1   TITLE: **Tidal breathing flow profiles during sleep in wheezing children measured by**
2   **impedance pneumography**

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1   **ABSTRACT**

2   For the first time, impedance pneumography (IP) enables a continuous analysis of the tidal breathing

3   flow volume (TBFV), overnight. We studied how corticosteroid inhalation treatments, sleep stage, and

4   time from sleep onset modify the nocturnal TBFV profiles of children. Seventy children, 1−5 years old

5   and with recurrent wheezing, underwent three, full-night TBFVs recordings at home, using IP. The first

6   recorded one week before ending a 3-months inhaled corticosteroids treatment, and remaining two,

7   2 and 4 weeks after treatment. TBFV profiles were grouped by hour from sleep onset and estimated

8   sleep stage. Compared with on-medication, the off-medication profiles showed lower volume at

9   exhalation peak flow, earlier interruption of expiration, and less convex middle expiration. The

10   differences in the first two features were significant during non-rapid eye movement (NREM), and the

11   differences in the third were more prominent during REM after 4 h of sleep. These combinations of

12   TBFV features, sleep phase, and sleep time potentially indicate airflow limitation in young children.

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15   **KEYWORDS**: lung function, tidal breathing, wheezing children, impedance pneumography

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1. INTRODUCTION

Tidal breathing flow volume (TBFV) analysis has been proposed as an alternative for detecting lower-airway obstruction in young children who are unable to cooperate with forced spirometry (Beydon et al., 2007). However, interpretation of TBFV profiles, particularly the expiratory limb, is challenging (Bates, 1998). Expiration is shaped not only by passive mechanical characteristics such as thoracopulmonary recoil and airway resistance (Otis et al., 1950), but also by the active braking during the early part of expiration and the active interruption of the expiration ending (Hutten et al., 2008). Airway narrowing directly alters passive characteristics, which triggers subject-dependent active adaptation strategies (Baldwin et al., 2006; Maarsingh et al., 2000; Morris and Lane, 1981). Moreover, passive and active characteristics are influenced by other factors such as instrumentation (Fleming et al., 1982), awareness state (Lodrup-Carlsen and Carlsen, 1993), and other respiratory conditions (Leonhardt et al., 2010).

Impedance pneumography (IP) allows the continuous recording of the tidal flow overnight, providing several advantages to TBFV profile analysis. Firstly, IP uses four surface skin electrodes to derive the respiratory flow noninvasively, from changes in the thoracic electrical impedance, which is proportional to lung aeration. Hence, unlike conventional pneumography (PNT) (Fleming et al., 1982), IP does not corrupt the shape of the TBFV profiles. Secondly, sleep is characterised by a decrease in respiratory musculature tone, which is accentuated further during the rapid eye movement (REM) stage (Horner, 2010). It has been hypothesized that a decrease in muscle tone increases the contribution of passive characteristics to the TBFV profile, revealing signs of obstruction (Gracia-Tabuenca et al., 2019). Thirdly, diseases such as asthma are influenced by many neural, hormonal, and autoimmune circadian factors. Asthma symptoms worsen late at night and early in the morning (Bohadana et al., 2002). Assessment of the nocturnal TBFV profiles recorded at home may reveal symptoms that go unnoticed by tests conducted in hospitals.

Previous studies have proven the feasibility of using IP to derive TBFV profiles during night sleep (Gracia-Tabuenca et al., 2019; Seppä et al., 2016) and the strong agreement between IP and PNT results in children (Seppä et al., 2013b) and infants (Malmberg et al., 2017), even under induced bronchoconstriction. The effect of interactions between asthma risk and sleep physiology on the shape of TBFV profiles has been studied for infants (Gracia-Tabuenca et al., 2019), but not for older children. During the first year of life, development of the thoracic cage (Allen and Gripp, 2002) and the nervous system (Rabbette et al., 1994) modifies breathing strategy. For example, dynamic maintenance of end-expiratory volume decreases (Colin et al., 1989), thoracoabdominal asynchrony (Guilleminault et al., 1982) decreases, and respiratory apnoeas become less common (Flores-Guevara

et al., 1982). It is unknown if these developmental changes affect the results observed in infants. Finally, lower airway obstruction increases with night progression, at least in adults with and without asthma (Bellia et al., 1989). However, whether TBFV profiles change with night progression has not been studied.

The present longitudinal study assessed the effect that the interruption of medication had on the TBFV profiles obtained from overnight IP recordings taken at home, for a group of wheezing children. It also investigated the extent to which the time from sleep onset, as well as REM and non-REM sleep stages, influenced these changes. These two main sleep stages were respectively estimated from regions of high and low respiration variability.

2. MATERIALS AND METHODS

2.1 Study subjects and data collection

Seventy children (age = 2.5 (0.9–5.7) years old (median and range)), who were prescribed 3 months of fluticasone propionate treatment --based on Finnish guidelines for obstructive bronchitis-- were enrolled in our study at Tampere University Hospital. Each patient had IP and electrocardiography (ECG) signals recorded at home for three nights. The first recording (Week -1) was performed 1 week before conclusion of the fluticasone treatment, and the second (Week 2) and third (Week 4) recordings were performed 2 and 4 weeks after treatment ended. Recordings were obtained using a custom-designed device developed at Tampere University of Technology (Seppä et al., 2013b). Electrode placement was as previously described (Seppä et al., 2013a). On the first recording day (Week -1), a trained nurse placed the electrodes and the device on the patient at the hospital and instructed the parents on the procedure. For the following recordings (Week 2 and Week 4), the parents placed and activated the device at home. A nurse contacted the families to confirm the planned recording nights. In all cases, the device started recording before the patient went to sleep and recorded until after the patient woke up the next morning. On each recording day, parents photographed the electrode locations and noted the time of sleep onset, wake-up time, periods of nocturnal awakening, times of bronchodilator intake, and respiratory symptoms, usually coughing, sneezing, and rhinorrhoea. Patients were classified according to the following two classification criteria. For the first classification criteria, a paediatric pulmonologist followed the patients for 6 months after the last recording and classified them as current asthma (CA-Y) if they had been prescribed a regular asthma controller, reported difficult nocturnal coughing, exercise-induced coughing, or shortness of breath relieved by the bronchodilator; possible current asthma (CA-P) if they did not fulfil the preceding criteria but were prescribed intermittent controller medication for treating

asthma symptoms; and no current asthma (CA-N) otherwise. For the second classification criterion, patients were classified as atopic if they responded positively in a skin-prick test against egg, cat, dog, birch, or timothy, or nonatopic otherwise. Classification criterion, demographic data, and bronchodilator use are summarised in Table 1. The Regional Ethics Committee of Tampere University Hospital approved the research protocol (Ethics Committee Code R14027), and the ethical guidelines of the Declaration of Helsinki were followed.

2.2 Data preprocessing

All the recordings were visually inspected by trained researchers who were blind to patient information. The researchers discarded sections corrupted by motion or other distorting events such as coughing, moving, or talking. Accepted sections of the recordings were automatically processed to derive minute-by-minute TBFV profiles, as previously detailed (Gracia-Tabuenca et al., 2019). In short, the ECG signal was used to filter out the cardiac artefact from the raw IP signal (Seppä et al., 2011). A Savitzky–Golay filter differentiated the resulting lung volume-oriented IP signal into a flow-oriented IP signal (Seppä et al., 2010), the remaining noise of which was further attenuated using a nonlinear projection filter (Gracia et al., 2017). Cleaned-up flow and volume IP signals were split into respiratory cycles, as recommended by Schmidt et al. (1998), and cycles were transformed into TBFV profiles. Resulting TBFV profiles were averaged in the flow-volume domain, as described by Sato and Robbins (2001), using a 20-TBFV moving window with a 5-TBFV overlap. Each averaged TBFV profile was normalised to unit volume and flow-scaled, making its time integral equal to 1 (Sato and Robbins, 2001).

For each profile, the following expiratory indices were measured as recommend by Bates et al., 2000; and Beydon et al., 2007: expiratory time (T_E), time to peak tidal expiratory flow (T_{PTEF}), their ratio (T_{PTEF}/T_E), equivalent volume ratio (V_{PTEF}/V_E), tidal expiratory flow when 50%, 25%, and 5% of the tidal volume remains in the lungs relative to peak tidal expiratory flow (TEF50/PTEF, TEF25/PTEF, and TEF05/PTEF, respectively). In addition, the index P_{FV} was calculated as the exponent of a power function fitted between PTEF and TEF05, as described previously (Gracia-Tabuenca et al., 2019). Figure 1 shows the indices measured in four representative profiles.

2.3 Sleep segmentation

The overnight recordings were segmented on the basis of two different methods: regions of high and low respiratory rate variability and time from sleep onset. Regions of high and low variability were automatically defined using a method similar to that proposed by Isler et al. (2016). In short, a respiration variability time series was formed using the median absolute deviation (MAD) of the

1   interbreath intervals (IBI) within a moving 5-min 50% overlap window. Subsequently, a line was fitted

2   to the variability time series and crossing points were marked. Regions of 5 min around the crossing

3   points were discarded. The remaining sections with the most samples over the fitted line were defined

4   as REM and NREM otherwise. An example of the process is shown in Figure 2. Although this

5   implementation could not be validated against polysomnography, the performance of our method

6   was putatively similar to that of the Isler et al. method (see the Discussion section). The time from

7   sleep onset regions were defined as 3-h bins centred at each hour starting from sleep onset. A

8   representative recording is shown in Figure 2. Sleep-onset time was set automatically as the beginning

9   of the first segment that had no motion artefacts for more than 5 min. Only one automatic sleep onset

10   was detected more than an hour before the time annotated by the parents. It was considered an error

11   and the annotated time was used.

12   **2.4 Statistical analysis**

13   In each recording, we calculated for each index the median of all-night values within the REM sections

14   and the median of all-night values within the NREM sections. Similarly, in each recording, we

15   calculated for each index and for each hourly bin the median of the REM values and the median of the

16   NREM values within each 3-h bin. If the number of indices within a bin was fewer than 20, that bin

17   was rejected. The same two procedures were followed for IBI, heart rate, and MAD(IBI) signals. The

18   following tests were performed on both: all-night medians (Table 2) and hourly bin medians (Figure

19   3). Wilcoxon rank sum was used to assess the differences between the REM and NREM medians within

20   each recording, separately for the three recording weeks. The same test was used to assess the

21   differences between recording weeks for each subject, separately for REM and NREM. The differences

22   between groups within each classification criterion and between bronchodilator use and no use were

23   assessed for each index, in each sleep stage, and in each recording day using the Wilcoxon rank sum

24   test. The characteristics of the subjects between groups or bronchodilator use were compared using

25   the Kruskal–Wallis test for continuous variables or the χ^2/Fisher's exact test for categorical variables

26   (Table 1). Bonferroni correction was applied in all tests. Moreover, Spearman rank correlation

27   coefficients were calculated between all-night median values and patient age for all weeks (Table 3).

28   **3. RESULTS**

29   Twenty-two recordings were rejected due to battery or electrode problems, or malfunctioning of the

30   prototype recorders. For the accepted recordings, the starting time was at a mean of 9:20 pm ($\pm$1:05)

31   and lasted 9.95 ($\pm$1.11) h (mean value (standard deviation). Of the accepted data, 28.33% ($\pm$4.47%)

32   was discarded for being corrupted or occurring between sleep stages, and 25.17% ($\pm$5.93%) was

1 classified as REM, slightly higher than reported by Traeger et al. (2005). Table 2 shows that neither

2 faulty recordings nor sleep efficiency depended on the recording week, and summarises all-night

3 medians for each index and recording week. Hourly bin medians for six selected indices and three

4 recording weeks are summarised in Figure 3.

5 MAD (IBI), heart rate, and respiratory rate showed similar results in on-medication and off-medication

6 recording weeks. Evidently, IBI variability was higher during REM than during NREM the whole night.

7 Only respiratory variability, respiratory rate, and T_E presented a weak but significant correlation ($p <$

8 0.05) with the patients' age for some combinations of sleep stage and recording day. However, heart

9 rate had a significant correlation with age ($p < 0.001$) for all stages and ages (Table 3). The correlation

10 of age with heart rate, and less significantly with respiratory rate, agrees with published results

11 (Scholle et al., 2011).

12 For the on-medication recordings (Week -1), absolute times T_E and T_{PTEF} were both significantly shorter

13 during REM for the whole night. However, their overnight median trends were different. The T_E

14 median slightly increased overnight for both sleep stages, whereas the T_{PTEF} median was constant for

15 NREM and decreased for REM in the first part of the night. As expected, the overnight median trend

16 for T_{PTEF}/T_E was the combination of the trend of T_{PTEF} and the inverted trend of T_E. For V_{PTEF}/V_E, the

17 trend of T_E was no longer present, but both NREM and REM presented a trend similar to that of T_{PTEF}.

18 However, unlike with T_{PTEF}, for V_{PTEF}/V_E, the NREM and REM median trends overlapped with each other

19 and, therefore, showed no significant differences overnight. On the end side of the TBFV profiles,

20 TEF05/PTEF was significantly lower for REM than for NREM during the whole night. In the middle part

21 of the profiles, P_{VF} showed a constant median during the whole night for NREM and REM. On the other

22 hand, TEF50/PTEF and TEF25/PTEF showed a decreasing trend, similar to that of V_{PTEF}/V_E, and a sleep-

23 stage differentiation similar to that of TEF05/PTEF. The time progression of TEF50/PTEF and

24 TEF25/PTEF seemed to be a combination of V_{PTEF}/V_E and TEF05/PTEF (not shown in Figure 3).

25 A comparison of the indices for on-medication (Week -1) with those for off-medication (Week 2 and

26 Week 4) showed there were no significant differences in IBI variability, heart rate, and respiratory

27 rate. Overnight median trends for T_E, T_{PTEF}, T_{PTEF}/T_E, and V_{PTEF}/V_E presented night progressions for off-

28 medication similar to those for on-medication. However, in the Week 4 recordings, all-night medians

29 for T_{PTEF}, T_{PTEF}/T_E, and V_{PTEF}/V_E were significantly lower during NREM. The most significant difference

30 was observed for V_{PTEF}/V_E ($p = 0.0019$), which also showed a significant decrease for all hourly bin

31 medians. Likewise, TEF05/PTEF increased in the Week 4 recordings for both sleep stages, but the

32 increase was statistically significant for all hourly bin medians only for NREM. Unlike in Week -1, P_{VF}

significantly increased in Week 4 for both sleep stages, but only in the second half of the night. Moreover, the increase in P_{VF} was higher for REM than for NREM.

Current asthma and skin-prick test classifications showed no significant differences for any index in any sleep stage on any recording day. However, the use of a bronchodilator showed significant differences ($p < 0.01$) in Week 4 for both sleep stages for all the indices in the middle part except TEF25/PTEF in NREM. Counterintuitively, the values of subjects who used a bronchodilator suggest that they presented greater obstruction than subject who did not use: during REM, P_{VF} was 0.89 (0.83 1.04) (median (interquartile range)) for bronchodilator use vs. no use 0.71 (0.67 0.77); TEF25/PTEF was 0.44 (0.39 0.46) vs. 0.53 (0.50 0.57); and TEF50/PTEF was 0.74 (0.68 0.77) vs. 0.82 (0.79 0.87). Similarly, during NREM, P_{VF} was 0.82 (0.73 0.92) vs 0.69 (0.64 0.74) and TEF50/PTEF was 0.77 (0.75 0.81) vs. 0.85 (0.80 0.89).

4. DISCUSSION

This study demonstrated that dividing the night into regions of higher and lower IBI variability, as an estimation of REM and NREM sleep, presented differences in the TBFV indices for both on-medication and off-medication recordings in children. Moreover, when assessed at different times from sleep onset, certain indices presented a decreasing averaged trend during REM. In addition, the interruption of treatment had a different effect on the early and late parts of the expiratory TBFV profile than on the middle part. Changes in the early and late expiration were significant during the whole night for NREM. Changes in the middle expiration were significant in the second part of the night and larger for REM.

Lower T_E and T_{PTEF} values for REM than for NREM have been observed in healthy and wheezing infants (Gracia-Tabuenca et al., 2019; Haddad et al., 1979), but not in adolescents (Tabachnik et al., 1981). We found that the ratio T_{PTEF}/T_E was lower for REM than for NREM but that V_{PTEF}/V_E was similar for both sleep stages. Such different results for these similar ratios can be explained by comparing the late part of expiration on the time and volume domains. For example, the profiles in Figure 1 (A) and (B) present similar V_{PTEF}/V_E, but T_{PTEF}/T_E is lower in (B) because in the late part, expiratory airflow is low. Hence, a longer time is needed to produce the same change in volume as in (A), where the flow is higher. Thus, our results suggest that for REM sleep, the later part of exhalation was interrupted less often, whereas for NREM, exhalation was interrupted more often before reaching resting volume, as is also suggested by a higher TEF05/PTEF during REM. Shorter and uninterrupted exhalation during REM may be due to the natural decrease in respiratory musculature tone in this sleep stage (Horner

1 R.L., 2010). Intercostal atony in REM leads to a more compliant chest that deflates faster (Mortola et

2 al., 1982; Otis et al., 1950). Intercostal atony together with a lower diaphragm tone decreases the

3 functional residual capacity (FRC) (Henderson-Smart and Read, 1979). This decrease has been linked

4 to uninterrupted or late interruption of expiration (Morris et al., 1998; Schmalisch et al., 2003).

5 The overnight decreasing trend in the REM bin medians, which is shared by T_{PTEF}, T_{PTEF}/T_E, V_{PTEF}/V_E,

6 TEF50/PTEF, and TEF25/PTEF, may have been caused by a shortening of post-inspiration inspiratory

7 activity (PIIA) during the night. For individuals of all ages, a decrease in T_{PTEF}, and therefore in T_{PTEF}/T_E

8 and V_{PTEF}/V_E, is commonly understood as a shortening of PIIA (Ent et al., 1998). Shorter PIIA would also

9 explain the lower TEF50/PTEF and TEF25/PTEF values because decreased expiratory braking leads to

10 higher PTEF (Walraven et al., 2003). The shortening of PIIA during the night may be due to multiple

11 factors such as a decrease in respiratory musculature tone during the night, as seen in asthmatic adults

12 (Steier et al., 2011); an adaptation to a circadian increase in airway resistance (Bellia et al., 1989); or

13 other circadian factors (Bohadana et al., 2002). In any case, changes in the sleep stage or night

14 progression did not seem to affect the number of concave profiles, as assessed by P_{VF}, or the

15 interruption of expiration, as assessed by TEF05/PTEF, at least for Week -1.

16 Changes in the off-medication TBFV profiles compared to the on-medication TBFV profiles were

17 presumably caused by an increased number of children presenting airflow limitation. Such changes in

18 the early, middle, and late parts of expiration agreed with the changes related to airflow limitation

19 reported in the following studies. In the early part, the significant decrease in V_{PTEF}/V_E, T_{PTEF}/T_E, and

20 T_{PTEF} was potentially caused by a shortening of PIIA. It has been speculated that individuals with airway

21 obstruction have short PIIA braking to accommodate for the slower passive expiration (Carlsen and

22 Carlsen, 1994; van der Ent et al., 1996). In the late part, the significant increase in TEF05/PTEF may be

23 due to the early interruption of expiration with the purpose of elevating the FRC to increase airway

24 calibre (Greenough et al., 1989; Wheatley et al., 1990). In the middle part, the significant increase in

25 P_{VF} was most likely due to an increase in concavity, as observed in infants (Benoist et al., 1994) and

26 adults (Williams et al., 1998). Bronchodilator use decreases airway obstruction, thus putatively making

27 the TBFV profiles less concave. However, our results show that profiles were more concave the days

28 where bronchodilator was used. This apparent contradiction can be explained as follows.

29 Bronchodilator use occurred mostly before the recording period and its effects are known to wear off

30 after a few hours. Therefore, any changes in the profiles because of bronchodilator use were likely

31 averaged out over the rest of the recording. Under these assumptions, bronchodilator use indicates

32 that on that recording day, parents notice airflow limitation and applied the medication, but for most

33 of the recording bronchodilator had no effects. This, together with the lack of correspondence

between indices and classification criteria, suggests that nocturnal TBFV analysis may better reflect occasional worsening of asthma rather than the presence of the condition.

Why early and late indices differ during all hourly bins for NREM but not for REM can be explained by the decrease in respiratory musculature tone during REM. During NREM, active strategies to compensate for obstruction, such as shortening PIIA or interrupting expiration, are potentially reflected as changes in early and late expiration. However, during REM, decreased musculature tone reduces the strength of active strategies. Why middle expiration differs during the second half of the night more strongly for REM can be explained by the increase in lower airway resistance with night progression (Bellia et al., 1989) and the decreased musculature tone in REM. During the first half of the night, active strategies compensate for lower airway resistance, so middle expiration is less affected. The increased resistance overnight, despite active compensation, is reflected as an increase in concave middle expiration. During REM, as the decreased musculature tone reduces the strength of active strategies, the concavity of middle expiration is accentuated.

Our study has the following limitations. Firstly, the REM and NREM regions were not based on conventional polysomnography but on an indirect classification based on IBI variability. We assumed that the accuracy of our method was similar to that of Isler et al. (2016) or greater than this because we rejected the 5 min between stages where misclassification is higher. The sensitivity and specificity of the method of Isler et al. compared against standard polysomnographic classification, is 83% and 78% for REM and 78% and 83% for NREM. Additionally, Willemen et al. (2014) have summarised several studies on adults which found accuracies greater than 80% when variability in respiratory rate was used to separate REM from NREM sleep Secondly, we assumed that IP maintains a high linearity with mouth airflow overnight. Physiological changes during NREM and REM could degrade the strong agreement between IP and PNT results shown for awake children. Finally, our study group was rather heterogeneous. Some patients may not have responded to the medication, some may not have presented asthma, and it is unlikely that all nonmedicated asthmatics would have suffered from airflow limitation on the recording nights. In addition, our study included a few children younger than 2 years. Before this age, maturation affects the shape of the TBFV profiles in the late (Colin et al., 1989) and early parts (Frey et al., 2001). However, in a previous study, we demonstrated that airflow limitation is reflected as an increased concavity of the middle part in infants (Gracia-Tabuenca et al., 2019). The current IP technique also has its limitations. Patient movement may cause the detachment of the electrodes or contamination of the recordings. In this study, 22 of the 210 recordings had to be rejected. Although the correspondence between IP and PNT is independent of posture (Seppä et al., 2010), posture could affect respiratory mechanics and hence TBFV shapes (Mayer et al., 2003).

Alternative electrodes such as textile electrodes and the effects of sleeping posture should be researched further.

5. CONCLUSION

We conclude that the analysis of TBFV profiles derived from nocturnal home IP recordings, holds the potential to monitor nocturnal symptoms in wheezing children. The IP system is easy to used at home on regular bases allowing for a frequent monitoring of patients' symptoms. Regular monitoring could aid doctors on adapting the appropriate treatment. We observed that the IP of young children with recurrent wheezing, who were recorded overnight, was influenced by medication, sleep stage, and time from sleep onset. Two indicators may suggest the presence of airflow limitation in children. Firstly, an increase in the concavity of the middle expiration during REM in the second half of the night, likely caused by the natural decrease in respiratory musculature tone and circadian factors, and, secondly, changes in early and late expiration, assessed by V_{PTEF}/V_E and TEF05/PTEF, respectively, during NREM sleep, likely caused by active obstruction compensatory strategies.

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FIGURE LEGENDS

2

3
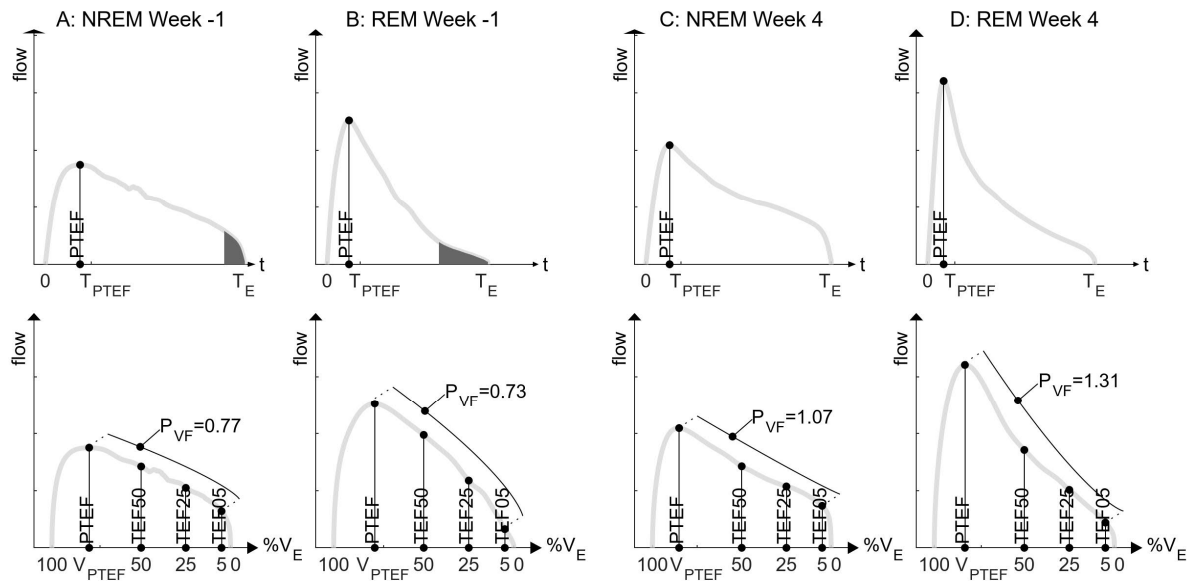
Figure 1. TBFV indices for four representative expiration limbs from the same patient extracted from NREM Week -1 (A), REM Week -1 (B), NREM Week 4 (C), and REM Week 4 (D). Upper plots show flow-time domain and lower plots show flow-volume domain . Volume is normalized to 1 and flow is scaled to have area of 1 in the flow-time domain. Light grey lines represent the expiration signals, vertical solid lines between points show distances, and solid line curves are the power-fitted curves, which are displaced for clarity and the dotted lines project where the curves should be located. The grey areas in the flow-time plots (A) and (B) are regions with the same area. They show that integrating the same volume (.) took a longer time in (B) than in (A) because the flow (Q) was lower ($V = \int Q \, \mathrm{d}t$).
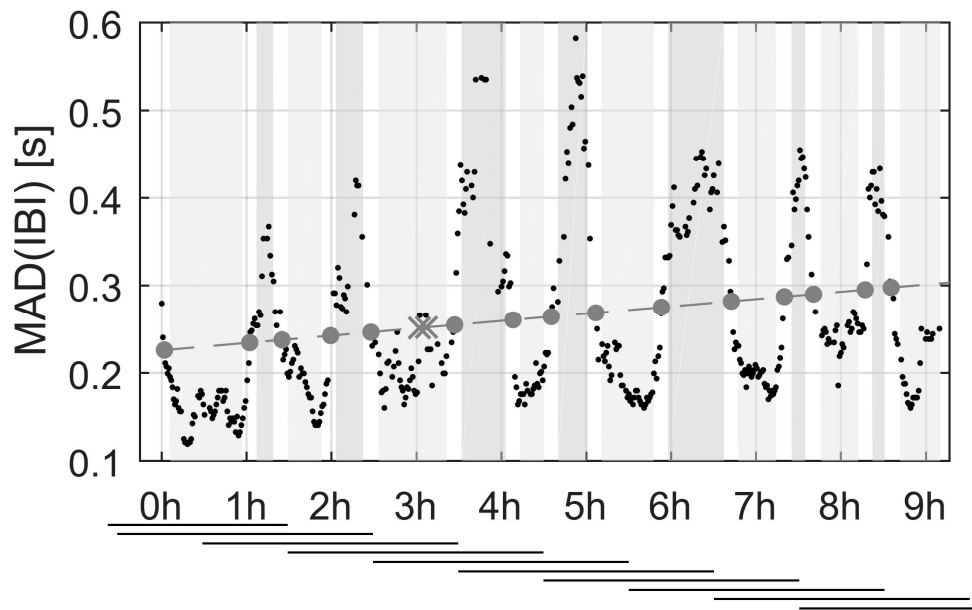
Figure 2. Two sleep segmentation methods: (upper) segments of high and low respiratory rate variability are shown as grey and light-grey boxes, respectively; (lower) solid lines indicate time from sleep onset in 3-h segments. The procedure presented in the text is based on the dotted-line signal (MAD(IBI)). The dashed line is the linear fit and the black dots are valid crossings. The abscissa shows the time from sleep onset in hours.
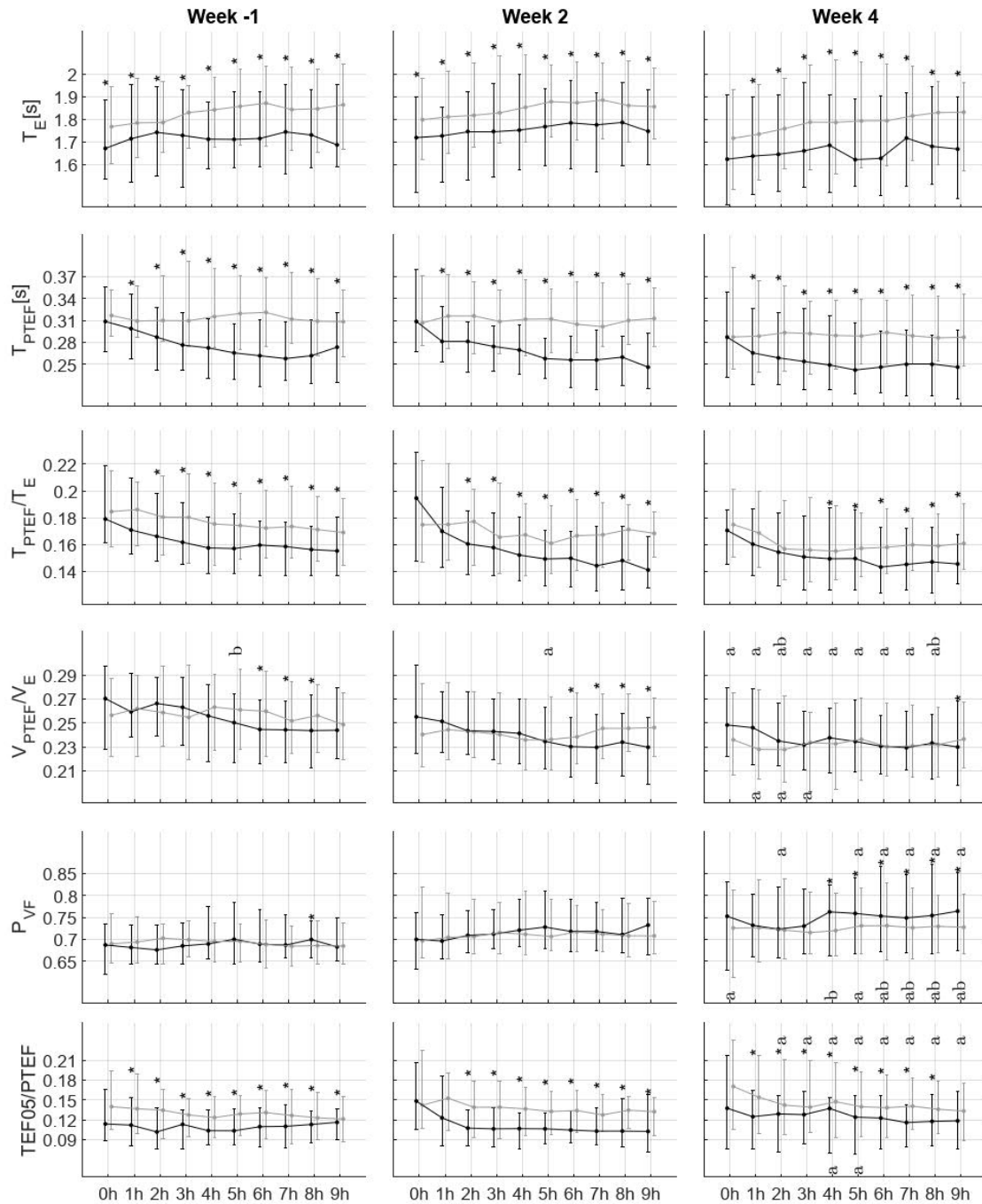
Figure 3. Averaged hourly progression of several indices grouped by recording week and sleep stage. Rows correspond to an index and the columns to a recording week. Within each plot, the *x*-axis is the time from sleep onset (in hours) and the *y*-axis is the index value. Dots and vertical lines are median and interquartile ranges of all patients at a given time for NREM (grey) and REM (black). *: significant difference ($p < 0.01$) between sleep stages; a: significant difference ($p < 0.05$) between Week -1 and Week 4; b: significant difference ($p < 0.05$) between Week 2 and Week 4. Letters on top of vertical lines for NREM and letters on bottom for REM. All *p* values were calculated using the Wilcoxon signed sum test after Bonferroni corrections ($n = 3$).

1   Table 1. *Characteristics of studied children.*

Groups	Current asthma			Skin prick	
	CA-N	CA-P	CA-Y	Nonatopic	Atopic
Subjects	16	16	36	40	28
Age [mo]	51.45 (18.23 77.07)	54.27 (40.07 80.70)	41.10 (15.73 78.63)	43.87 (17.77 67.50)	51.23 (15.73 80.70)
Male	12	10	22	26	18
Broncho-Week -1	2	0	2	2	2
Broncho-Week 2	1	4	7	9	3
Broncho-Week 4	3	6	7	11	5

2

3   Subjects were classified according to two classification criteria: current asthma and skin-prick test.

4   The first criteria consist on tree groups: no current asthma (CA-N), probable current asthma (CA-P),

5   and current asthma (CA-Y). The second criteria consist on two groups: nonatopic and atopic. Age (in

6   months) is given as the median (range). The entries for Broncho-Week -1, Broncho-Week 2, and

7   Broncho-Week 4 are the number of subjects who used a bronchodilator in Week -1, Week 2, and Week

8   4, respectively. No significant difference was found between groups within each criterion for any

9   characteristic as determined by the Kruskal–Wallis test (continuous variables) or the χ^2/Fisher's exact

10   test (categorical variables).

1 Table 2. *Median of the TBFV parameters during estimated NREM and REM sections overnight. Values*
2 *are grouped according to the recording week.*

		Week -1	Week 2	Week 4
Subjects		62	64	62
T_{REM}/T_{Total} [%]		0.25 (0.22 0.29)	0.24 (0.21 0.28)	0.24 (0.21 0.29)
MAD(IBI) [s]	NREM	0.13 (0.12 0.14)	0.13 (0.11 0.15)	0.13 (0.12 0.14)
	REM	0.28 (0.25 0.34) *	0.30 (0.26 0.33) *	0.29 (0.25 0.34) *
Heart rate [bpm]	NREM	83.30 (77.37 89.86)	83.53 (75.47 92.11)	84.94 (79.66 92.95)
	REM	89.90 (82.54 95.80) *	89.07 (81.85 97.04) *	89.41 (84.91 97.91) *
Mean(IBI) [bpm]	NREM	19.33 (18.32 22.35)	19.57 (17.89 21.85)	20.47 (18.21 23.04)
	REM	20.44 (18.17 22.01)	19.92 (18.40 22.69)	20.93 (18.93 23.62)
T_E [s]	NREM	1.85 (1.65 2.00)	1.87 (1.71 2.04)	1.82 (1.59 2.00)
	REM	1.71 (1.59 1.92) *	1.75 (1.59 1.96) *	1.64 (1.50 1.94) *
T_{PTEF} [s]	NREM	0.32 (0.27 0.37)	0.32 (0.27 0.37)	0.29 (0.24 0.34) a
	REM	0.27 (0.24 0.32) *	0.27 (0.24 0.29) *	0.26 (0.22 0.29) *
T_{PTEF}/T_E	NREM	0.17 (0.15 0.20)	0.17 (0.14 0.20)	0.16 (0.14 0.19) a
	REM	0.16 (0.14 0.19) *	0.15 (0.13 0.18) *	0.15 (0.13 0.18) *
V_{PTEF}/V_E	NREM	0.25 (0.22 0.29)	0.24 (0.21 0.28)	0.23 (0.20 0.27) a
	REM	0.26 (0.23 0.28)	0.24 (0.21 0.26)	0.23 (0.21 0.27) a
TEF50/PTEF	NREM	0.87 (0.84 0.89)	0.85 (0.80 0.88)	0.84 (0.79 0.88) a, Br
	REM	0.85 (0.81 0.88) *	0.81 (0.79 0.86) *	0.80 (0.76 0.87) *, a, b, Br
TEF25/PTEF	NREM	0.57 (0.53 0.61)	0.57 (0.51 0.60)	0.53 (0.48 0.60)
	REM	0.54 (0.52 0.57) *	0.52 (0.48 0.56) *	0.50 (0.45 0.56) *, a, b, Br
P_{VF}	NREM	0.68 (0.64 0.73)	0.69 (0.65 0.75)	0.71 (0.66 0.80) a, Br
	REM	0.69 (0.65 0.75)	0.72 (0.67 0.78)	0.75 (0.68 0.85) *, a, b, Br
TEF05/PTEF	NREM	0.13 (0.09 0.16)	0.14 (0.10 0.18)	0.14 (0.10 0.21) a
	REM	0.11 (0.09 0.14) *	0.11 (0.08 0.13) *	0.12 (0.08 0.16) *, a

3 Values are given as median (0.25 0.75 (quartiles)). Columns are recording weeks: Week -1 is one week
4 before end of treatment, Week 2 is two weeks after end of treatment, and Week 4 is 4 weeks after
5 end of treatment. Indices are defined in the text. *: significant difference ($p < 0.01$) between sleep
6 stages within each week. a: significant difference ($p < 0.05$) between Week -1 and Week 4. b:
7 significant difference ($p < 0.05$) between Week 2 and Week 4. Significant differences were calculated
8 using the Wilcoxon signed sum test. Br: significant difference ($p < 0.01$) between subjects who used a
9 bronchodilator that recording day and subjects who did not, calculated using the Wilcoxon rank sum
10 test. Bonferroni correction ($n = 3$) was applied to all p values.

11

1   Table 3. *Spearman correlation coefficients between selected indices and patient age during NREM and*

2   *REM recorded in the week under treatment (Week -1).*

		Week -1	Week 2	Week 4
MAD(IBI) [s]	NREM	0.29 (0.02) *	0.35 (0.01) *	0.13 (0.33)
	REM	-0.01 (0.97)	0.10 (0.45)	-0.01 (0.96)
Heart rate [bpm]	NREM	-0.42 (0.00) ‡	-0,40 (0.00) ‡	-0.49 (0.00) ‡
	REM	-0.42 (0.00) ‡	-0.44 (0.00) ‡	-0.50 (0.00) ‡
Respiration rate [bpm]	NREM	0.17 (0.17)	0.13 (0.03) *	0.20 (0.13)
	REM	0.26 (0.04) *	0.23 (0.04) *	0.33 (0.01) *
T_E [s]	NREM	0.17 (0.19)	0.13 (0.30)	0.19 (0.14)
	REM	0.21 (0.09)	0.23 (0.07)	0.34 (0.01) *

3   Correlation tested using Spearman's rank correlation rho (ρ). *: $p < 0.0001$, ‡: $p < 0.0001$. The indices

4   not included in the table had a nonsignificant correlation with $p > 0.05$.