Pulse Transit Time Improves Detection of Sleep Respiratory Events and Microarousals in Children*

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Objectives: To evaluate the additional information provided by pulse transit time (PTT), a noninvasive tool, when using during polysomnography for the diagnosis of sleep breathing disorders in a pediatric population.
Main findings: Respiratory and microarousals events were scored twice. The first scoring was performed using nasal pressure, thermistors, thoracic and abdominal movements, and oxygen saturation. The second scoring, blinded to the first scoring, was performed using PTT in combination with all the other signals. Microarousals were scored once visually on the EEG trace (cortical arousals [CAs]) and once using the PTT signal (autonomic arousals [AAs]) blinded to EEG. For the whole group of 16 children studied (mean age, 9.5 years), there was no significant difference between the respiratory disturbance index (RDI) with or without PTT analysis (22.4 ± 13.5/h vs 20.4 ± 14.3/h; not significant [mean ± SD]). Among the children exhibiting a "without PTT" RDI < 30/h, 5 of 12 children (41.66%) showed a clinically significant ≥ 5/h increase in RDI when using PTT. AAs detected by PTT were significantly more frequent than CAs during rapid eye movement (REM) sleep (7.4 ± 3.9/h vs 3.2 ± 2.3/h; p < 0.001) and slow wave sleep (SWS) [6.0 ± 4.3/h vs 0.6 ± 0.5/h; p < 0.0001].
Conclusions: The quantification of respiratory effort using PTT improves the detection of respiratory events in children. The detection of microarousals is improved particularly in REM and SWS. *(CHEST 2005; 127:722–730)*

Key words: children; microarousal; nasal pressure; pulse transit time; sleep apnea

Abbreviations: AA = autonomic arousal; CA = cortical arousal; IQR = interquartile range; NP = nasal pressure; NS = not significant; Pes = esophageal pressure; PTT = pulse transit time; RDI = respiratory disturbance index; REM = rapid eye movement; SaO₂ = oxygen saturation; SWS = slow wave sleep

Hypopneas and upper airway resistance episodes represent the most frequent polysomnographic abnormalities occurring in children with sleep-disordered breathing.[1] These events may be just as clinically important as complete apneas in terms of producing sleep fragmentation and cognitive dysfunction. Their polysomnographic features can be summarized by three different patterns: (1) a variable reduction in flow (from inspiratory flow limitation to hypopnea), (2) an increase in respiratory effort, and (3) the occurrence of a microarousal ending the respiratory event. Thus, to detect and classify hypopneas and upper airway resistance episodes, sensitive and quantitative measures of flow, respiratory effort, and microarousals should be used.

Thermistors have been widely used to assess airflow but are more qualitative than quantitative, leading to inadequate scoring of hypopneas.[2] In adults, technology has improved to incorporate methods with better validity and reliability, such as nasal pressure (NP) measurements.[2,3] Data tend to demonstrate that in children NP is also of interest.[4,5]

Our group has previously demonstrated, in adults, that pulse transit time (PTT) is as accurate as esophageal pressure (Pes) for measuring respiratory effort both in frank and subtle respiratory events.[6]

PTT is inversely correlated to BP. During an obstructive event, Pes becomes more and more negative during every inspiratory phase. Concurrent values of systolic BP decrease inspiration after inspiration, whereas PTT values increase (Fig 1). This explains the good correlation between the amplitude of PTT oscillations between inspiration and expiration and the magnitude of negative pleural swings as measured by esophageal manometry. The optimal method for identifying respiratory events and sleep fragmentation therefore appears to associate Pes or PTT and NP. To date, the role of PTT as a measure of arousal and respiratory effort in children with sleep-disordered breathing has been evaluated only in one very recent study.[7]

It has been demonstrated that microarousals can be graded in four different levels.[8] The two first steps of arousal are represented by δ bursts and K complex bursts, called subcortical or "autonomic" arousals. There is a brainstem center that synchronizes these δ bursts and K complex bursts with the simultaneous cardiac activation. Thus, an autonomic microarousal can be identified by the characterization of an autonomic stimulation such as tachycardia or a rise in BP. The BP surges associated with microarousals can also be detected by PTT (transient dip in PTT), thus offering the possibility of estimating sleep fragmentation. These autonomic activations might represent the primary form of arousal response during sleep preceding the appearance of CAs that are usually assessed by α waves on EEG, associated or not with electromyogram activation.[9] Not all autonomic activations lead to a secondary CA, depending on the level of cortex arousability.[8] In children, the respiratory events do not seem to terminate with the systematic occurrence of an identifiable CA.[10] One can hypothesize that in this context, the majority of arousals ending the respiratory events are limited to AAs that remain undetected using classical visual analysis of EEG.[9]

In the present study, we used NP for measuring flow and PTT as a quantitative measurement of respiratory effort to identify sleep respiratory abnormalities in 16 consecutive children. Sleep fragmen-
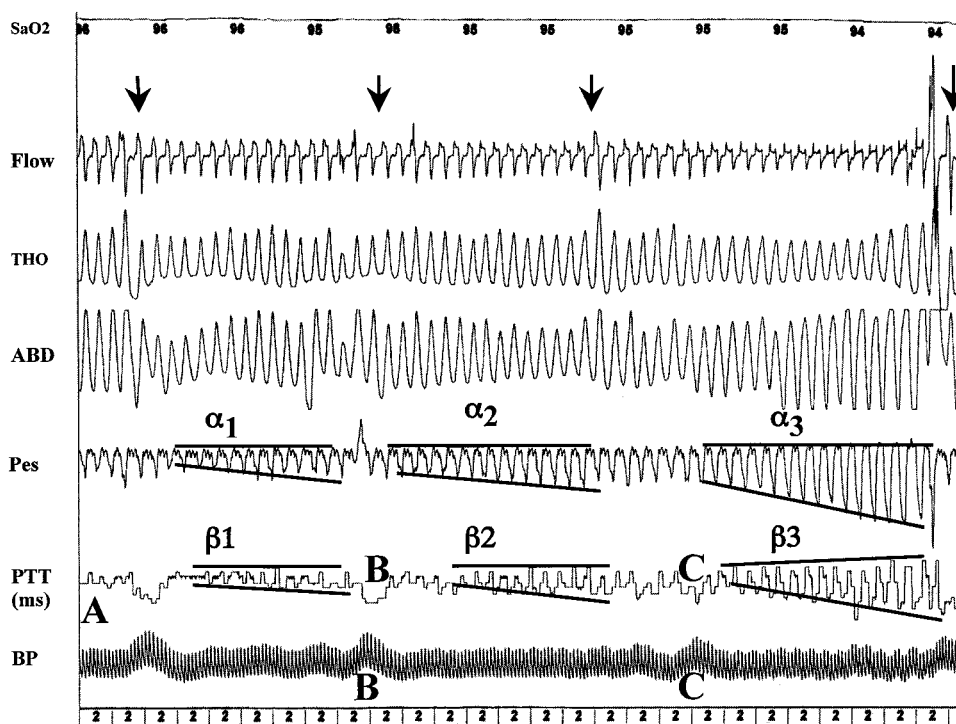

FIGURE 1. PTT: graphic examples showing its ability to recognize increases in respiratory effort and to detect microarousals. The respiratory events presented correspond to obstructive hypopneas ended by cortical microarousals (arrows). This figure demonstrates SaO_2, thorax (THO) and abdominal (ABD) inductance plethysmography, Pes, PTT, and BP using a Finapres (BP). Respiratory effort: the increases in ΔPTT are proportional to the increases in Pes. α1 and β1 demonstrate a smaller increase than α2 and β2, which demonstrate a smaller increase than α3 and β3. Higher is the increase in NPs as assessed by Pes; higher is the variation in ΔPTT. Microarousals: BP measurements by Finapres (A) are provided. At time of a microarousal, note that a pointed increase in BP (B) is associated with an abrupt transient dip in PTT and a rapid return to baseline. Arrows indicate the disappearance of inspiratory flow limitation occurring concurrently with the cortical microarousal.

tation was assessed by visual analysis of EEG (American Sleep Disorders Association rules[9]), whereas autonomic activations were identified using PTT. The aims of the study were as follows: (1) to determine the ability of PTT to improve the detection of abnormal respiratory events during sleep, and (2) to compare CAs and AAs in children during the different sleep stages.

MATERIALS AND METHODS

Patients

Eighteen unselected consecutive children referred for suspected sleep-disordered breathing were prospectively included in the study.

Polysomnography

All children underwent full-night polysomnography. Continuous recordings were taken of EEG with electrode positions C3/A2-C4/A1-Cz/O1 of the international 10–20 electrode placement system, eye movements, chin electromyogram, and ECG with modified V_2 lead. Airflow was measured with NP, associated with the sum of buccal and nasal thermistor signals. Respiration was monitored with uncalibrated inductance plethysmography. An additional signal of respiratory effort (ie, PTT) was recorded concurrently. Oxygen saturation (SaO_2) was measured using a pulse oximeter (Biox-Ohmeda 3700; Ohmeda; Liberty Corner, NJ).

Sleep studies were scored using standard techniques and criteria.[9,11,12] Microarousals ending respiratory events were called respiratory-related microarousals.

Method of PTT Measurement

PTT is the time taken by the arterial pressure wave to travel from the aortic valve to the periphery and is recorded as the time delay between the ECG R-wave and the arrival of the corresponding pulse wave at the finger.[13,14] Measuring PTT needs to incorporate ECG leads for the recognition of the R-wave and oximetric photoplethysmography (usually a finger probe) to assess the arrival of the pulse wave in the periphery.

PTT is measured as the interval between the ECG R-wave and the subsequent arrival of the pulse wave at the finger (usually the point on the pulse waveform that is 50% the height of the maximum value). PTT is approximately 200 to 300 ms when using the finger probe, and is measured with an accuracy of 2 ms. PTT values are available with every heartbeat and are typically oversampled at 5 Hz to ensure no values are neglected. PTT was recorded by an RM50 (DeVilbiss; Parcay-Meslay, France) or an HypnoPTT (Tyco Health Care; Mallinckrodt; Villers Les Nancy, France).

Data Analysis

The same observer scored abnormal respiratory events during sleep twice. Respiratory disturbance index (RDI) 1 was obtained by taking into account NP, thermistors, thoracic and abdominal movements, and SaO_2 signals (Fig 2). During this step, CAs were visually scored on EEG. The second scoring, blinded to the first scoring (RDI 2), was performed using PTT in combination with the other signals. During this procedure, AAs were identified on PTT blinded to EEG signals.

Statistical Analysis

A paired t test was used to compare quantitative variables, and a χ^2 test was used for qualitative variables. Results are shown as mean ± SD, and significance was accepted at $p < 0.05$. The normality has been systematically checked before using parametric tests. As graphical presentations such as "difference plots" are more accurate than linear regression analysis, a Bland and Altman plot is presented to compare the results of the two sleep studies scorings.

RESULTS

Patients

On the 18 children initially included, 2 children were finally not taken into account for data analysis because of technical problems during PTT recordings. Population characteristics and main polysomnographic data are summarized in Table 1. Snoring was a constant symptom. Fifty percent of the children exhibited mouth breathing during wakefulness, 44% had daytime sleepiness, and 6% had enuresis. Six of the 16 children were obese (body mass index above the 18th percentile). None of the children demonstrated a failure to thrive.

Scoring of Abnormal Nocturnal Respiratory Events

Mainly because of prominent mouth breathing, NP was not interpretable for 20 ± 20% of the total duration of polysomnographic recordings. For the whole group, there was no significant difference between RDI 1 and RDI 2 (20.4 ± 14.3/h vs 22.4 ± 13.5/h, respectively; not significant [NS]) [mean ± SD]. The Bland and Altman representation (Fig 3) shows that the bias (mean of the differences) is 1.99 events per hour (95% confidence interval, − 1.03 to 5.68). The bias is not significantly different from 0 for the whole group ($p > 0.2$, NS). Among the children exhibiting a "without PTT" RDI < 30/h, 5 of 12 children (41.66%) showed a clinically significant ≥ 5/h increase in RDI when using PTT.

Assessment of Sleep Fragmentation

The autonomic activation index was significantly higher than the CA index both during rapid eye movement (REM) sleep (7.4 ± 3.9/h vs 3.2 ± 2.3/h; $p < 0.001$) and slow wave sleep (SWS) [6.0 ± 4.3/h vs 0.6 ± 0.5/h; $p < 0.0001$]. This was true for respiratory-related and nonrespiratory-related arousal indexes (Table 2, Fig 4).

Relationships Between the Number of Respiratory Events Scored and Respiratory-Related Autonomic and Cortical Microarousal Indexes

RDI 2 was systematically higher than the number of scored cortical microarousals (Fig 5, left panel). This
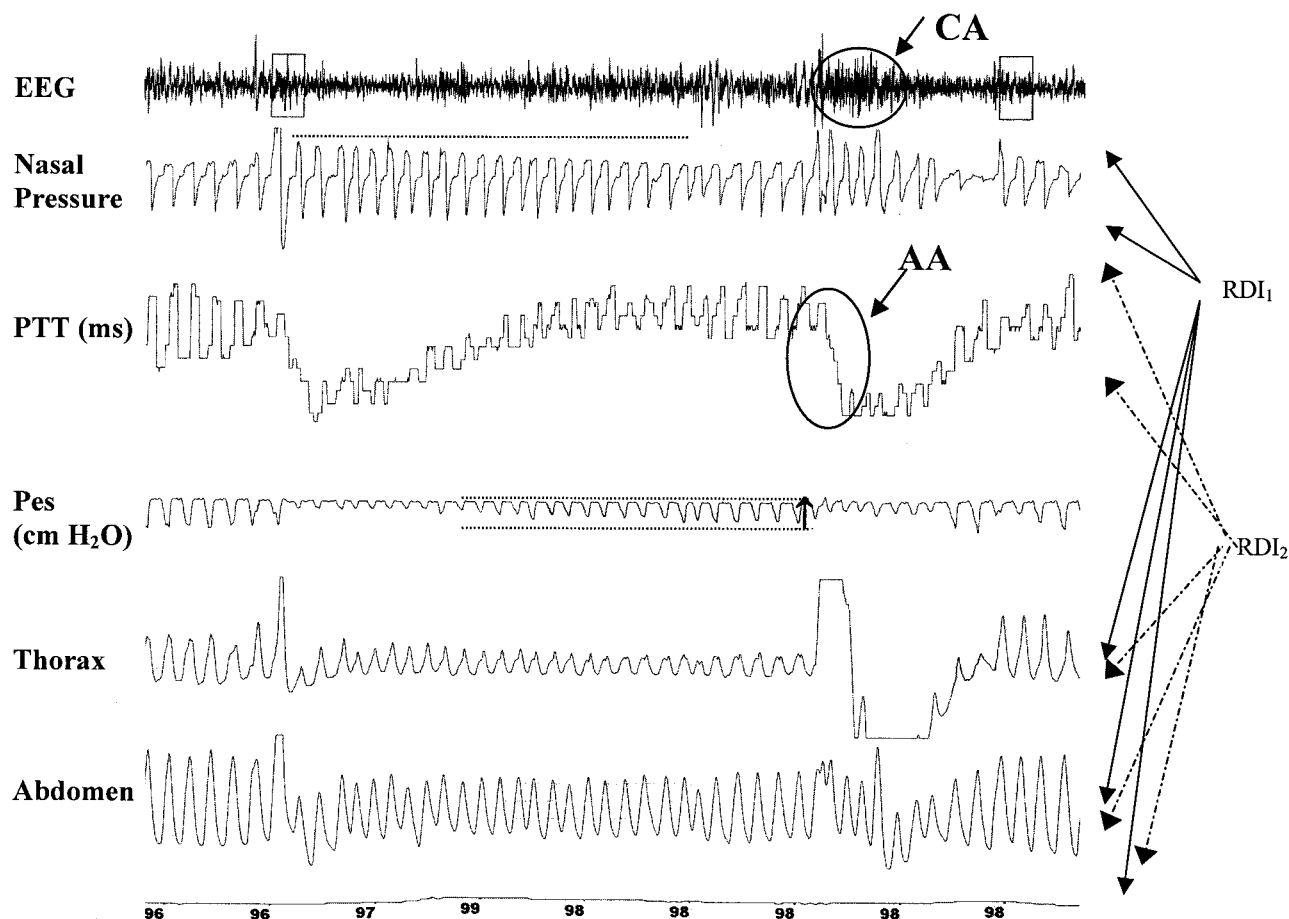
FIGURE 2. Data analysis. The figure shows all the channels recorded during the study to assess abnormal respiratory events and sleep fragmentation. The same observer scored abnormal respiratory events during sleep twice. RDI 1 was obtained by taking into account NP, thermistors, thoracic and abdominal movements, and SaO_2 signals. During this step, CAs were visually scored on EEG using American Sleep Disorders Association criteria. The second scoring blinded to the first one (RDI 2) was performed using PTT in combination with the other signals. During this procedure, AAs were identified on PTT blinded to EEG signals. Pes is figured to show an example of PTT ability to recognize increases in respiratory effort. In this study, none of the children underwent Pes recordings.

suggests that some respiratory events were not ended by a CA. Indeed, when using AAs, the relationship between RDI 2 and AA moved close to the line of identity (Fig 5, *right panel*).

DISCUSSION

Optimization of the Detection of Subtle Respiratory Events by the Use of PTT

In adults, NP as a tool for quantifying airflow has demonstrated its ability to markedly increase the detection of nonapneic events compared to thermistors.[2,3] Mouth breathing is a clinical finding reported in up to 90% of children presenting with suspected obstructive sleep apnea.[15–16] Thus, this signal could be less accurate in children with pre-dominant mouth breathing. In the current study, the NP signal was not interpretable for a 20% of the total duration of polysomnographic recordings. This is twice the percentage observed in an adult population.[17] However, NP is more likely than thermistors to detect obstructive apneas and hypopneas in infants and children, and this superiority is particularly marked for hypopneas.[5] The use of NP was able to double the number of detected respiratory events compared to thermistors: 27.2/h vs 14.5/h,[4] whereas measurements of expired carbon dioxide miss 79% of respiratory events detected by NP.[18] NP is now recommended both for adult and pediatric populations as the noninvasive reference method for assessing airflow.[2–5] Thus, we decided to compare NP alone vs NP with PTT. For the whole group, there

Table 1—Patient Characteristics*

Characteristics	Data
Patients, No.	16
Male/female gender, No.	11/5
Age, yr	9.5 ± 2.6 (6.5–15)
Body mass index	19.3 ± 3.6 (13.9–25.9)
RDI 2, h	22.4 ± 13.4 (1.2–50.6)
SaO_2 mean, %	96.5 ± 1.8 (91–98.5)
%TP < 90%	0 ± 0 (0.00–0.02)
SWS of TST, %	27.9 ± 8.7 (12.7–41.5)
REM sleep of TST, %	20.7 ± 5.6 (7.3–28.6)

*Data are presented as mean ± SD (range) unless otherwise indicated. %TP < 90% = percentage of time spent below 90% of SaO_2; TST = total sleep time.

Table 2—Microarousals*

Microarousals	Cortical	Autonomic	p Value
Respiratory related			
Stage 1–2	9.3 ± 10.2	11.5 ± 7.6	0.24
SWS	0.2 ± 0.3	1.1 ± 1.6	0.025†
REM sleep	2.1 ± 2.3	4.9 ± 3.6	0.0001†
Nonrespiratory related			
Stage 1–2	9.4 ± 7.2	9.2 ± 8.8	0.90
SWS	0.4 ± 0.3	5.0 ± 3.9	0.0002†
REM sleep	1.1 ± 0.7	2.5 ± 3.9	0.006†
Total			
Stage 1–2	18.5 ± 12.7	21.1 ± 9.6	0.43
SWS	0.6 ± 0.5	6.0 ± 4.3	0.0001†
REM sleep	3.2 ± 2.3	7.4 ± 3.9	0.0001†

*Data are presented as mean No. of microarousals per hour of sleep ± SD.
†Indicates significance.

was only a slight improvement in the detection of respiratory events using PTT signal (22.4 ± 13.5/h vs 20.4 ± 14.3; NS). For the respiratory events in which there was a small airflow reduction and no desaturation, the additional information provided by PTT in terms of increased respiratory effort and in demonstrating the occurrence of a microarousal allowed the recognition of more respiratory events. This is in agreement with our previous findings in an adult population with moderate sleep apnea syndrome.[6] Whether this is due to the detection of respiratory effort or to the identification of autonomic microarousal is difficult to determine. If the contribution of the detection of the autonomic arousal is prominent, this could partly explain the close rela-

tionship between arousals and respiratory events as figured in Figure 5. As snoring children have less collapsible airway than adult snorers, the proportion of hypopneas and upper airway resistance episodes is likely prominent in the pediatric population.[1,19,20] Normal children compensate for a relatively narrow airway by increasing upper airway neuromotor tone and central ventilatory drive.[1,21] The ability of PTT to specifically improve detection of this category of respiratory events reinforces its appeal in children.

Potential Technical Limitations of PTT in Children

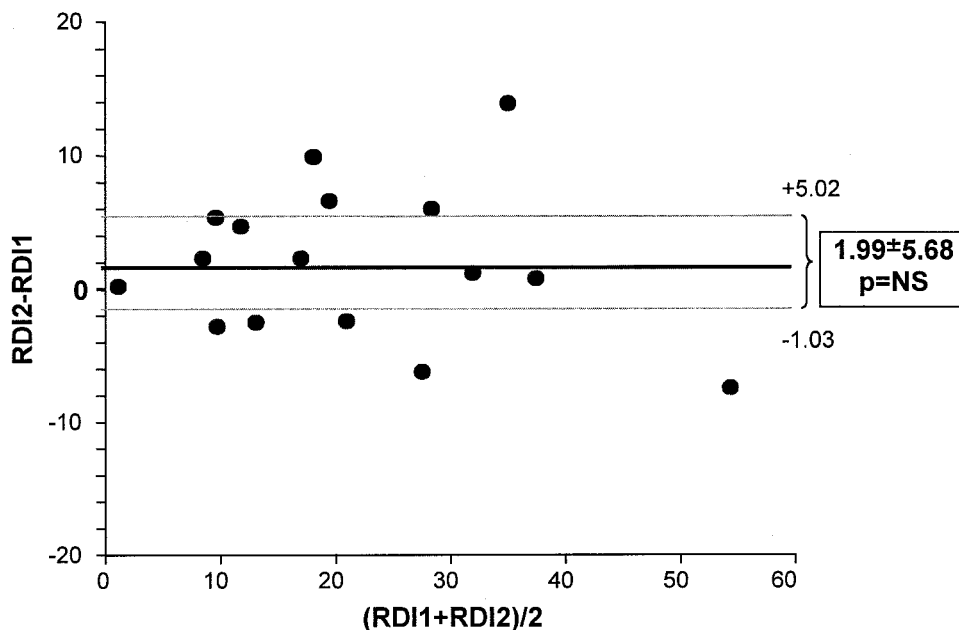An accurate PTT signal was not obtained in 2 of 18 children (11%) studied. This was mainly explained

FIGURE 3. Bland and Altman plot (Y axis: RDI 2 − RDI 1; X axis: mean of RDI 1 and RDI 2) showing mean of the differences (bias), presented with the two times SD interval.
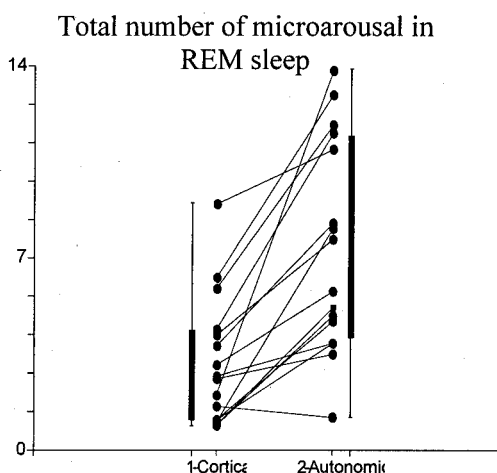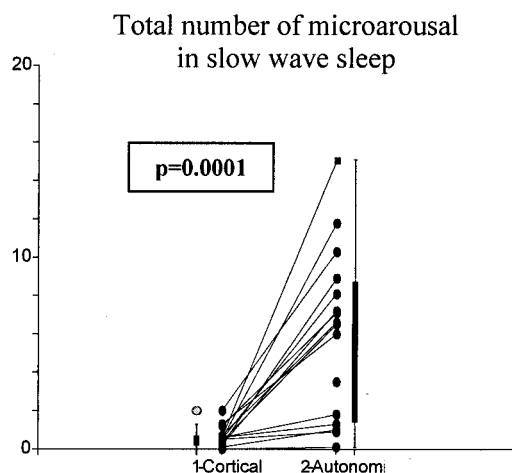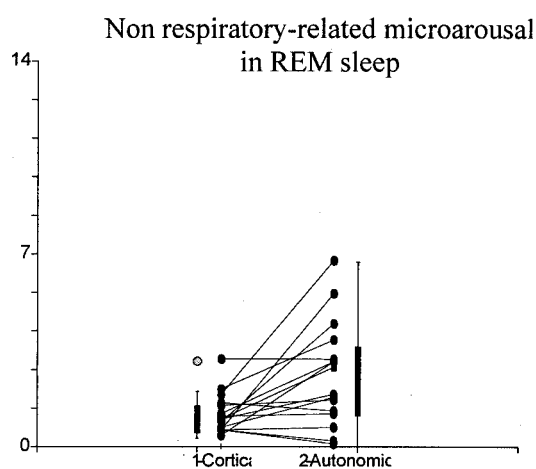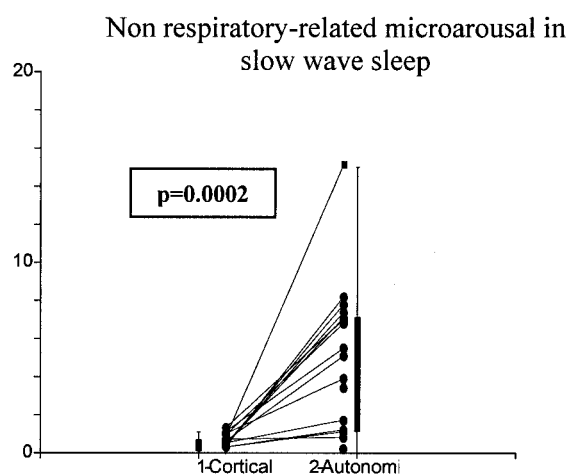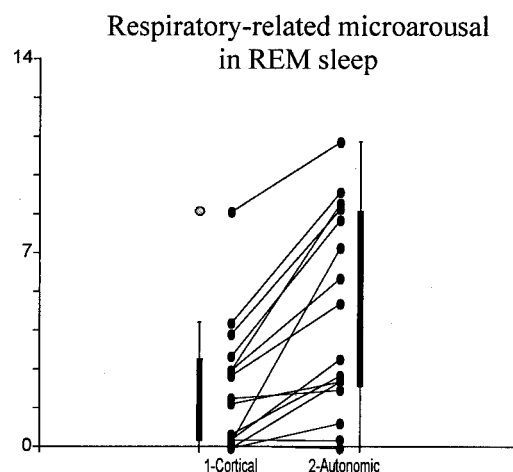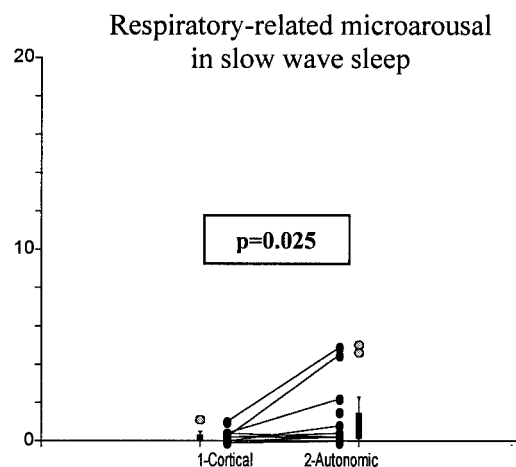
FIGURE 4. Comparison between cortical and autonomic activations during SWS and REM sleep. For the boxes: the line drawn through the middle of the box is the median, and the top and bottom lines are the 25th and 75th percentiles (the box represents the middle 50% of the data). The length of the box is thus the interquartile range (IQR). The upper adjacent value is the largest observation that is less than or equal to the 75th percentile plus 1.5 times IQR. The lower adjacent value is the smallest observation that is greater than or equal to the 25th percentile minus 1.5 times IQR.

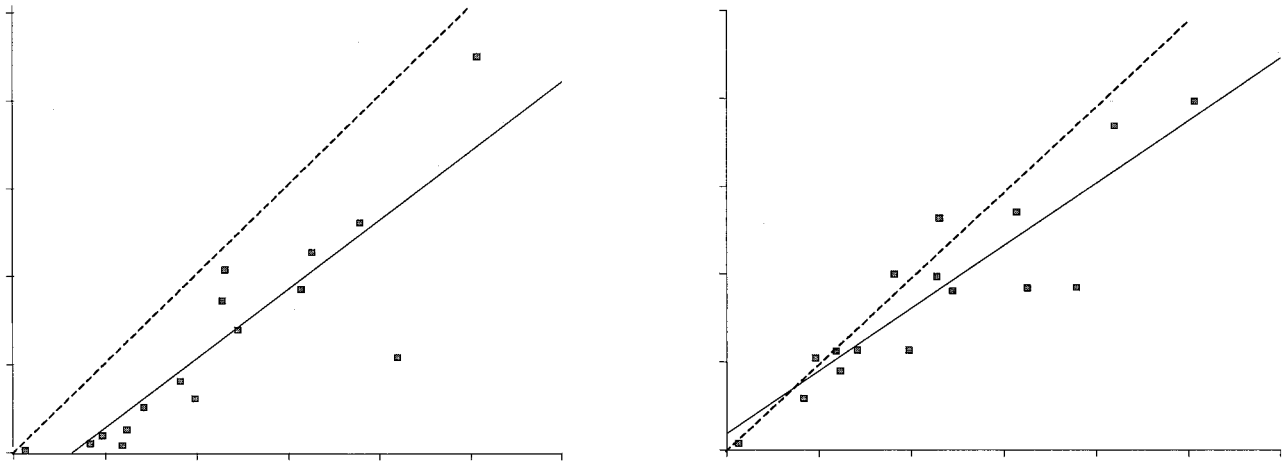FIGURE 5. Relationships between the number of respiratory events scored and the respiratory-related autonomic or cortical microarousal indexes. RDI 2 was systematically higher than the number of scored cortical microarousals (*left panel*). This suggested that some respiratory events were not ended by a microarousal. Indeed, when using AAs, which may represent a more sensitive method of detection, RDI 2 and AA moved close together on the line of identity (*right panel*). It means that the autonomic activation index is probably of interest for improving the characterization of respiratory sleep fragmentation.

by movement artifacts. Agitation in these two children resulted in overall poor quality signals. Other respiratory signals usually fail in the same proportion in a pediatric setting. For example, Trang et al[5] faced the same problem in 17% of the studied subjects when using NP in a pediatric population. Thus, it is nor a specific neither a significant drawback of PTT in this clinical context.

Should PTT Have Been Validated Against Pes as a Measure of Inspiratory Effort in Children?

In adults, there is an excellent correlation between the size of Pes swings and the size of inspiratory-expiratory PTT swings.[22] In adults, PTT is as accurate as Pes to separate central and obstructive events[23] and to characterize subtle respiratory events.[6] Katz et al[7] reported a correlation between ΔPes and ΔPTT in children. An article recently published[24] also demonstrated, in awake children, a good correlation between the induced respiratory effort (breathing against known resistances) and the amplitude of PTT variations. However, a catheter inserted through the nose down to the distal portion of the esophagus can *per se* induce sleep fragmentation[25] and might modify the characteristics of upper airway collapse. In infants, the presence of the catheter leads to a significant reduction in the number of respiratory events.[26] This could be explained by the fact that the catheter separates the tongue from the posterior pharyngeal wall or by the stimulation of the local pharyngeal receptors, allowing a

reflex activation of the upper airway dilator muscles.[26] Lastly, the ethical committee of our institution was highly reluctant to allow the use of Pes in children.

Thus, in the field of sleep medicine, PTT has now been validated as an accurate tool for semiquantitatively measure respiratory effort in adults and children. Moreover, PTT, as opposed to Pes, does not modify upper airway dynamics or disturb sleep.

Comparison of Cortical and Autonomic Activations Detected in the Different Sleep Stages

To date, there are several reports showing the ability of different autonomic markers in identifying arousals.[27] In normal subjects[28–29] during spontaneous or evoked arousals, increases in ventilation, heart rate, and BP (and as a consequence decreases in PTT) may occur even in the absence of CAs, reflecting the activation of the brainstem-arousing systems. This has been also shown in obstructive sleep apnea patients.[30–31]

The link between autonomic and EEG changes during arousals suggests that change in cerebral and cardiovascular activity shares a similar pattern of neural activation, suggesting a common generator located at the brainstem level. It may well be that some respiratory events can terminate through subcortical polysynaptic reflexes without CA. Sleep fragmentation could potentially be better detected using autonomic markers, and autonomic activation may thus be better related to daytime symptoms. Even if

further studies are needed, it seems that autonomic activations correlate with symptoms at least as well as CAs.[32] Finally, it is obvious that these autonomic markers are much easier to use and can be implemented outside of highly specialized sleep laboratories. Overall, there are many reasons to recommend the use of these tools in various clinical conditions, as the detection of sleep fragmentation is helpful for the management of several sleep disorders.

Our study is the first one to have systematically examined respiratory-related and nonrespiratory-related autonomic activations in children. We found that taking into account such microarousals allowed a better detection compared to EEG-detected microarousals. This was particularly true in REM and in SWS.

In SWS, the CA threshold is known to be higher, and not all autonomic activations lead to a secondary CA as detected by α waves. However, K complex or δ bursts that are usually associated with AAs[8] are impossible to detect in this sleep stage. Stage 3–4 corresponds to separate physiologic mechanisms and polygraphic patterns compared to stage 2. As a consequence, the polygraphic ventilatory patterns are very different to what is observed during stage 2 or REM sleep. In these particular sleep stages, there are progressive increases in respiratory effort and in upper airway resistance, ended by microarousals and followed by an abrupt normalization in inspiratory effort (crescendo-decrescendo aspect) and disappearance of inspiratory flow limitation. In contrast, stage 3–4 is characterized by long runs of persistent inspiratory flow limitation. Maximum increases in upper airway resistance and long runs of persistent inspiratory flow limitation have been observed, even in healthy subjects associated with stable but very high levels of respiratory effort. As the level of inspiratory effort is usually considered as the main triggering mechanism for microarousals, sleep disruption can occur during this situation in stage 3–4. Using PTT, we were able to demonstrate a significant number of autonomic activations during this period. Moreover, in our experience, respiratory events in stage 3–4 are more frequent in children than in adults.

In REM sleep, the CA threshold is higher compared to stage 1–2; and, again, it is possible that some autonomic activations are not associated with CAs. However, autonomic tone is highly variable during phasic REM sleep. Thus, some fluctuations in PTT could falsely be scored as microarousals, although they might correspond to spontaneous surges in BP occurring physiologically during REM sleep. The issue therefore is the specificity of PTT in scoring microarousals particularly in REM sleep. In children, respiratory events seem to be not systemati-

cally terminated with the occurrence of an identifiable CA.[10] It would be crucial to correlate autonomic activations with objective measurement of daytime sleepiness and cognitive function in children. In our study, half of the children complained of daytime sleepiness, although there were few cortical microarousals. In adults, inducing sleep fragmentation with subcortical arousals (K complex) results in daytime cognitive dysfunction.[33] We speculate that the same is probably true in children. Thus, detecting microarousals with PTT could be an important argument in the therapeutic decision for these children.

Conclusion

Using PTT with other respiratory signals including NP allowed a better identification of significant respiratory events, particularly in the mild-to-moderate spectrum of the disease. Using PTT also improved the detection of arousals in REM and SWS. These AAs seem to better correlate with the number of respiratory events. Whether this kind of sleep fragmentation is also responsible for specific daytime consequences remain to be demonstrated. PTT signal could also help in identifying and characterizing hypopneas when the NP signal is lost, *ie*, 20% of the recording time in the present study.

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