Clinical Investigations

Respiration

Respiration 2013;85:312–318
DOI: 10.1159/000342010

Received: March 5, 2012
Accepted after revision: June 25, 2012
Published online: September 11, 2012

Feasibility of Noninvasive Single-Channel Automated Differentiation of Obstructive and Central Hypopneas with Nasal Airflow

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Key Words
Central sleep hypopnea · Esophageal pressure · Home monitoring · Obstructive sleep hypopnea · Sleep disordered breathing

Abstract
Background: The identification of obstructive and central hypopneas is considered challenging in clinical practice. Presently, obstructive and central hypopneas are usually not differentiated or scores lack reliability due to the technical limitations of standard polysomnography. Esophageal pressure measurement is the gold-standard for identifying these events but its invasiveness deters its usage in daily practice. ***Objectives:*** To determine the feasibility and efficacy of an automatic noninvasive analysis method for the differentiation of obstructive and central hypopneas based solely on a single-channel nasal airflow signal. The obtained results are compared with gold-standard esophageal pressure scores. ***Methods:*** A total of 41 patients underwent full night polysomnography with systematic esophageal pressure recording. Two experts in sleep medicine independently differentiated hypopneas with the gold-standard esophageal pressure signal. Features were automatically extracted from the nasal airflow signal of each annotated hypopnea to train and test the automatic analysis method. Interscorer agreement between automatic and visual scorers was measured with Cohen's kappa statistic (κ). ***Results:*** A total of 1,237 hypopneas were visually differentiated. The automatic analysis achieved an interscorer agreement of $\kappa = 0.37$ and an accuracy of 69% for scorer A, $\kappa = 0.40$ and 70% for scorer B and $\kappa = 0.41$ and 71% for the agreed scores of scorers A and B. ***Conclusions:*** The promising results obtained in this pilot study demonstrate the feasibility of noninvasive single-channel hypopnea differentiation. Further development of this method may help improving initial diagnosis with home screening devices and offering a means of therapy selection and/or control.

Introduction

The differentiation of obstructive and central events in sleep-disordered breathing (SDB) is of importance for diagnosis and appropriate choice of treatment. However, the identification of these events is, at present, still considered a challenging task as it requires quantitative and/or qualitative assessment of ventilatory effort, such as calibrated respiratory inductance plethysmography (RIP), diaphragmatic/intercostal electromyography or esopha-

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geal pressure (Pes) manometry [1]. An inadequate measurement of respiratory effort during sleep can lead to an incorrect diagnosis of obstructive and central apnea/hypopnea syndrome. Chest and abdominal wall movements recorded by RIP are taken for routine clinical diagnosis as they usually suffice for the differentiation of obstructive and central apneas [1–6]. However, abdominal wall motion is influenced by lung volume and posture, while chest wall movement is small in patients with truncal obesity, leading to an overestimation of central events [7]. Alternatively, respiratory events with flow limitation or presence of respiratory effort are conventionally scored as obstructive events, resulting in an underestimation of central events [8]. Hence, RIP belts fall short, particularly in the differentiation of subtle respiratory events such as hypopneas [1–4, 6–9], which is why this study will exclusively focus on the complex task of hypopnea differentiation. In contrast, Pes manometry is still considered the gold-standard technique for assessing respiratory effort [1, 2]. However, its invasiveness and complexity deter its usage in clinical routine [10].

A noninvasive method that permits a reliable identification of obstructive and central events with only a single-channel airflow signal could be clinically meaningful for initial routine diagnosis and screening with domestic respiratory polygraph devices that usually only record a small number of channels [11]. Besides, this technique could also be relevant for treatment with continuous positive airway pressure devices that usually only target upper airway obstruction and in most cases exclusively record the airflow signal [12]. Several noninvasive methods have been suggested for the detection and/or differentiation of central and obstructive apneas/hypopneas, such as diaphragmatic/intercostal electromyography [7], pulse-transit time [6], forced oscillation technique [13–15] and artificial neural networks [16]. However, most of these methods require multichannel and complex technical procedures that are usually not feasible in clinical practice, limiting their widespread adoption.

In this pilot study we explore the feasibility of a novel automatic analysis method for noninvasively identifying central and obstructive hypopneas with only nasal airflow, a signal that is commonly used in daily clinical practice. Our method automatically extracts the features that best characterize obstructive and central hypopneas in the airflow signal and should permit their differentiation. To ensure clinical validity, our method is trained and then tested with visual hypopnea scorings that were annotated by two experts who employed the gold-standard Pes signal.

Materials and Methods

Study Subjects

The studied population consisted of 41 patients (7 female, 34 male; age 52.8 ± 15.6 years; BMI 28.7 ± 4.7; apnea/hypopnea index 14.9 ± 12.1/h, range 1.1–56.2; hypopnea index 10.2 ± 6.6/h, range 1–27.3) at the sleep laboratories of Bethanien Hospital in Solingen, Germany. The clinical protocol was approved by the hospital's ethics committee and written patient consent was acquired for inclusion in this study.

Sleep Study

Polysomnography (PSG) was obtained in the usual manner [2, 17]. Pes was systematically recorded with a unidirectional pressure-tip catheter (Unisensor, Attikon, Switzerland) and pressure amplifier (Standard instruments, Karlsruhe, Germany). The catheter was introduced through the patient's nostrils after spraying the nasopharynx with Xylocaine and positioned in the lower third of the esophagus [18, 19]. Respiratory airflow was monitored with a nasal cannula connected to a pressure transducer system (Weinmann GmbH, Hamburg, Germany). Briefly, other signals recorded included arterial oxygen saturation, body position, cardiac pulse, thoracic and abdominal RIP belts, C3-A2/C4-A1 electroencephalogram channels, right/left electrooculograms, one submental electromyogram, a leg-electromyogram and an electrocardiographic signal.

Hypopnea Scoring Criteria

Polysomnograms were analyzed by a staff laboratory technician at the laboratories of the Bethanien Hospital in Solingen, Germany. Hypopneas were identified according to standard criteria [2] that define a hypopnea as an event with a minimal duration of 10 s and a clear decrease (>50%) from baseline in the amplitude of a valid measure of breathing during sleep, associated with either an oxygen desaturation of >3% or an arousal. Hypopneas were scored for the whole range of sleeping time of each patient. The beginning and end of the hypopnea events were marked and stored in a computer program (Somnolab, Weinmann GmbH) for computer-supported visual analysis.

A hypopnea was scored as a central hypopnea when the criteria as outlined in the Report of an American Academy of Sleep Medicine Task Force [2 p.672] applied: 'Reduction of airflow' as mentioned before, 'the event lasts 10 seconds or longer' and 'a clear reduction in Pes swings from baseline'. Baseline is defined 'as the mean amplitude of stable breathing and oxygenation in the two minutes preceding onset of the event'. Mixed hypopneas were not included in this study.

Interscorer Agreement

The unweighted Cohen's kappa statistic (κ) [20] was applied to evaluate the agreement between two scorers (human or automatic) in the classification of central and obstructive hypopneas. κ is equal to 1 for a perfect agreement between two scorers while 0 indicates an interscorer agreement only due to chance.

Data Analysis

The visual hypopnea time markers were used to extract the hypopnea segment of the airflow signal (hflow), a 5-second interval after hflow and the 2-min segment prior to the hypopnea's onset (flow2min; fig. 1), according to the aforementioned definition of the 'baseline'. Respiratory periods were automatically detected, extracted and separately processed [21].

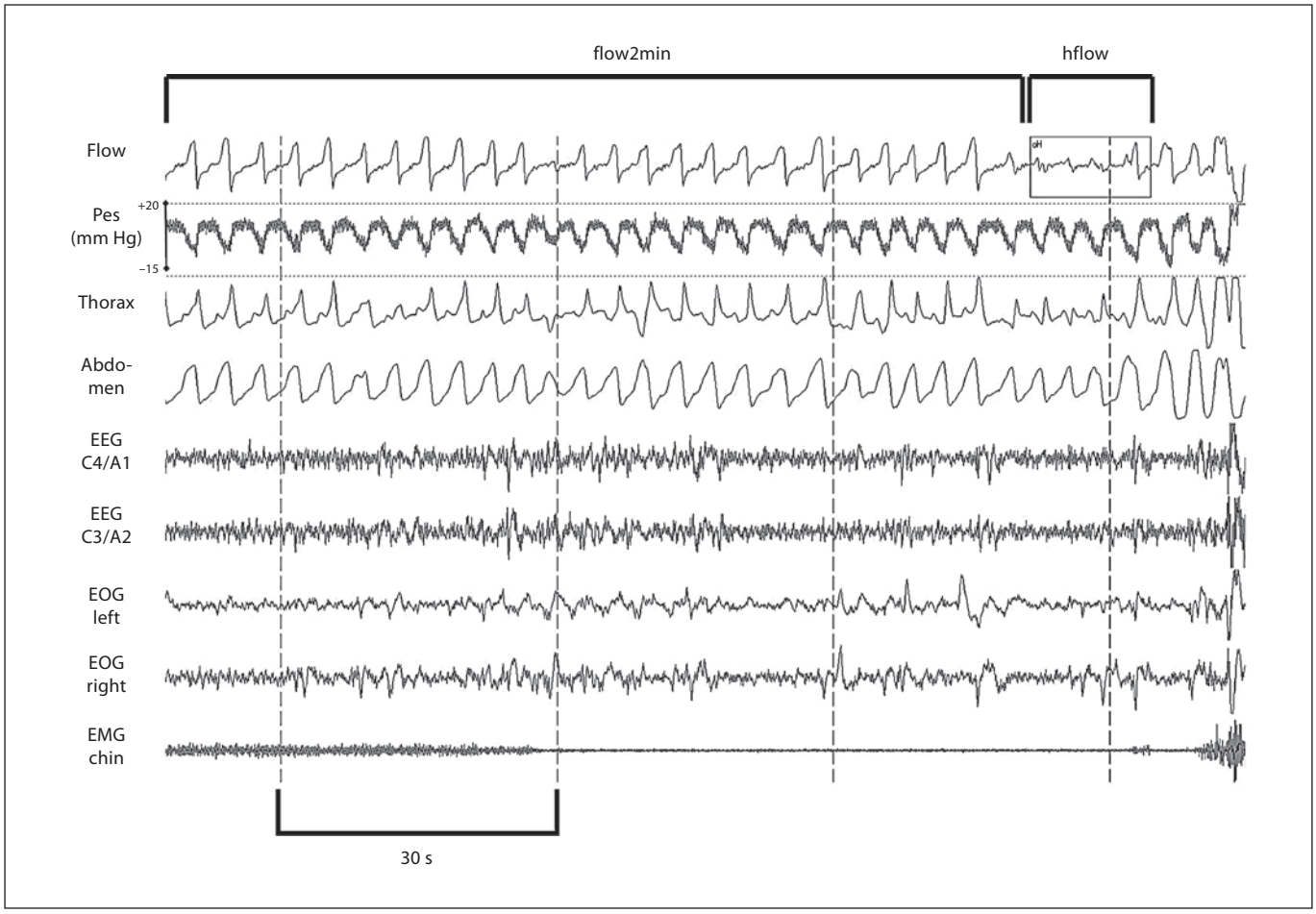

Fig. 1. Sample PSG depicting an obstructive hypopnea with the hflow marked, a 5-second interval after hflow and the flow2min. An inspiration corresponds to a decreasing Pes curve and the corresponding increasing airflow curve. Note the Pes signal in comparison to the RIP belts (thorax/abdomen), all of which reflect respiratory effort.

Table 1. Features extracted from the nasal airflow signal to characterize a hypopnea

Feature number	Description
1	Number of detected inspirations in flow2min
2	Number of detected inspirations in hflow divided by the number of inspirations in flow2min
3	Difference between the mean value of the maxima of the inspirations in flowmin and hflow
4	Median of the values of the maxima in an hflow in relation to median value of the maxima in flow2min
5	Crescendo index: Pearson's correlation coefficient for the amplitude maxima of the inspirations in hflow and in the 5 s after its end
6	Abrupt ending index: amplitude difference between the last inspiration of hflow and the first inspiration after its end in proportion to the maximum in hflow
7	Percentage of inspirations with IFL (flattening) in flow2min
8	Percentage of inspirations with IFL (flattening) in hflow

The automatic hypopnea differentiation method was based on a previous study [22] that required the Pes signal for the analysis of inspiratory flow limitation (IFL). To overcome this constraint, we implemented a noninvasive automatic flattening analysis method [21] that only requires the airflow signal for assessment of IFL. Then, novel features that best characterize obstructive and central hypopneas (table 1) were extracted only from the airflow signal.

To overcome patient-dependence, the hypopnea events of all our patients were assembled in a common pool of hypopneas. Then, each individual hypopnea event was randomly distributed with a hold-out cross-correlation algorithm into either a training (40% of events) or a test set (60% of events) to achieve full independence of the data between both sets (fig. 2). Discriminant analysis [23] was applied as a computational fast yet powerful classifier that was then trained and tested on the commented sets.

Comparison of Automatic Airflow Scorings with Visual Analyses

Two experts in sleep medicine (scorers A and B) independently differentiated hypopnea episodes into central or obstructive with the Pes signal. Both scorers were explicitly advised to follow the before-mentioned hypopnea scoring criteria in order to obtain the maximum possible agreement, while being blinded to the other scorer's results. The κ statistic was calculated to assess the interscorer agreement, the agreement between automatic and individual visual scores, and the agreed hypopnea scores.

Results

Scorer A and scorer B differentiated a total of 1,237 hypopneas. Both scorers agreed on 85% of central and 90% of obstructive hypopneas (table 2), generating a κ value of 0.74 (SE = 0.02). Hence, the gold-standard hypopnea scorings for which scorers A and B agreed consisted of 1,083 hypopneas (table 2).

The recordings of 5 patients were required for the training of the noninvasive flattening analysis method (fig. 2), which analyzes the airflow and Pes signals of each individual inspiration in a recording (independently of the scored hypopneas) [21]. Hence, the patients with the smallest number of detected hypopneas were selected for this purpose. A total of 23,282 inspirations were extracted from these recordings and employed for the noninvasive flattening training. The hypopneas of these patients (7 hypopneas for each scorer's individual hypopnea set and 6 hypopneas for both scorers' consensual set) were excluded from the analysis. Due to technical constraints of the automatic airflow signal analysis, automatic preprocessing discarded additionally 64 hypopneas (5%) of the individual and 57 hypopneas (5%) of the consensual sets.

The totals for the hypopnea sets therefore resulted in 1,166 hypopneas for each scorer's individual set and 1,020 for both scorers' agreed set. Of these sets, only 40% of the hypopneas (467 and 408, respectively) were required to

Table 2. Results for scorer A versus scorer B

	Scorer A		Total
	central hypopnea	obstructive hypopnea	
Scorer B			
Central hypopnea	436	80	516
Obstructive hypopnea	74	647	721
Total	510	727	1,237

Table 3. Results for automatic analysis versus individual scores

	Automatic		Subtotal	Total
	central hypopnea	obstructive hypopnea		
Scorer A				
Central hypopnea	192	93	285	699
Obstructive hypopnea	125	289	414	
Scorer B				
Central hypopnea	209	76	285	699
Obstructive hypopnea	133	281	414	

Table 4. Interscorer agreement results represented by κ

	Scorer A vs. automatic	Scorer B vs. automatic	Scorers A/B (agreed) vs. automatic
Cohen's κ	0.37	0.40	0.41
SE	0.04	0.04	0.04
95% CI	0.30–0.44	0.33–0.47	0.33–0.48

Table 5. Results for automatic analysis versus agreed scores of scorers A/B

	Automatic		Total
	central hypopnea	obstructive hypopnea	
Scorers A/B			
Central hypopnea	161	81	242
Obstructive hypopnea	94	275	369
Total			611

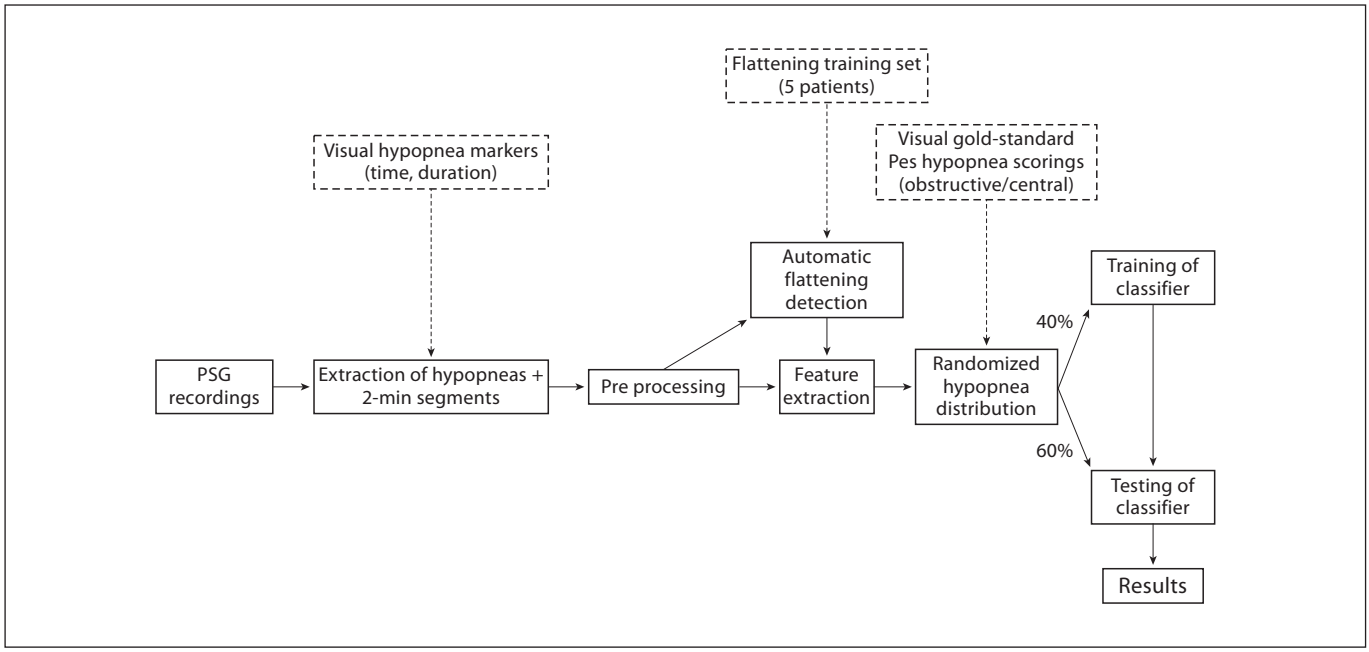

Fig. 2. Sequential diagram of the design of the automatic classifier. Each PSG recording's airflow signal is individually analyzed and the corresponding hypopneas are extracted using the visual hypopnea time markers. During preprocessing, all inspirations are extracted for each hypopnea. The inspirations are assessed for IFL with the noninvasive IFL analysis method and features are extracted from the hypopnea's flow signal. After creating a random test and training set, these features are forwarded to our classifiers, which are trained and tested. Their scoring results are compared to the visual, gold-standard Pes scorings obtained by human experts.

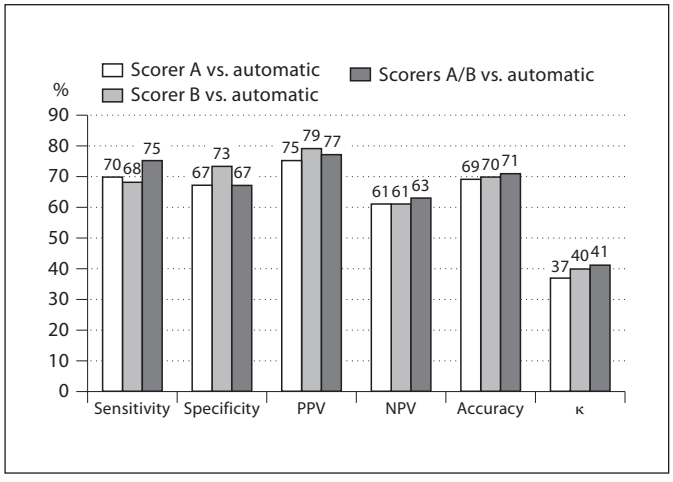

Fig. 3. Classification results of the automatic system in comparison to the visual, gold-standard Pes annotations of scorer A, scorer B and the agreed results of both scorers.

train the automatic analysis method while 60% (699 and 611, respectively) were used for testing (fig. 2). The hypopneas were randomly distributed to ensure full independence between both sets.

For the evaluation of the classification results, true positives were defined as obstructive hypopneas (sensitivity) and true negatives as central hypopneas (specificity). Compared with the results of scorer A, the automatic analysis achieved a sensitivity of 70%, a specificity of 67%, a positive predictive value of 75%, a negative predictive value of 61% and an overall accuracy of 69% (table 3; fig. 3), obtaining an agreement of $\kappa = 0.37$ (table 4). Compared to the scores of scorer B, a sensitivity of 68%, a specificity of 73%, a positive predictive value of 79%, a negative predictive value of 61%, an accuracy of 70% (table 3; fig. 3) and an agreement of $\kappa = 0.40$ (table 4) was obtained for the automatic analysis. Compared to the consensual results of scorers A and B, the automatic analysis achieved a sensitivity of 75%, a specificity of 67%, a positive predictive value of 77%, a negative predictive value of 63%, an accuracy of 71% (table 5; fig. 3) and an agreement of $\kappa = 0.41$ (table 4).

Discussion

The obtained results seem promising and show that an automated method with the features outlined in table 1 permits the differentiation of central and obstructive hypopnea events using only nasal airflow. The results obtained with the automatic method should be considered of clinical value as they were compared to gold-standard visual Pes scorings of two human experts.

The values for κ (0.37–0.41) obtained with the automatic, single-channel analysis (table 4) are on par with results (0.35–0.45) reported by others [13, 24] comparing automatic versus visual interscorer agreement. Our results are also in accord with recently published results [25] for noninvasive hypopnea differentiation. The obtained κ values are superior to those usually reported (κ = 0.31) for apnea/hypopnea human interscorer agreement [26]. The overall results for the automatic hypopnea analysis seem promising as the obtained accuracy values of 69–71% (fig. 3) are similar to those reported (approx. 75%) for noninvasive multiple-channel analysis without using Pes [22, 27]. It should be remarked that in comparison to visual, multiple-channel PSG methods [22, 27], our automatic analysis only employed a single, noninvasive channel for the hypopnea differentiation process. Unlike most methods relying on multiple-channel standard PSG signals which tend to over classify central to the detriment of obstructive hypopneas [7], the automatic analysis here showed a balanced identification performance of central and obstructive hypopneas, as the identification of obstructive (sensitivity of 68–75%) was similar to that of central hypopneas (specificity of 67–73%), (fig. 3).

The automatic classifier employed here is a supervised machine-learning classifier, as it requires a training set to learn how to converge with the scoring results of human experts [23]. During the learning process, the automated classifier learns to differentiate between central and obstructive hypopneas using only the features listed in table 1 without the Pes signal. Once the learning is completed, the performance of the classifier needs to be tested on an independent set of hypopnea events (test set; fig. 2). Training and test sets here are independent as hypopnea events were randomly distributed between both sets.

As could be expected, the agreed scores of both scorers A and B on a test set of 611 hypopneas (table 5) were the results for which the automatic classifier achieved the best outcome as they represent the more consistent training and test base. The human scorers A and B showed a high interscorer agreement (κ = 0.74) between their scores, surpassing other reported interscorer agreement values for multicenter (κ = 0.31) [26] and same-center raters (κ = 0.50) [13]. This is probably due to the clear indications and classification criteria that were previously provided to the scorers and to the simplified task of the scorers that only had to differentiate between obstructive versus central hypopneas, in contrast to the usual AHI or multiple-event detection that were analyzed in the mentioned studies [13, 26].

As a pilot study, the size of our training and test groups is limited, such that the obtained outcome could vary if a larger group is employed. Thus, the generalization capability of the obtained outcome as well as the robustness of the presented method should increase if separate patient groups and larger training and test sets are used. Nonetheless, given the complexity and experimental nature of the Pes signal's acquisition, the test set of 699 hypopneas (table 3) employed here still represents one of the most extensive sets with Pes-validated hypopnea scorings in recent literature [13, 16, 22, 24, 25] and should suffice to underline the feasibility of the presented method.

The automatic detection and identification of SDB events with a flow channel is a complex and demanding task, especially if other PSG signals are not available. Hypopneas in this study were manually detected in the PSG signals according to standard criteria [2]. Nonetheless, recent studies [28, 29] have shown several new methods for a reliable flow-based identification of SDB events. Its combination and interaction with the methodology presented here could be further explored in a continuative study.

In conclusion, the results of the automatic analysis method presented in this pilot study have shown the feasibility of noninvasive single-channel flow-based hypopnea differentiation. Further data still needs to be acquired to develop and validate this method before final implementation in home polygraph and/or continuous positive airway pressure devices. However, its adoption would already improve present clinical situations in which hypopneas are mostly labeled as obstructive [8] or not even differentiated at all. As this system requires only a single-channel nasal airflow signal, which is already routinely acquired in clinical scenarios, with continuous positive airway pressure and with home diagnosis devices, the presented method should be of facile adoption.

Acknowledgments

The authors would like to thank M. Treml, W. Galetke, N. Anduleit and K. Richter of the Zentrum für Schlaf und Beatmungsmedizin, Krankenhaus Bethanien, Solingen, Germany, and K. Pietruska, C. Krauss, M. Saka, D. Sommermeyer and B. Schöller of MCC GmbH & Co. KG, Karlsruhe, Germany, for their assistance and support during the development of this study.

This work was supported in part by the Spanish Ministerio de Ciencia e Innovación under grant TEC2010–21703-C03–01 and CIBER de Bioingeniería, Biomateriales y Nanomedicina (CIBER-BBN), Spain.

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