface electrodes, surface EMG abdominal-muscle electrodes (see Fig. 1) neck-microphone (measuring breathing sound in power), calibrated transcutaneous CO2 electrode, and a position sensor. All children were video monitored with video synchronized to recording. Recordings were performed for at least 7 ½ hours during nocturnal sleep with schedule following home-routine. Variables were monitored on a Somnomedic $^{TM}$ computerized sleep-system. All polysomnograms had electric and bio-calibrations completed at beginning and end of recordings.

### 2.2. Usage of Pes monitoring

#### 2.2.1. History

Esophageal manometry (Pes) used for many years, was first calibrated (cm/H2O) before any recording so that changes in inspiratory effort could be calculated for each inspiration. Review of recordings showed that increased inspiratory effort corresponded to increased negative peak in the Pes tracing that could progressively become more negative as the child slept. This incremental increase in negative pressure, representing changing respiratory efforts, would typically lead to a change in EEG with re-appearance of alpha and beta EEG rhythms (rhythms seen with arousal), which then correlated with a decrease in the Pes negative pressure peak, suggesting a return to normal inspiratory effort and breathing. This effect was seen regardless of body position or sleep stage (REM and NREM) [12]. These changes in respiratory effort were often associated with variation of the monitored oxygen saturation curve.

An initial systematic investigation performed on 30 children found pediatric cases with positive history of snoring during sleep and associated signs/symptoms such as unexplained fatigue, daytime behavioral changes and nocturnal sleep-disruption, with mouth breathing and increased respiratory efforts without oxygen saturation drops of 3% during the entire night of PSG [12]. Following these initial studies, we performed a systematic two night study using Pes that included five children between 14 and 17 years of age.

On the first night, children were monitored with Pes and previously described standard montage. On the second night, each child also wore a full face mask and a pneumotachograph. Due to the equipment and research apparatus, sleep was significantly curtailed in this second night of research compared to the baseline established in the first night. REM sleep was not observed in three of the five subjects and was clearly reduced in the last two.

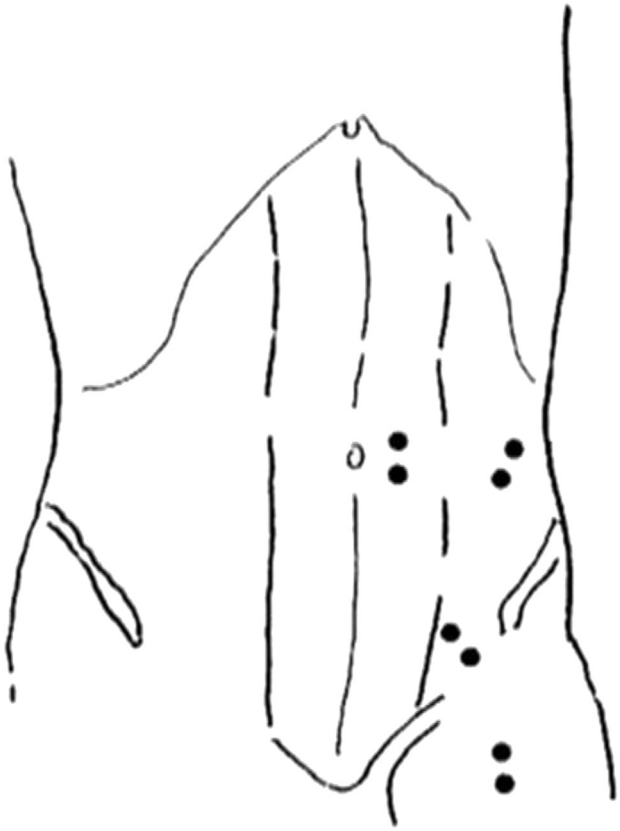

**Fig. 1.** Electrode placement for expiratory muscle recording.
Recording electrode placement (note electrodes are placed on both right and left side of abdomen and best electrodes are selected depending of body-position).

Additionally, the study showed a mean of 90% (±1.5%) of total sleep time been spent in stage-2 NREM sleep. As shown previously in young adults [13], there was an association of "flow limitation" (as indicated by the pneumotachograph) with decreased tidal volume and increased inspiratory effort, with successive flow limited breaths, but no change in oximetry [12–14]. Termination of successive epochs of the abnormal breathing pattern varied somewhat in duration, but as previously observed in young adults the termination of the sequence was always related to an EEG arousal [13]. Although variable in duration, the termination of flow limitation was always associated with an EEG change with burst of alpha and beta waves (indicating an arousal) but again, not necessarily associated with a change in oxygen saturation of ≥3%. Of note, EEG patterns seen with changes in "inspiratory effort" were shorter than 3 s in duration. . As shown in Fig. 2 obtained from a "historical child", there is a progressive increase in effort from the beginning until the end of the recording over 15 min. Looking more closely, during this sequence, there were some short EEG changes associated with a modest decrease in the negative peak Pes or a plateau for two to four breaths. Of note, the brief duration of EEG changes were not associated with a sufficient to return to baseline effort (see Fig. 2).

On the same figure (#-2) "autonomic activation" (ie brain-stem stimulation) was demonstrated, by the change in finger plethysmography showing a down-slope of the curve, indicating-per convention-a sympathetic activation. These infrequent recordings with very long persistence of UA resistance without return to normal breathing indicate that different factors lead to a brain-response to abnormal breathing during sleep: Here, there is an activation of reflexes impinging on the brainstem, indicated by the sympathetic activation noted (see Fig. 2), such activation is often associated with a very short cortical stimulation indicated by the very brief duration of change in EEG. Such stimulation is not long enough to bring the UA to full patency. Finally, as indicated in the figure there is a longer EEG cortical change leading to return to normal breathing. Known factors impacting on responses to abnormal breathing are sleep-states and stages; but also as example, the "blunting" of the arousal response-related to the repetitive disturbances of sleep-. The figure shows that the change in oxygen saturation was not a 3% drop when the upper-airway fully re-opened. These historical investigations indicated that re-opening of UA is a complex phenomenon.

### 2.3. Pes recording and calculation of Ti/Te/$T_{TOT}$

When monitoring "flow limitation" associated with increased respiratory effort demonstrated with Pes, another pattern was found: a progressive change in the duration of both inspiratory time (Ti) and expiratory time (Te) was observed, while the total breath duration ($T_{TOT}$) stayed constant [13,14]. There was variability in the duration of the period with such abnormal breathing before an EEG change was seen, the duration of the breath-sequence varying between 10 and 25 s. To analyze the phenomenon, the findings had been normalized, with each sequence considered as a duration of "100%" and the sequence then subdivided in "10%" sub-segments. When combining all data obtained in all the identified sequences, it was seen that all sequences (or periods of abnormal breathing) ended with an EEG arousal without a 3% oxygen desaturation. In the study, EEG arousals were noted when the mean Ti decreased to a mean that was 72–83% of the initial Ti duration. With Ti decrease

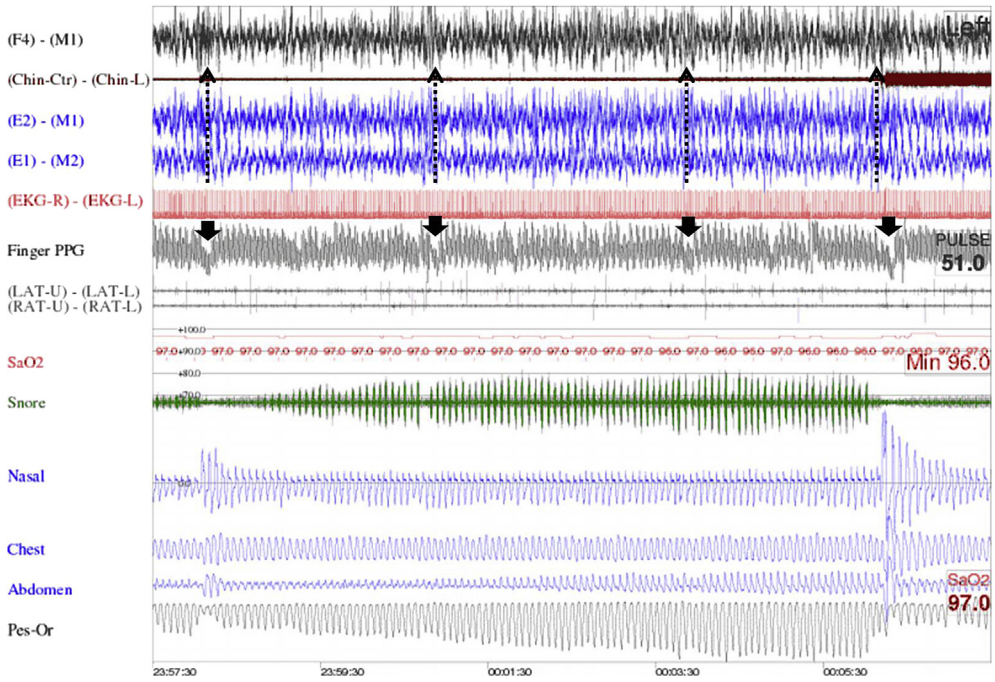


**Fig. 2.** Esophageal manometry (Pes)-and continuous inspiratory effort.
Esophageal manometry indicates a continuous abnormal inspiratory effort lasting 15 min in a teen-age boy known nightly snorer for at least 7 years: The bottom tracing shows Pes recording with peak negative pressure becoming more negative from beginning till end of segment with EEG arousal (Channel-1 from top) and increase in chin-EMG activity (channel −2 from top). Channel 11 from top is the nasal cannula recording indicating flow limitation but no hypopnea-apnea, oxygen saturation is continuously at 96% (Channel-9 from top)Finger-pulse-plethysmography (PPG, Channel 4 from top) shows downward swings indicating (per convention and calibration) an activation of the sympathetic tone (**full black arrow**). Evaluation of EEG at 30 s recording speed indicate that a change in EEG occurred with each autonomic activation, but the changes responded to the changes described by Terzano et al. [6] as a pattern seen as a "Phase A2 of the cyclic-alternating-pattern" (**dotted arrows**). These were a type of arousal but not sufficient to reopen the upper-airway and to eliminate the upper-airway-resistance. A complete awakening was needed The interpretation (see text) was that the teen-ager who was known to be a very loud snorer for at least 7 years, and presented a short-frenulum (birth) had progressively "blunted" responses to abnormal efforts (and the reflexes involved in responses to effort) and had adjusted in taking larger breaths.

there was a simultaneous lengthening of Te, the total breathing time remaining fairly constant. Fig. 3 demonstrates this change in the duration of inspiratory and expiratory time during time of abnormal breathing without evidence of apnea, hypopnea or oximetry change. There was a noted EEG arousal when Ti reached a too long duration. In summary, it was observed that the upper airway resistance led to change in timing of inspiratory and expiratory cycles, but such mechanism of response reached a certain limit: an EEG arousal was noted when the timing of inspiration and expiration (normally about 40/60% of Ttot) that tried to compensate for the abnormal inspiratory effort related to the UA resistance, reached a certain value leading to sleep disturbance and on the long run, sleep fragmentation, but avoiding drop in saturation.

### 2.4. Study

We investigated if some of the patterns historically mentioned using more sophisticated recording or investigative approaches than currently used, could be still identified particularly without Pes recording.

#### 2.4.1. Ti and Te

In our study, 85 children had simultaneous Pes and nasal cannula recording. We investigated if we could observe firsthand the phenomenon of change in Ti and Te.

Fifteen pre-pubertal children were identified with such changes. There was an EEG change with alpha burst with return to normal Ti and Te duration following the EEG changes, and absence of 3% change in oxygen saturation. In these children, toward end of the recording, Pes was pulled and the nasal cannula was left as sole marker of abnormal breathing during sleep (see Figs. 3 and 4). The investigation showed that the pattern recognized years ago with Pes could also be recognized with nasal cannula. Additionally, the change in EEG toward alpha/beta rhythms could be found when the duration of inspiration and expiration varied too much from baseline. This change in Ti and Te duration without change in Ttot (ie duration of the respiratory cycle) is indicative of abnormal breathing during sleep and it is corrected by a disturbance of sleep.

#### 2.4.2. Flow limitation

Flow limitation is defined as the flattening of the peak of the nasal cannula-pressure transducer wave contour with disappearance of the normal round presentation of the peak of the inspiratory phase of the breath (Figs. 5–7). The duration of flow limitation is calculated from the time of the start of flattening to the time when the wave contour normalizes or returns to baseline. At least four consecutive breaths must demonstrate this abnormal pattern. The duration of the "flow limitation" is calculated from the beginning of the inspiratory curve associated with the flattening, until the inspiratory curve returns to a normal "round" pattern of the curve. In a 30 s epoch, if more than 15 s flow limitation is observed, the epoch is scored as positive for flow limitation, if there was less than 15 s, the epoch is scored as normal breathing. .

Comparison of recordings with both Pes recording and nasal cannula indicates that the studied signal correlates with the inspiratory phase of the breath. While Pes can give information on the expiratory phase, the nasal cannula is unable to give valid information on expiratory flow limitation (EFL). The time occupied by all segments scored as "flow limited" are added and a "time with flow limitation" is determined in minutes. This time is compared to

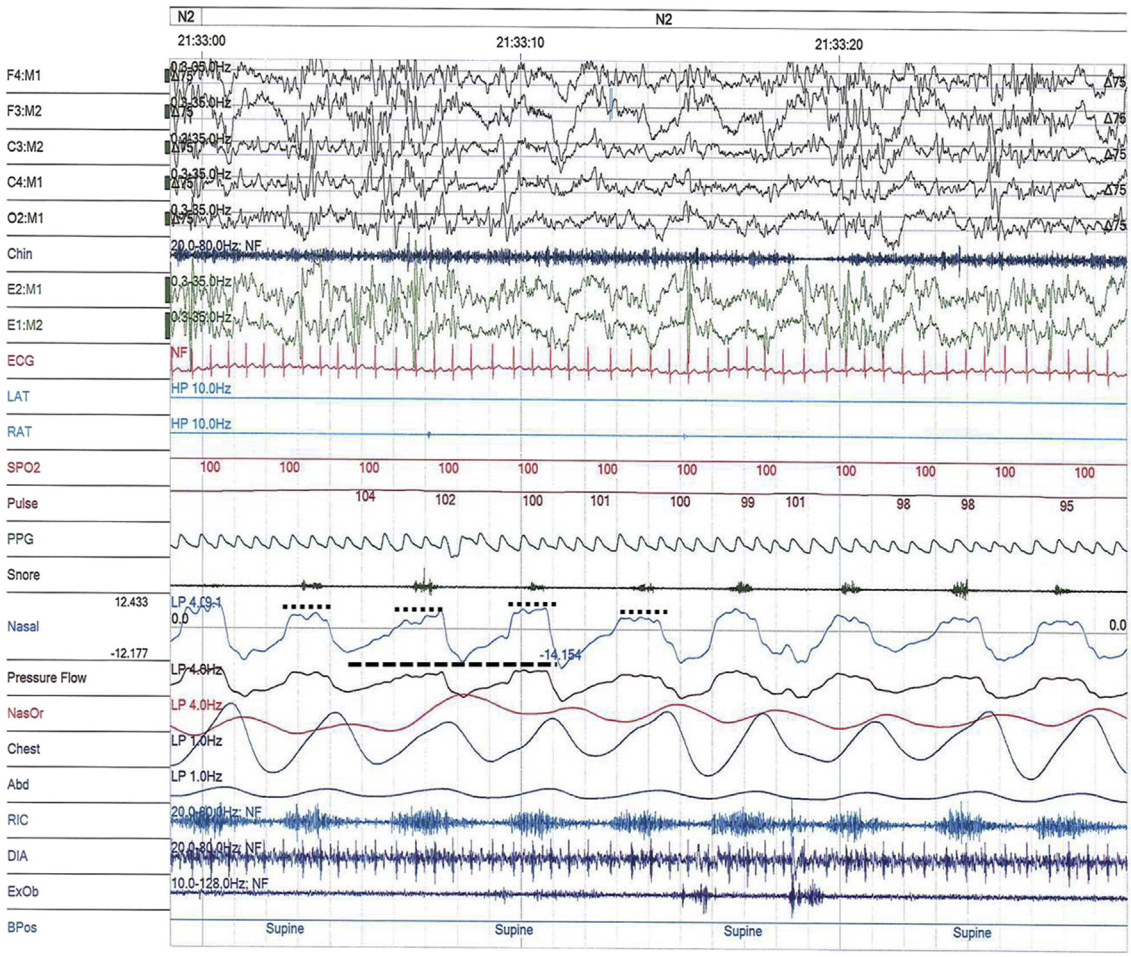


**Fig. 3.** Change in Ti and Te.
Example of a sequence with flow limitation and occurrence of change in Ti and Te indicated on nasal cannula channel (Channel 16 from top) in stage 2 NREM sleep (indicated by doted …. line)-. Breaths 3,5 7 and 8 showed lengthening of Ti with shortening of Te (indicated by - - - Line) (30 s segment).

the total sleep time of the recording and a percentage of flow limitation to total sleep time is obtained. For some children, the percentage of flow limitation in NREM and REM sleep can be calculated but our study focused on total sleep time. Children in the control group presented with a mean time with flow limitation of 3 ± 3% of the total sleep time. In the studied patients with abnormal breathing, the mean time of flow limitation was 37 ± 15% of total sleep time (see Fig. 5). There was no overlap between the control and study groups. The lowest percentage of flow limitation in the patient group was 12%, and the highest was 92% of nocturnal sleep. Conservatively, we considered that subjects with an inspiratory flow limitation (IFL) above 20% had abnormal breathing during sleep. In our review, 87% of recordings obtained from the symptomatic children had flow limitation above 30% of sleep time. Nasal CPAP was able to eliminate all evidence of "flow limitation".

Home recording without monitoring of EEG channels is clearly a problem for accurate diagnosis of SDB in children. However, the nasal cannula used in home recording may be as good as that in an in-lab recording for observation of "flow-limitation". The major and most common problem is displacement of the cannula, a frequent problem in children. If not displaced, the nasal cannula may give valid information regarding "flow limitation" (see Fig. 6). Some home study systems have aimed at measuring "flow limitation" as shown in the figure (see Fig. 5) but absence of EEG recording is however, a clear handicap. If automatic analysis of the nasal wave contours can easily be performed by a dedicated computer programs as seen in Fig. 6, other patterns of abnormal breathing during sleep leading to EEG arousal without hypoxemia might also be more easily identified with computer-analyses than visual analyses.

### 2.4.3. FFT and flow-limitation

Investigation of epochs of "flow-limitation" show that visually scored sleep and EEG-arousals often do not demonstrate presence of "sleep disruption" till the end of a "flow limitation" sequence. However investigation of the EEG during a series of sequences have been performed using Fast-Fourier-Transform [FFT] analysis with computer. The dissection of the EEG wave power using initially a 4 s window and later on a 1 s window demonstrates an increase in slow (0.25–2 Hz) delta, alpha and beta waves compared to analyses without "flow limitation". FFT studies were performed only on a subgroup of children (n = 20) with flow limitation and age and gender match controls (see Table 1). Before submitting the EEG recorded from the C3/A2 electrode to FFT analysis, a visual preparation of the recording was performed: segments with "flow-limitation" were identified and extracted independent of sleep-stage as were the segments without evidence of flow-limitation; also presence of segments with artifacts involving EEG and/or flow recording were eliminated from the study. The EEG segments either in the flow limitation group or the non-flow limitation group were kept in a temporal presentation before being submitted to FFT analysis, performed here, on 2 s window. The comparison of the tabulation of the two groups indicated a significant difference in the percentage of

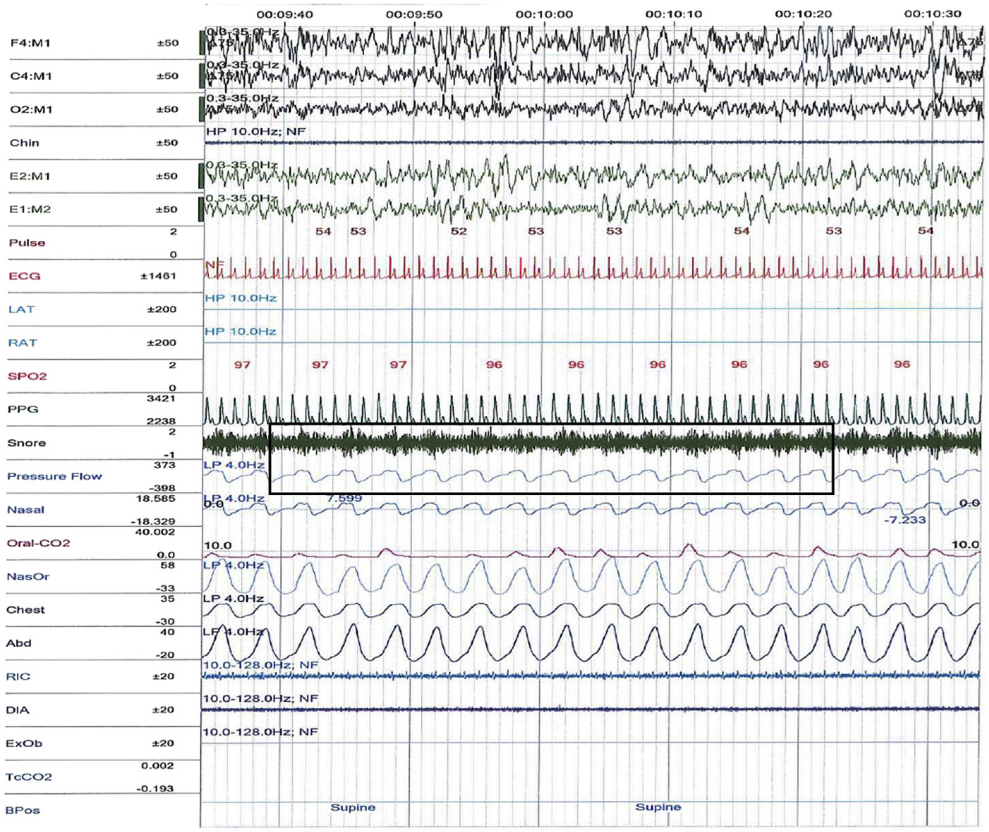


**Fig. 4.** Snoring, Flow limitation and change in Ti and Te.
Example of a sequence with snoring and changes in Ti and Te (1 min segment) associated with some flow limitation The box outline the breaths with changes in ti and te and snoring.

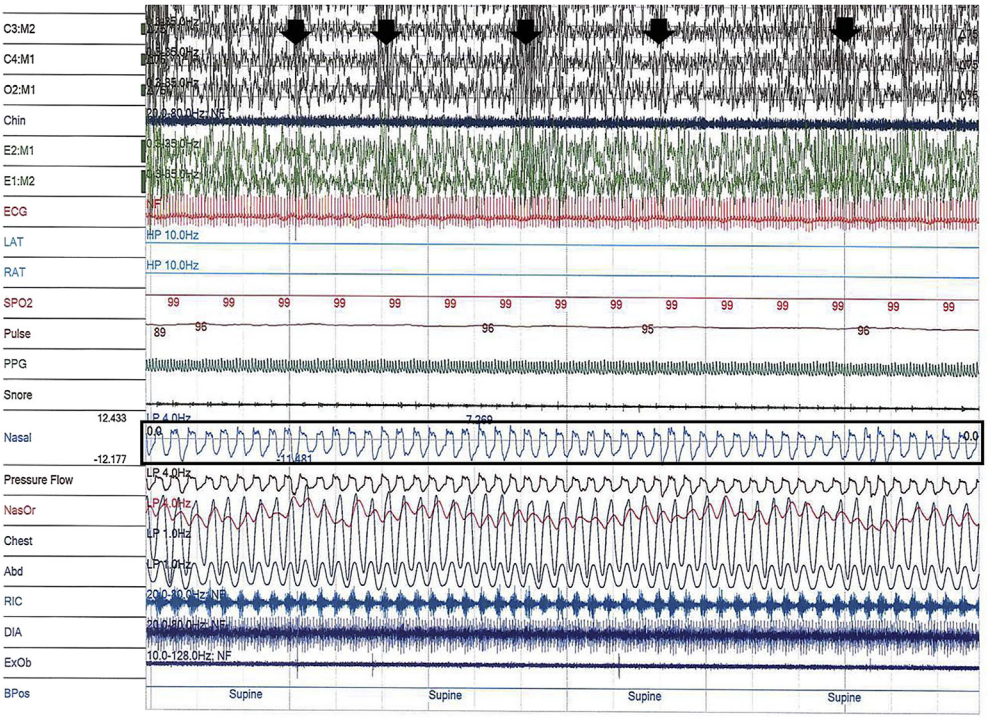


**Fig. 5.** Flow limitation.
150 s recording of "flow limitation" in a 10 years old symptomatic child. Nasal cannula (channel 16 from top) shows the continuous flattening of the signal. The black box outline the continuously flow limited breaths (channel 17 derives from nasal cannula" it is the "root/fourth" of the same signal that at time may show better the "flattening of the flow wave curve contour") Note no snoring is present, but the 5 EEG channels (channel 1-5 from top indicates clearly presence of cyclic-alternating-pattern [6] Despite the compressed view examination of the EEG leads indicates segments with faster frequencies and different amplitudes indicated with black arrows, supporting presence of cyclic-alternating- pattern recording.

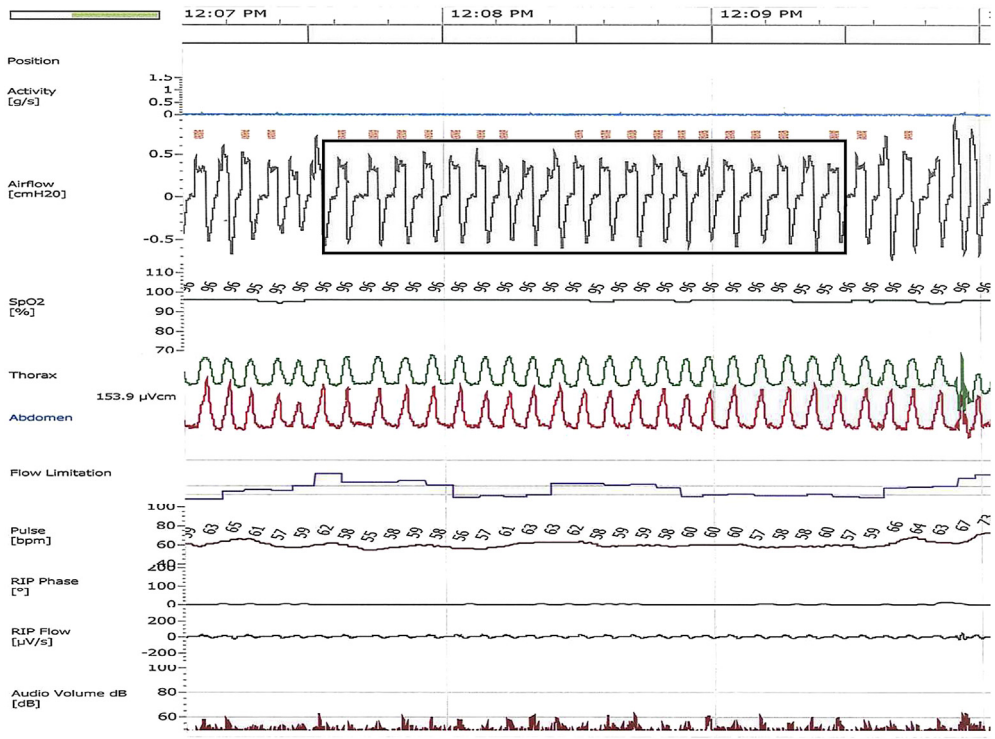


**Fig. 6.** Flow Limitation with a type 3 recorder.
Some 4 channel recorders (here a NOX $^{TM}$ (Iceland) recorder) may clearly show flow limitation, but the absence of EEG monitoring renders such finding of limited use at this time). The box indicates the segment with clear "flow-limitation".

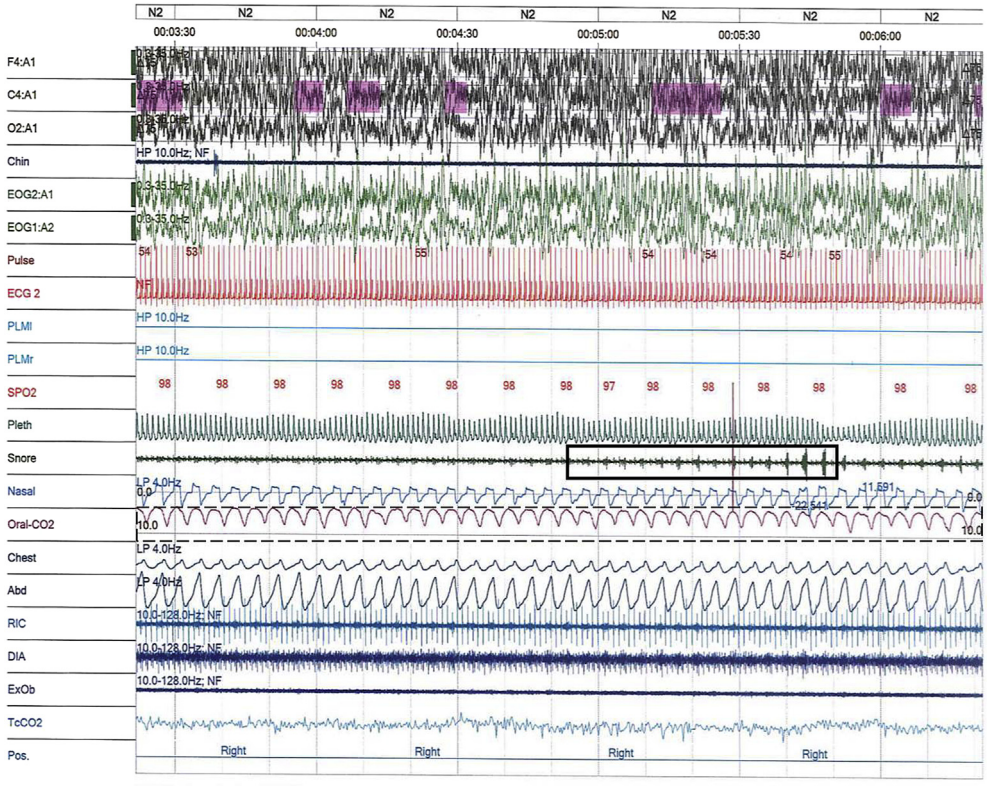


**Fig. 7.** Monitoring of mouth-breathing. Channel 15 from top indicates continuous mouth-breathing monitored with scoop (channel labeled Oral-CO2). It is associated here with flow limitation and snoring develops after mouth breathing (indicated in box).

slow delta, alpha and high theta powers (beta power was non-significantly increased) in the selected EEG derivation in the children with associated "flow-limitation" versus those without flow-limitation as seen in Table 1. As in a previous investigation

**Table-1**
Total NREM sleep analysis from C3/A2 EEG derivation on 20 SDB children and age and gender matched controls.

| EEG Mean Relative Power ($\mu V^2$) | SDB children n = 20 | Controls n = 10 |
|---|---|---|
| EEG Mean Relative Power ($\mu V^2$) | | Controls n = 20 |
| Delta 1 (0.50–2.00 Hz) | 630,1 ± 128 | 353.0 ± 163* |
| Delta 2 (2.25–4.00 Hz) | 207.0 ± 78 | 2341.0 ± 78 |
| Theta (4.25–8.00 Hz) | 82.0 ± 49 | 175.0 ± 60* |
| Alpha (8.25–12.00 Hz) | 110.0 ± 38 | 52.3 ± 38* |
| Sigma (12.25–16.00 Hz) | 29.7 ± 27 | 75.0 ± 41 |
| Beta (>16.00 Hz) | 11.3 ± 8 | 8.8 ± 8 |

Relative power (%) of different EEG bands during NREM sleep The data are presented in micro volt-square. The relative mean power (and standard deviation) of each frequency band analyzed on 20 SDB children and age- and gender-matched controls is presented. * indicates significant difference at p = 0.01.
As can be seen the FFT analysis shows overall significant differences in "Delta-1", Theta and alpha frequency bands, Beta frequencies are increased, but results did not reach significance, in SDB children. The interpretation is that there is an overall increase in fast frequencies and in slow delta during sleep. The abnormal breathing events continuously disturb sleep (alpha-relative power increase and relative power decrease in theta), and there is a continuous effort to maintain sleep and react against this disruption indicated by the increase in "slow delta" band. A similar type of finding was obtained in young adults when comparing "Upper-airway-resistance-syndrome" patients with normal controls (see reference 15 and associated figure in text).

comparing "upper-airway-resistance-syndrome" in young adults to matched controls [15], the interpretation is that there is a continuous disruption of sleep overall: There is an overall increase in faster frequencies and in slow delta during sleep and not solely when a flow limitation sequence ends. The abnormal breathing events (ie the "flow limitation" associated with each breath) continuously disturb sleep (alpha, fast theta relative power increases): There is a continuous effort to maintain sleep and to react against this disruption as shown by the increase in "slow delta" band, but there is an indication of the continuous-low key-sleep disturbance indicated by the abnormal decrease in theta rhythms and increase in alpha rhythms. See and insert Table 1) (—see also text of reference15-and the figure in the reference). Computerized EEG analysis allows better recognition of subtle sleep disturbances than visual analysis that will only identified the more important disturbances lasting long enough to be picked-up by the human-eye. All computerized-sleep-recording systems today provide FTT analyses of a selected EEG derivation (as does our recording system) which can be evaluated in a compress format for entire night.

### *2.4.4. Monitoring of respiratory muscle activity: "Diaphragm-intercostal" EMG (inspiratory muscles) oblique and rectus muscle activity (expiratory muscles), and transcutaneous CO2 electrode readings.*

In the 1990s, investigation of surface electrodes placed laterally in the fourth, fifth, and sixth intercostal spaces had shown that in slim subjects, changes in the EMG discharge patterns could be indicative of more recruitment of muscle fibers and obstructive breathing [16]. Comparison between these changes in EMG discharge and peak negative Pes values has been performed, demonstrating a good correlation between the two visual patterns and their termination with EEG arousal without hypoxia. Thereafter, usage of mathematical integration of the surface EMG signal was done and a program allowing quantification of respiratory effort during sleep was published [16,17]. Such visual findings were also clearly present in pre-pubertal children, and associated with sequences terminating with EEG arousals. Presence of such increase in surface diaphragmatic/intercostal EMG discharges with an incrementally increasing or "crescendo" presentation, ultimately terminating with an EEG arousal without hypoxia was documented in 300 nocturnal recordings obtained on pre-pubertal children during NREM sleep (see Fig. 8). As a visual pattern, the change in the amplitude of the surface EMG discharge is easily recognizable. When Pes is not available, monitoring of surface EMG can give information of the respiratory effort. Using 15 min recording length segments, obtained during NREM sleep on randomly taken PSGs recorded from 150 of the 500 SDB children studied for flow limitation, we verified this finding. The visual pattern of the "diaphragm-intercostal" burst is variable with each inspiration and each increase correlated with an increased amplitude of respiratory noise ("snoring") recorded by the microphone placed on the neck.

As mentioned earlier, a nasal cannula pressure transducer cannot reliably detect expiratory flow limitation (EFL), but systematic monitoring of expiratory muscles can help recognizing EFL in PSG. Typically, expiration is a passive process without firing of accessory muscles. Expiratory muscles recording electrodes were placed as indicated on Fig. 1, and systematic recording of rib-cage inspiratory muscles and abdominal expiratory muscles was performed. Out of 500 PSGs studied for flow limitation, we identified 187 PSGs with clear presentation of EFL indicated by abnormal appearance of expiratory muscle discharges. The segments with expiratory muscle discharges lasted from 1 to 3 min and were all interrupted by the same EEG-switch to alpha-beta EEG activity without oxygen desaturation as discussed above. Of note, the pattern of "flow limitation" changed with more pronounced flow limitation and/or increased inspiratory snoring particularly with development of EFL (see Figs. 9–11). Expiratory noises ("expiratory snoring") were rarely noted (in 2/150 PSGs) in association with appearance of expiratory muscle discharges (Figs. 9 and 10). Expiratory muscle discharges can be obtained with appropriate placement of the EMG electrodes, particularly in children; that rarely have abdominal obesity a condition which may render more difficult study of expiratory-muscle-discharges. The EMG bursts are a visual pattern easily observed when scoring PSGs.

Our review of PSGs with recording of inspiratory and expiratory muscle activities with simultaneous nasal cannula recording showed that children do not present initially with both inspiratory and expiratory-muscle discharges: The expiratory-muscle-discharges were always noted once flow-limitation was clear. Usually a more pronounced "flow-limitation" was recorded first and there was the secondary development of the expiratory-muscle-discharges. This progression of changes can be easily visually identified when scoring PSGs: First, there is the pattern of" flow limitation" noted on the nasal cannula wave curve, and in our study, the pattern and recording of snoring appeared always after some change in the nasal cannula wave contour. We noted that "inspiratory snoring" was the most commonly seen and the combination of both inspiratory and expiratory snoring was very rarely noted (2/150) (Fig. 11).

The sequence of events following observation of these patterns (flow limitation, inspiratory-muscle-discharges, expiratory-muscle-discharges) was then variable. Some children proceeded to present only flow-limitation terminated by indication of sleep disturbance with presence of a segment of predominance of EEG fast activities of various duration followed by return to presence of a normal nasal cannula wave contour ie termination of abnormal breathing, while others (187/500)demonstrated presence and progressive increase in expiratory EMG discharges, with PSG indication of simultaneous occurrence of IFL and EFL. These patterns ended again with a change in EEG waves with indication of presence of fast EEG activity, commonly associated with changes in the PPG-recording and return to a normal nasal cannula flow curve and complete disappearance of expiratory muscle activity.

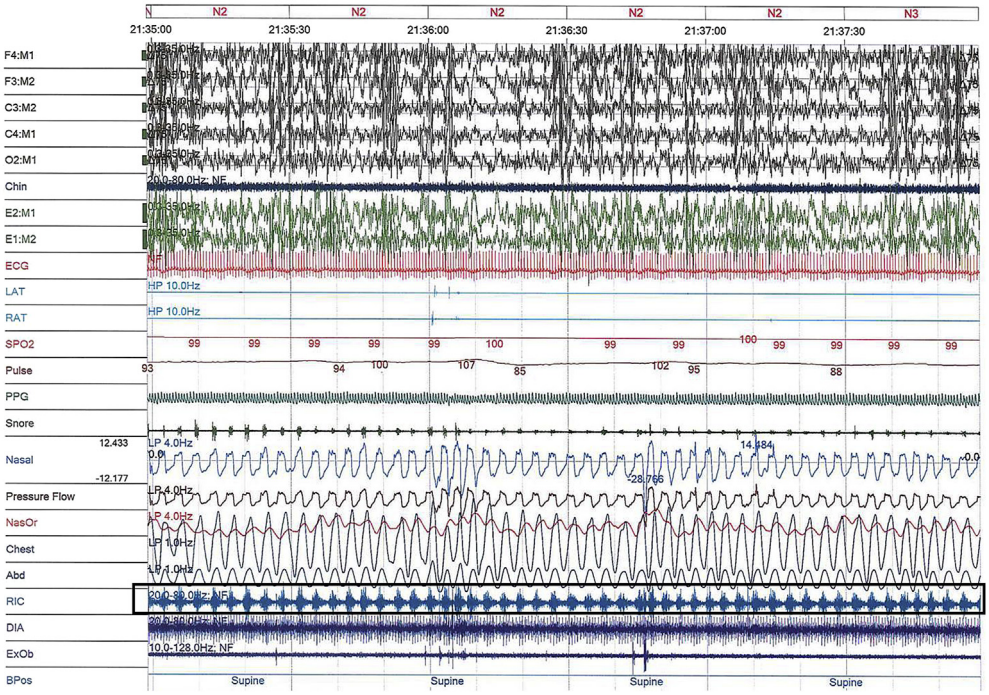


**Fig. 8.** Inspiratory-muscle-monitoring.
Recording of combination of diaphragm-rib-cage muscles on channel 21 from top (black box). As can be seen the muscle discharges are clearly visible in this segment of recording with flow-limitation (channels 16,17 from top) and snoring (channel 15 from top) Note "oralCO2" is the channel recording mouth-breathing with our scoop.

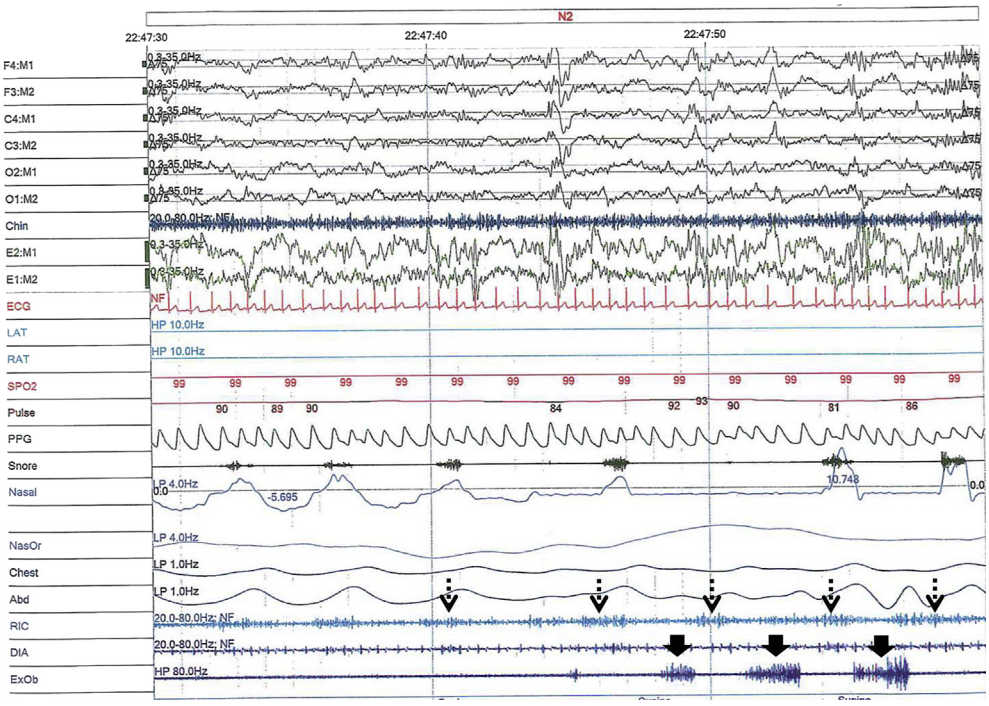


**Fig. 9.** Expiratory-muscle recording.
Appearance of expiratory-flow-limitation as indicated by activation of expiratory-muscles as seen on channel 23 (bottom channel **(black arrow)** The dotted arrows indicate the firing of the rib-cage inspiratory muscles.

### *2.4.5. Mouth-breathing*

Another pattern commonly observed, was the presence of "mouth-breathing during sleep". Mouth breathing is a known manifestation of abnormal breathing during sleep [8,9,19]. We systematically monitored for the presence of mouth breathing in PSGs, initially with a thermistor and thereafter we developed a "scoop" to obtain a very clear signal [18] (see Figs. 7 and 10). The bigger issue was to determine what amount of mouth breathing during sleep was a normal phenomenon. Fitzpatrick et al. had concluded that normal individuals spent a mean of 5% of their

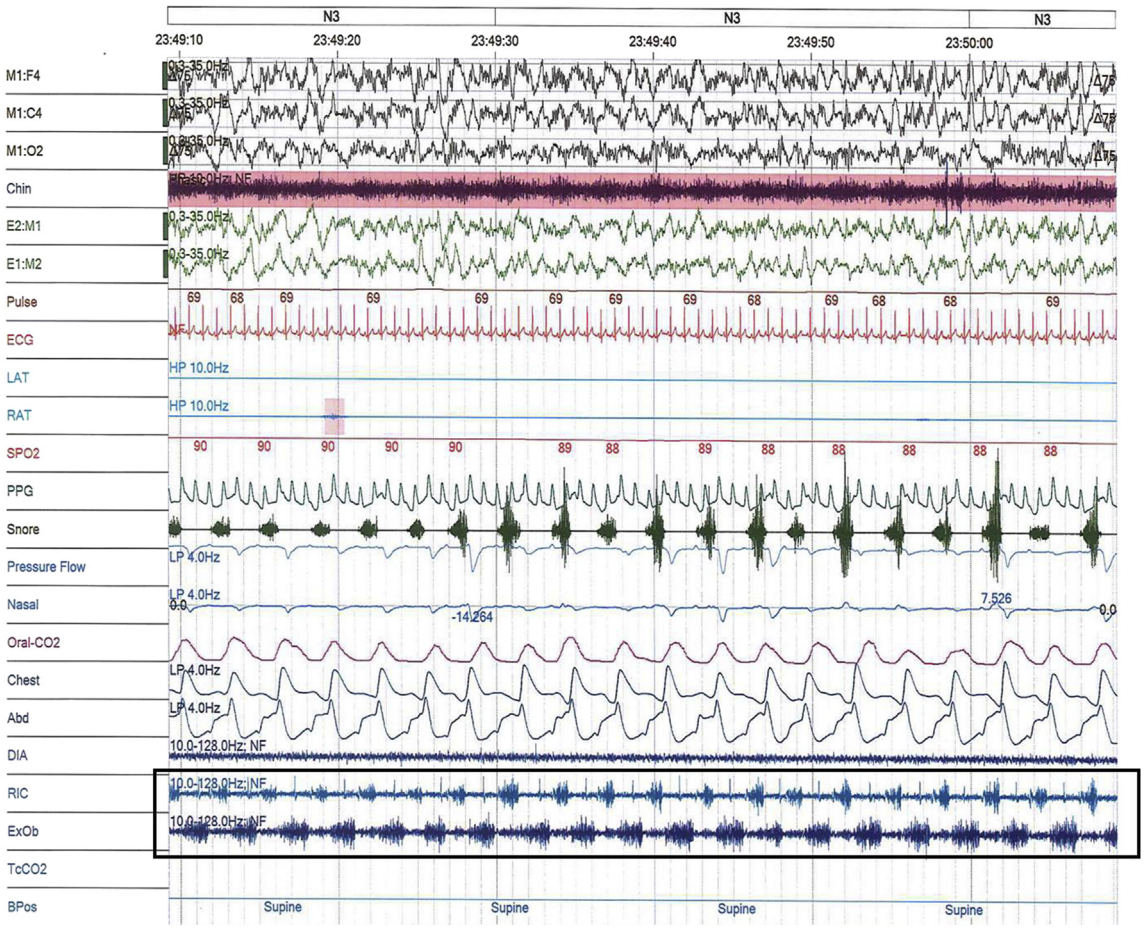


**Fig. 10.** Expiratory-muscle-discharges.
Recording segment of 120 s with both inspiratory and expiratory muscle activity (channel 20 and 20 from top)[black box]. The bottom channel (expiratory-muscle activity) is continuously demonstrating involvement of expiratory muscles with presence of flow limitation (channels 14,15) and snoring (channel 13).

sleep-time with mouth breathing [9]. We had found in a prior study a percentage very closely related[8] with a mean of 5% and a range of 0–10% of TST. We analyzed the recordings of our 60 normal controls and found again a mean of 5% of TST of 5 ± 2.1% with again a range of 0–10% of TST, and we noted presence of mouth breathing in all sleep-stages and states with a peak during stage 1 NREM sleep. No body position (supine versus side sleeping) was noted to preferentially demonstrate mouth breathing. Considering the findings obtained on normal and previously reported [8,9], we considered a cut-off point of 10% of mouth breathing during TST. Scoring of mouth breathing was performed based on 30 s epochs: if indication of mouth-breathing derived from our "scoop" recording or a mouth thermistor was more than 50% of the epoch, it was scored as "mouth-breathing +". A percentage of time spent mouth-breathing during sleep was then calculated based on TST.

Mouth-breathing may have been present before sleep-onset, and mouth-breathing may thus have been present at sleep-onset. In the review of our 500 children with SDB, 63% (n = 315) children presented with at least 15% time with mouth-breathing during sleep. In this study, no predominant body position (i.e. supine vs. side sleeping) or predominant sleep stage could be shown to be associated with mouth-breathing. Flow limitation was noted with and without mouth breathing but subjects with an abnormal percentage of mouth-breathing always demonstrated segments of the recording with flow limitation. Behaviorally, mouth breathing maybe associated with drooling, particularly in children younger than 5 years of age. In our study drooling, confirmed by video-analysis was shown as present in only 38/315 children with abnormal amount of mouth-breathing. Fig. 6 presents a 3 min segment of mouth breathing recording obtained with our "scoop." [18] Snoring was commonly associated with mouth-breathing, although 76/315 children had mouth breathing without any associated snoring noises. There was a temporal relationship between mouth-breathing and snoring observed in our group:, mouth-breathing always preceded snoring. When "flow-limitation" was present, change in EEG pattern with visual recognition of alpha/beta EEG pattern, always led to interruption of "flow-limitation", but such interruption did not always coincide with the end of mouth-breathing. In our study, out of 315 recognized with abnormal amount of mouth breathing, only 11 had interruption of flow-limitation and with a corresponding end of mouth-breathing. Thus, EEG arousals may interrupt monitoring of flow-limitation but not necessarily consistently affect the continued presence of mouth breathing.

### *2.4.6. Transcutaneous CO2 monitoring*

Twelve children 5–10 years of age, with valid recording of transcutaneous CO2 during TST, had the evolution of their transcutaneous CO2 waveforms studied in three conditions: 5 min before expiratory-muscle discharges, during the time of expiratory-muscle discharges, and 5 min after termination of expiratory-muscle discharges. Transcutaneous CO2 electrodes were all

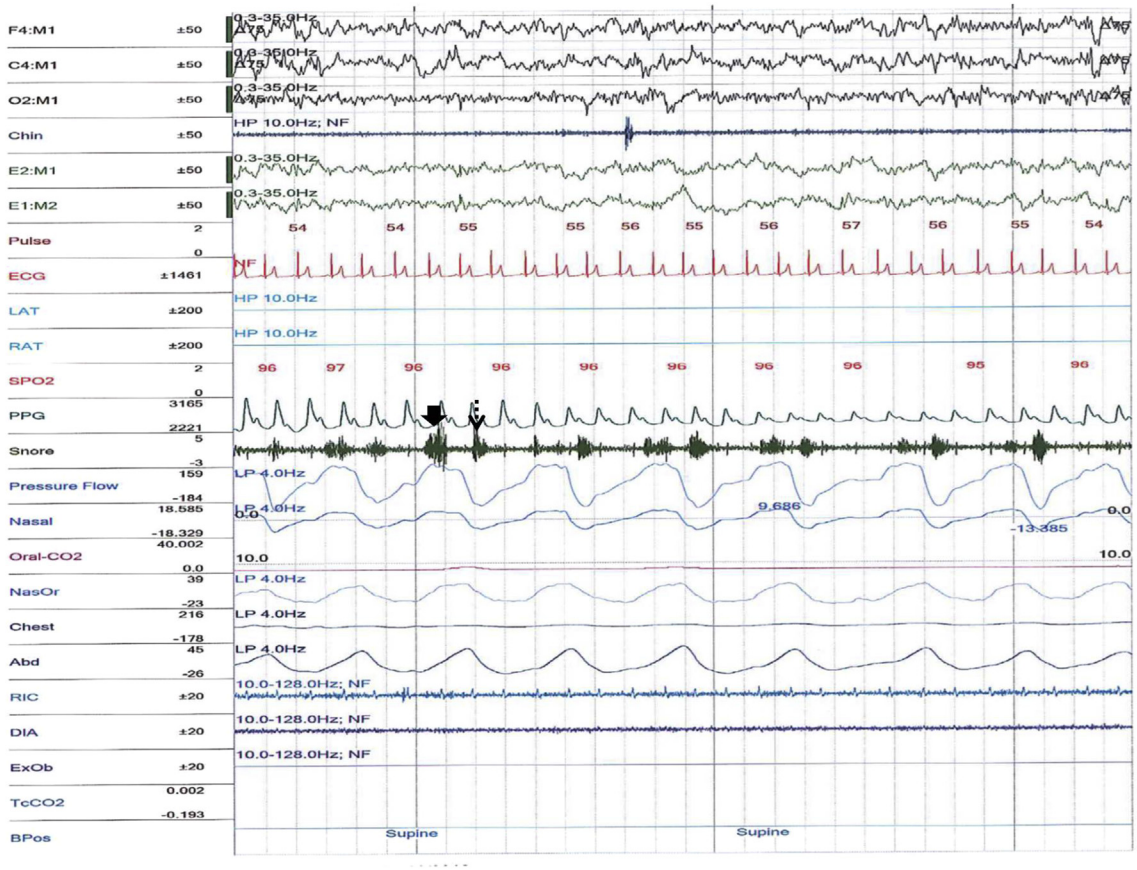


**Fig. 11.** Inspiratory and expiratory snoring.
Simultaneous inspiratory and expiratory snoring noises (channel 13 from top) were rarely noted [arrows indicate inspiratory and expiratory snoring].

calibrated at the beginning of recording as per the recommendation of the manufacturer. A 20 s delay was expected in the reading of the transcutaneous electrode curve. There were segments where an increase in TcCO2 readings was observed with the presence of IFL. Even greater changes were noted at segments with both IFL and EFL.

After this exploratory investigation, we systematically studied the $TcCO_2$ curves during all night recordings omitting artifactual recordings obtained when the electrode was not well placed or well calibrated. Of the 100 subjects studied, 78 had valid TcCO2 recordings. Oscillations of the $TcCO_2$ electrode wave contour were associated with long stretches of flow limitation and decrease of the TcCO2 values were associated with visually recognized occurrence of alpha/beta waves on EEG. In a variable number of flow-limitation segments, an "oscillatory" pattern could be noted with progressive increase in TcCO2 and reduction with each clear EEG change. This pattern of "oscillation" was most obvious in recording segments with simultaneous demonstration of IFL and EFL indicated by presence of abdominal expiratory muscle activity (n = 42). To compare the recording segments with presence of TcCO2 increase, we "normalized" segments independently of the length of the segment between "onset" and "offset" of the TcCO2 increase and decrease. The total segment was given a value of 100% duration, and we considered the starting CO2 reading value (called "0") and the value at time of the EEG change compare to the baseline. All segments with valid recordings were during NREM sleep. We tabulated all results obtained on recording segments from the 42 subjects with valid recordings. The "delta increase" of the TcCO2 reading between beginning and end of TcCO2 increase were closely related with a mean of 6.2 ± 1.1 torrs (n = 42 subjects) before occurrence of EEG change.

### 2.4.7. *Relation of different patterns to each other*

As indicated above, presence of mouth breathing was seen when "flow limitation" was present, but may have persisted even without flow limitation. But there was a temporal organization for the other patterns noted and reported here (See Fig. 12: Flow limitation was always noted first. If snoring was noted in the recording, it was noted always after occurrence of flow-limitation. Inspiratory snoring was most commonly seen with flow-limitation, and the combination of both inspiratory and expiratory snoring was very rarely noted (2/150) in our survey. When flow-limitation and snoring were noted, there were then 2 possible outcomes: 1) either a change in EEG pattern (considered an "arousal response") and return to a pattern of normal breathing, or 2) development and progressive increase in expiratory-muscle-discharges (observed in 182 of 500 recordings), with demonstration of both IFL and EFL. When such pattern was noted with no artefactual recording of TcCO2, the above described oscillatory pattern of the TcCO2 electrode curve could be seen. This succession of events ended with a change in the EEG pattern with occurrence of alpha/beta short segments [Fig. 11] and return to a normal nasal cannula flow curve and complete disappearance of expiratory muscle activity.

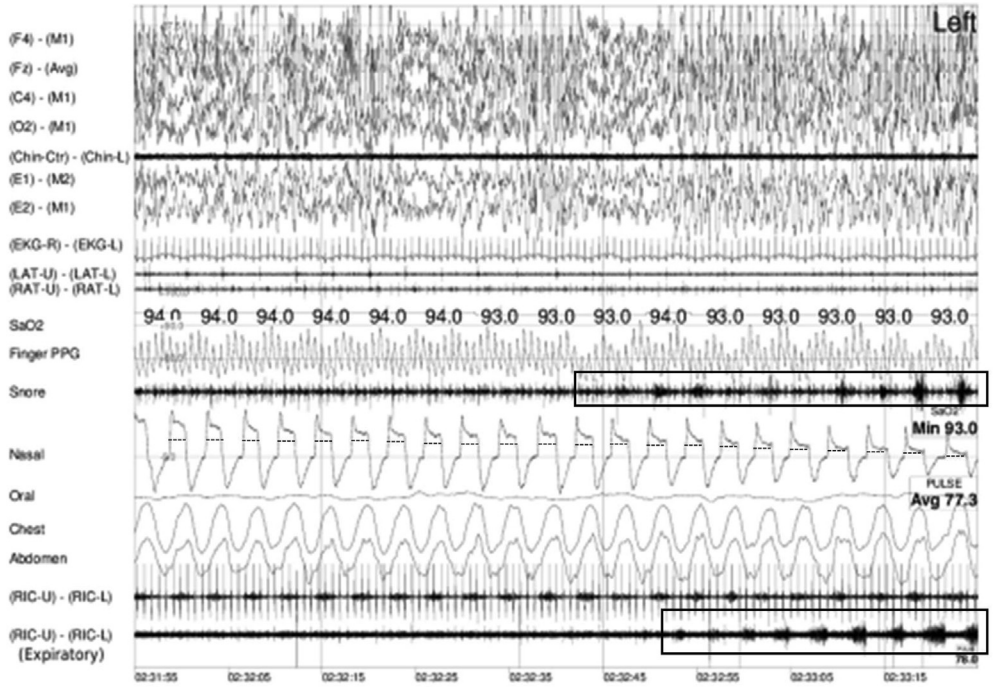


**Fig. 12.** Progression overtime of indicators of abnormal breathing during sleep.
Flow limitation then snoring and finally expiratory muscle activity occur. Note no change in oximetry, but EEG arousal is triggered. Snoring [top box] begins before occurrence of Expiratory-muscle-activity [bottom box].

### 2.5. Normal subjects

None of the described patterns were observed in the 60 normal children during their one night PSG.

### 2.6. Nasal CPAP trial

All studied subjects were placed on nasal CPAP and monitored for 1 night of CPAP titration. Titration was based on elimination of "flow-limitation" and not on elimination of hypopneas associated with oxygen saturation drop. All patterns described above were abolished with appropriate application of CPAP.

## 3. Discussion

This report is a descriptive presentation of patterns seen in nocturnal PSG of children with clinical complaints evoking SDB, and associated with clinical evaluation suggestive of a narrow UA. Investigation with Pes demonstrated more easily detectable abnormalities in the recordings than with monitoring only with the nasal cannula pressure transducer as clearly indicated by studies performed years ago, but the addition of information from other non-invasive variables during PSG substituted this information. Without measurement of Pes, the most important signal indicative of abnormal breathing during sleep is the nasal cannula pressure transducer. A clear change in the normal wave contour obtained from this sensor indicates the presence of "flow limitation." Studies of flow limitation have previously been done in adults and children [20]. Based on a large study performed on a sample from the general population, Palombini et al. helped us to determine a cut-off point between normal and pathologic flow limitation for adults [30% of TST} [20]. Our pediatric dataset shows that the cut-off point between normal and pathologic should be lower in children. Conservatively, based on our results, the cut-off point should not be higher than 20% of TST. Both cut-off points (for adults and children) are probably too conservative, but they allow us to recognize pathology and begin treatment earlier than the current practice. Some of the patterns that we mentioned such as snoring have been reviewed by others. The report of chronic snoring is commonly considered an indicator for further nocturnal investigation, and as an example, the treatment of the (supposed) cause of chronic snoring was shown to have a beneficial impact on some cognitive impairment [21]. Studies of mouth breathing have been done for many years. Its negative impact on orofacial development, specifically the size of the UA, has been well documented, particularly in the orthodontic literature [22–27]. The schema presented in Fig. 13 illustrates the combined negative sequelae associated with mouth breathing. Mouth breathing induces negative feedback on orofacial development and worsens SDB [27]. Similarly, non-restoration of nasal breathing during sleep is an indicator of

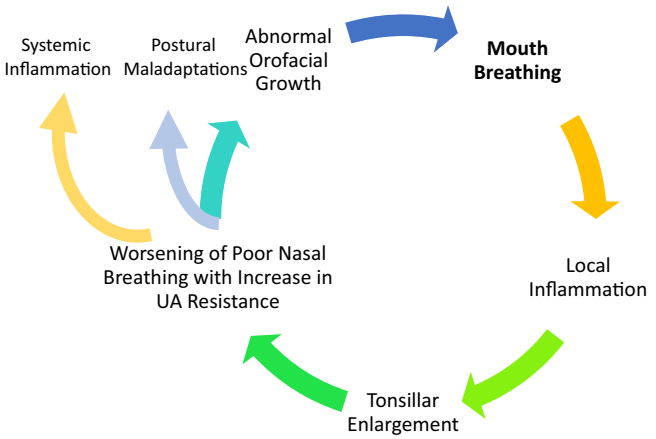


**Fig. 13.** Mouth-breathing and its negative impacts.
The many negative impacts of mouth breathing are summarized in the Schema with indication of the induced vicious cycles.

failed treatment of SDB, with the inevitable recurrence of clinical symptoms of sleep apnea within a variable time [28]. It is interesting to note that mouth-breathing-time during sleep does not overlap with "flow-limitation-time during sleep", but "flow-limitation" is calculated on nasal flow, and of course, calculation of "nasal flow" may not be possible with mouth breathing. There is a variable persistence of some degree of nasal flow with "mouth-breathing" and our study did not calculate this variability. Such investigation would require more sophisticated recording equipment as a first-step.

When considering breathing, one key variable should be change in end-tidal CO2. But it is difficult to obtain a good recording of end-tidal CO2 at the nose, particularly in pre-pubertal children. Attempts by several groups, including ours, have shown variable and often unreliable results. The cyclic phenomenon of nasal turbinate enlargements (varying from left to the right turbinates in variable cycle length) presents a difficulty in measuring flow from each nostril independently. These difficulties are also increased when simultaneously using a nasal cannula and monitoring end-tidal CO2 in a child's nose which can hinder the creation of a valid quantifiable inspiratory flow curve. These technical issues are not well resolved. Monitoring of $TcCO_2$ is thus a valid and important option, even if hypoventilation syndrome during sleep is not suspected in the studied children. We can see oscillation of the $TcCO_2$ curve with abnormal breathing leading to changes in EEG patterns, again without a decrease in oxygen saturation. $TcCO_2$ may be difficult to monitor at this time given the variable accuracy of commercially available transcutaneous-electrodes. These electrodes may be prone to artifact given the need for precise placement. That said, a useful recording can be obtained with a $TcCO_2$ and appropriate electrode placement. In the recent past, a Finnish team of researchers [29] have performed several studies using monitored $TcCO_2$ findings in adults with abnormal upper-airway resistance and have demonstrated the importance of monitoring $TcCO_2$, again more important than oximetry.

Our study had only one goal: to demonstrate that nocturnal PSG contains much more information about breathing than the AHI alone, and that to ignore these indicators will always delay the recognition of a problem with breathing during sleep. We have given illustrations of each pattern described above and in the legend of each illustration we have indicated the proportion of PSGs from our cohort which reflected the reported pattern.

How much sleep disturbance do these patterns induce? The study of the visual analysis of EEG as currently used is inadequate and misleading. An arousal response is triggered in less than 300 ms but scoring guidelines require 3 s of EEG change to score an arousal. The Terzano et al. group realized such a problem years ago and developed the "Cyclic-alternating-pattern scoring system during NREM sleep" and defined a "Phase A2 of the cyclic alternating pattern (CAP)" [6,30] as an example of an EEG arousal not scorable by AASM criteria [11]. The AASM scoring system is still visually based. For years computerized analysis of EEG has been performed using FFT. This technique is certainly not the most sophisticated by far to-day, but all computerized-sleep-systems used in sleep-laboratories can perform such analyses on the EEG collected during sleep for one EEG derivation. In our own past investigations for example, we provided results obtained on young adults with "upper-airway-resistance-syndrome"-UARS- compared to matched controls [15] (see also figure in referenced-text- [15]). Since these studies, the concept of a change in indicators of normal sleep based on computerized analyses of relative power of different EEG bands looked at in successive analytic "windows" has been very much used. The "time-window" used has decreased with more recent computerized-sleep-systems. Our own system (Somnomedic $^{TM}$) uses a 1 s window. To demonstrate this, we present in Table 1 the result of such analysis for 20 children with re-occurring "flow-limitation" versus analysis performed on 20 age- and gender-matched controls. Our presentation did not investigate the "arousal responses" terminating events, and the example presented here is only given as an example to further work: The findings shown in Table 1 indicate that during total NREM sleep in association with "flow-limitation" there is a continuous disturbance of sleep (as shown also in the figure analyzing UARS-patient- sleep in reference 15). The interpretation of the EEG changes is similar in both children and young-adults cases: abnormal breathing has a continuous impact on the brain, the cortex is continuously informed and normal sleep is never really present with a near-continuous state of "arousal" (increase in relative power of alpha, decrease in relative power of theta-see Table 1) despite the "push" for sleep (increase in slow delta). Further large studies of FFT changes associated with flow limitation are needed. Our study indicated that duration of the presented patterns varied, also that several patterns were noted in succession, most probably indicating a "worsening" of the UA resistance. Our study did not try to address this issue. Similarly some children had only flow limitation, some further developed snoring, expiratory −flow- limitation etc before having a change in EEG and return to normal breathing: again our study did not addressed why such differences existed. Clearly further analyses are needed addressing these differences. Our goal is more limited: these abnormal breathing patterns are recognizable in pediatric PSG. They indicate presence of abnormal breathing during sleep. They should be recognized independently of oxygen saturation. They should also be eliminated when treatments are applied.

In summary, this analysis summarizes breathing-patterns that can be visually recognized in nocturnal PSG even when AHI is low. They indicate disturbances of breathing and occur earlier than AH associated with a decrease in oxygen saturation by 3% or more. The described breathing-patterns are associated with daytime complaints and clinical findings. They are not present in PSGs of normal controls and are not present when appropriate nasal CPAP pressure is applied to the child during sleep.

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## Conflict of interest

The ICMJE Uniform Disclosure Form for Potential Conflicts of Interest associated with this article can be viewed by clicking on the following link: https://doi.org/10.1016/j.sleep.2018.11.001.

## References

[1] Romero-Corral A, Caples SM, Lopez-Jimenez F, et al. Interactions between obesity and obstructive sleep apnea: implications for treatment. Chest 2010;137(3):711–9.
[2] Arens R, Muzumdar H. Childhood obesity and obstructive sleep apnea syndrome. J Appl Physiol 2010;108(2):436–44.
[3] Schwab RJ, Pasirstein M, Pierson R, et al. Identification of upper airway anatomic risk factors for obstructive sleep apnea with volumetric magnetic resonance imaging. Am J Respir Crit Care Med 2003;168(5):522–30.
[4] Serebrisky D, Cordero R, Mandeli J, et al. Assessment of inspiratory flow limitation in children with sleep-disordered breathing by a nasal cannula pressure transducer system. Pediatr Pulmonol 2002;33(5):380–7.
[5] Guilleminault C, Winkle R, Korobkin R, et al. Children and nocturnal snoring: evaluation of the effects of sleep related respiratory resistive load and daytime functioning. Eur J Pediatr 1982;139(3):165–71.
[6] Terzano MG, Parrino L, Sherieri A, et al. Atlas, rules, and recording techniques for the scoring of cyclic alternating pattern (CAP) in human sleep. Sleep Med 2001;2(6):537–53.

[7] Iber C, Ancoli-Israel S, Chesson A, et al. The AASM manual for the scoring of sleep and associated events: rules, terminology and technical specifications. Westchester, IL: American Academy of Sleep Medicine; 2007. 2007.
[8] Lee S-Y, Guilleminault C, Chiu H-Y, et al. Mouth breathing, "nasal disuse," and pediatric sleep-disordered breathing. Sleep Breath 2015;19(4):1257–64.
[9] Fitzpatrick MF, McLean H, Urton AM, et al. Effect of nasal or oral breathing route on upper airway resistance during sleep. Eur Respir J 2003;22(5):827–32.
[10] Huang YS, Guilleminault C, Lee LA, et al. Treatment outcomes of adenotonsillectomy for children with obstructive sleep apnea: a prospective longitudinal study. Sleep 2014;37:71–6.
[11] Arora N, Meskill G, Guilleminault C. The role of flow limitation as an important diagnostic tool and clinical finding in mild sleep-disordered breathing. Sleep Sci 2015;8(3):134–42.
[12] Guilleminault C, Korobkin R, Winkle R. A review of 50 children with obstructive sleep apnea syndrome. Lung 1981;159(5):275–87.
[13] Stoohs R, Guilleminault C. Snoring during NREM sleep: respiratory timing, esophageal pressure and EEG arousal. Respir Physiol 1991;85(2):151–67.
[14] Stoohs R, Skrobal A, Guilleminault C. Does snoring intensity predict flow limitation or respiratory effort during sleep? Respir Physiol 1993;92(1):27–38.
[15] Guilleminault C, Kim YD, Chowdhuri S, et al. Sleep and daytime sleepiness in upper airway resistance syndrome compared to obstructive sleep apnea syndrome. EurRespirJ 2001;17:1–10.
[16] Stoohs RA, Blum HC, Knaack L, et al. Non-invasive estimation of esophageal pressure based on intercostal EMG monitoring. Conf Proc IEEE Eng Med Biol Soc 2004;5:3867–9.
[17] Stoohs RA, Blum H-C, Knaack L, et al. Comparison of pleural pressure and transcutaneous diaphragmatic electromyogram in obstructive sleep apnea syndrome. Sleep 2005;28(3):321–9.
[18] Carrillo O, Sullivan SS, Black J. A novel method for detecting oral breathing (abstract). Sleep 2010;33:A139.
[19] Fitzpatrick MF, McLean H, Urton AM, et al. Effect of nasal or oral breathing route on upper airway resistance during sleep. Eur Respir J 2003;22(5):827–32.
[20] Palombini LO, Tufik S, Rapoport DM, et al. Inspiratory flow limitation in a normal population of adults in São Paulo, Brazil. Sleep 2013;36(11):1663–8.
[21] Gozal D, Pope Jr DW. Snoring during early childhood and academic performance at ages thirteen to fourteen years. Pediatrics 2001;107(6):1394–9.
[22] Adenoids Linder-Aronson S. Their effect on mode of breathing and nasal airflow and their relationship to characteristics of the facial skeleton and the denition. A biometric, rhino-manometric and cephalometro-radiographic study on children with and without adenoids. Acta Otolaryngol Suppl 1970;265:1–132.
[23] McNamara JA. Influence of respiratory pattern on craniofacial growth. Angle Orthod 1981;51(4):269–300.
[24] Limme M. Orthognathic and orthodontic consequences of mouth breathing. Acta Oto-Rhino-Laryngol Belg 1993;47(2):145–55.
[25] Ricketts MR. Respiratory obstructions and their relation to tongue posture. Cleft Palate Bull 1958;8:4–5.
[26] Huang Y-S, Guilleminault C. Pediatric obstructive sleep apnea and the critical role of oral-facial growth: evidences. Front Neurol 2012;3:184.
[27] Guilleminault C, Huang Y-S. From oral facial dysfunction to dysmorphism and the onset of pediatric OSA. Sleep Med Rev 2018;40:203–14.
[28] Guilleminault C, Sullivan SS. Towards restoration of continuous nasal breathing as the ultimate treatment goal in pediatric obstructive sleep apnea. Enliven: Pediatr Neonatol Biol. 2014;1(1):001.
[29] Rimpilä V, Saaresranta T, Huhtala H, et al. Transcutaneous CO2 plateau as setpoint for respiratory drive during upper airway flow-limitation. Respir Physiol Neurobiol 2014;191:44–51.
[30] Lopes MC, Rosa A, Roizenblatt S, et al. Cyclic alternating pattern in peripubertal children. Sleep 2005;28(2):215–9.