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Editors

Advances in the Diagnosis and Treatment of Sleep Apnea

Filling the Gap Between Physicians and Engineers

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Preface

Sleep apnea is a sleep disorder with a very high prevalence and many health consequences. As such it is a major health burden (Benjafield et al., 2019). Sleep apnea has been systematically explored only a little more than 40 years now (Guilleminault & Dement, 1978). Major impacts of sleep apnea are sleepiness and associated risks for accidents (Bonsignore et al., 2021). Major health impacts are cardiovascular risk and pathophysiological traits, even if this is currently much debated when focusing on the apnea-hypopnea index as the measure for sleep apnea severity (Arnaud et al., 2020). Sleep apnea is a disorder which is a chronic condition and can be treated successfully.

The disorders of sleep-disordered breathing have largely supported the growth of sleep medicine in general from a small specialty field to a major spectrum of disorders in the arena of medical specialties. This activity helped to convert the niche field of sleep research into sleep medicine, a clinical discipline with its own departments, its own center certification, physician certification, dedicated conferences, journals, and research activities. The recognition and importance have grown so much that the new International Classification of Disorders by WHO in its 11th version, being launched in 2022, has added a new section on sleep and wake disorders with its own range of codes. This worldwide recognition will enable the growth of medical education on sleep physiology, sleep pathology, and specific sleep disorders.

The diagnostic field for sleep disorders, and for sleep apnea specifically, is strongly linked to the development of new and recent methods, which allow long-term recording and analysis of physiological functions during sleep. Sleep and sleep apnea are not just identified by taking a single blood sample or by a single measurement by a physician at a visit, but sleep recording requires the continuous recording of biosignals. This is comparable to monitoring of vital functions during anesthesia or intensive care. Because of this methodological challenge, biomedical engineering as well as new sensor and analysis technologies are closely linked to the development of sleep apnea diagnosis. New technologies helped to a large extent develop new diagnostic and treatment modalities for sleep-disordered breathing. Sleep apnea diagnostic research is now linked to the development of new wearables, nearables, and smartphone apps, and profits much from the ubiquitous development of photoplethysmography recording everywhere.

Artificial intelligence is playing a very important role in analyzing sleep recordings and, particularly, in automatizing several of the stages of sleep apnea diagnosis. Since the generalization of computerized analysis in the 1990s, automated processing of cardiorespiratory and neuromuscular signals from polysomnographic studies provided a number of indices able to assist sleep experts in the characterization of the disease (Shokoueinejad et al., 2017). Parameterization of the influence of apneic events on biological system dynamics has relied on widely known techniques from the engineering field, such as spectral and nonlinear analysis. Currently, there is a demand for novel alternative metrics able to overcome the limitations of the standard apnea-hypopnea index concerning its low association with patient symptoms and outcomes (Malhotra et al., 2021). In this regard, signal processing and pattern recognition are going to play a key role. In addition, machine learning has also shown its usefulness in the last decades (Uddin et al., 2018) and, like many other areas in our society, sleep apnea diagnosis is rapidly entering the deep learning era (Mostafa et al., 2019) and big data. These new analytical techniques, along with the advances in health device development, are the main hope for reaching a reliable diagnostic paradigm shift. One that finally could cope with the disease prevalence, personalized interventions, and runaway spending.

Beyond the widespread application of machine learning methods to automate polysomnography scoring and to provide sleep experts with tools for automated diagnosis, artificial intelligence has also the potential to significantly improve the management of sleep apnea treatment. Recent advances in the framework of big data together with remote monitoring capability of novel treatment devices are able to promote conventional sleep medicine towards a real personalized medicine. Identification of refined clinical phenotypes of patients will allow the development of precision interventions, enabling the quick identification of the treatment option that best fits the particular characteristics of a patient (Watson & Fernández., 2021). Similarly, machine learning is able to accurately model patient's adherence from usage data (pressure setting, residual respiratory events, mask leaks) derived from portable treatment devices, improving the efficacy of available therapies (Goldstein et al., 2020). Thus, artificial intelligence is going to significantly change the management of sleep apnea treatment in the short term.

This volume gives a basis of current knowledge on sleep research, sleep medicine, and sleep apnea, with a strong focus on new challenges and new research directions in the diagnosis of sleep apnea and its treatment. The volume contains three sections: the first one is on physiology and pathophysiology, the second one is on diagnostic advances, and the third one is on treatment advances. Each chapter author was asked to not only describe the state of the art but also develop visions for future research as seen from their special angle and viewpoint.

As editors, we think that the volume can serve as an introduction to the field of sleep-disordered breathing, can serve as a basis for educating in sleep-disordered breathing, and can immediately stimulate and trigger new research in physiology, clinical trials, and biomedical engineering for sensors and analysis methodologies.

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Contents

Airflow Analysis in the Context of Sleep Apnea

14

Verónica Barroso-García, Jorge Jiménez-García, Gonzalo C. Gutiérrez-Tobal, and Roberto Hornero

Abstract

The airflow (AF) is a physiological signal involved in the overnight polysomnography (PSG) that reflects the respiratory activity. This signal is able to show the particularities of sleep apnea and is therefore used to define apneic events. In this regard, a growing number of studies have shown the usefulness of employing the overnight airflow as the only or combined information source for diagnosing sleep apnea in both children and adults. Due to its easy acquisition and interpretation, this biosignal has been widely analyzed by means of different signal processing techniques. In this chapter, we review the main methodological approaches applied to characterize and extract relevant information from this signal. In view of the results, we can conclude that the overnight airflow successfully reflects the particularities caused by the occurrence of apneic and hypopneic events and provides useful information for obtaining relevant biomarkers that characterize this disease.

Keywords

Airflow · Automatic analysis · Sleep apnea · Sleep disorders

14.1 Introduction

Simplification of sleep apnea diagnosis has become a major concern in the field of sleep medicine and the motivation of several investigations in recent years. Currently, the standard method for diagnosing the disease in children and adults remains overnight polysomnography (PSG) (Jon, 2009; Patil et al., 2007). This is an effective medical test, but it has some limitations that should be pointed out. Firstly, a high number of physiological parameters are monitored during PSG, which requires appropriate and expensive

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acquisition equipment (Collop et al., 2007; Ryan et al., 1995). In addition, specialized medical staff should be present during its performance. Then, they should visually assess all acquired recordings, which makes it a complex and intensive task (Collop et al., 2007; Ryan et al., 1995). Another limitation is that patient should spend a night hospitalized in a sleep unit. This involves sleeping in a different environment than usual, which can affect sleep development and characteristics (Bennett & Kinnear, 1999). Moreover, the large number of sensors attached to the patient's body can be very uncomfortable and even distressing, particularly for children (Jon, 2009). It should also be noted that not all hospitals have specialized sleep units, or these are overwhelmed by increasing demand. This fact hinders access to PSG, which causes long waiting lists, thereby leading to diagnosis and treatment delays (Alonso-Álvarez et al., 2015; Ghegan et al., 2006).

Accordingly, great efforts have been made to search and develop simpler alternative methods that help diagnose the sleep apnea. A common approach is to automatically analyze physiological signals with ability to reflect the particularities of the disease (Álvarez et al., 2020; Koley & Dey, 2013c). In this regard, apneic and hypopneic events are defined based on airflow reductions (Berry et al., 2012). When the respiratory cessation is partial (hypopnea), the amount of inspired and expired air is limited. Consequently, airflow (AF) signal experiences a reduction of between 30% and 90% (Berry et al., 2012). When the respiratory cessation is total (apnea), the airflow into the lungs is blocked, causing AF signal to present a $\geq$90% reduction and values ≈ 0 (Barroso-García et al., 2020; Berry et al., 2012). Hence, the analysis of this signal is a natural way of determining the presence and severity of the disease.

Regarding the overnight AF acquisition, the American Academy of Sleep Medicine (AASM) recommends using a thermistor sensor to suitably identify apneas and a nasal pressure sensor to identify hypopneas (Berry et al., 2012). Thermistor sensor is placed in the nostrils and mouth from patient to measure the difference of temperature between inspired (cold air) and expired air (warm air). In the case of nasal pressure sensor, it is also placed in the nostrils from patient to measure the pressure changes that occur during inspiration, when airway pressure is negative respect to atmospheric, and during expiration, when airway pressure becomes positive. Thereby, AF signal acquired by these sensors allows modeling the behavior of respiratory activity and detecting the abnormalities caused by apneic and hypopneic events (Berry et al., 2012). The specifications for routine PSG recordings indicate that AF should be acquired at a minimum sampling rate of 25 Hz, being 100 Hz the recommended rate (Iber et al., 2007).

AF signal can be obtained by means of a portable equipment with built-in thermistor sensor and/or nasal pressure sensor (Collop et al., 2007; Flemons et al., 2003; Tan et al., 2015). Thus, the required equipment is less expensive than for PSG as fewer signals are monitored (Collop et al., 2007). Moreover, the portable equipment can be used at patient's home, without disturbing their usual sleep patterns (Bennett & Kinnear, 1999). This test is also less uncomfortable due to a decreased number of sensors involved. Another advantage is that a single channel is analyzed (AF), resulting in a less complex and less time-consuming task (Ferber et al., 1994). All this would make the diagnostic test more accessible, which would reduce waiting lists and streamline diagnosis. Therefore, the use of AF is a potentially promising way for simplifying sleep apnea diagnosis.

All the above mentioned have led multiple works to be focused on the automatic analysis and characterization of the AF signal, in both pediatric and adult sleep apnea context (Gutiérrez-Tobal et al., 2021; Mendonca et al., 2019). These analyses are conducted from three different perspectives: (i) the evolution of AF signal in the time domain, (ii) its characterization in the frequency domain, and (iii) its study in the time–frequency domain. Thus, the main techniques used to analyze the behavior of AF in the presence of apneic events from these three methodological approaches are reviewed in Sects. 14.2, 14.3, and

14.4 of this chapter. In addition, Sect. 14.5 is devoted to studies that combine the aforementioned approaches. Finally, the discussion and conclusions of our study are presented in Sect. 14.6.

14.2 Analysis in Time Domain

As can be seen in Fig. 14.1, apneic events alter the behavior of AF in the time domain by causing significant reductions in its amplitude. Thus, several studies have focused on automatic detection of these events based on the temporal analysis of AF signal.

One of the first approaches to analyze the information of AF focused on the analysis of the instantaneous respiratory amplitude (IRA) and interval (IRI) signals, directly obtained from AF (Várady et al., 2002). Várady et al. (2002) used the raw AF and respiratory inductive plethysmography (RIP) signals and the IRA and IRI surrogates of them to discriminate between apnea, hypopnea, and normal breathing segments. An artificial neural network (ANN) fed with the IRI and IRA from AF was subsequently trained to perform the detection task.

Cabrero-Canosa et al. (2004) proposed an algorithm based on the identification of respiratory cycles and quantification of AF, in combination with the information provided by other biosignals (Cabrero-Canosa et al., 2004). In their study, symbolic classification was used to determine intervals of normal respiration and different types of airflow reduction (apnea, total reduction; hypopnea, clear reduction). These intervals were subsequently grouped and classified as apneic events or normal respiration.

Other approaches combined the information of AF and thoracic effort signals to detect and classify apneic events as obstructive, mixed, or central (Fontenla-Romero et al., 2005). The apneic segments were identified from AF signal by applying a moving average filter together with an adaptive threshold. Then, these segments were classified according to their origin using the additional information provided by the thoracic effort.

In the study of Pépin et al. (2009), an automatic time-domain analysis of the AF signal from a Holter device with an additional nasal pressure sensor was performed and compared to the medical specialists' annotations. The algorithm relied on the calculation of period, inspiratory surface, and maximum amplitude of breathing cycles. From the information provided by these features, amplitude reductions and cessations lasting at least 10 s were scored, and the apnea–hypopnea index (AHI) was automatically obtained.

The work of Álvarez-Estévez and Moret-Bonillo (2009) proposed the application of fuzzy reasoning methodology to detect apneic events from AF combined with other PSG-derived signals. The method relied on amplitude reductions of AF and oximetric desaturations to build reasoning units, which allow the fuzzy algorithm to determine if these reductions were actual apneic events.

Aydoğan et al. (2016) employed the nasal pressure AF jointly with the thoracic effort and the oxygen saturation (SpO_2) signals to evaluate two automatic scoring algorithms (Aydoğan et al., 2016). These algorithms calculated the

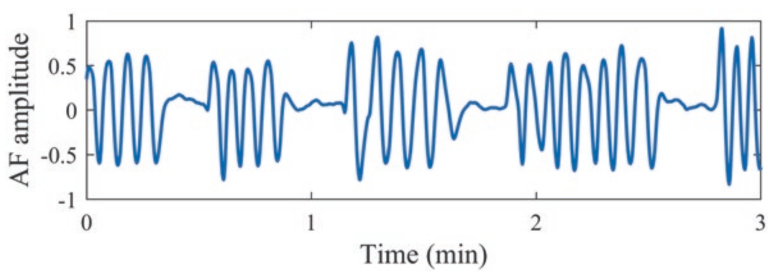

Fig. 14.1 Apneic events presented in overnight airflow (AF) signal. Sleep apnea causes reductions in AF amplitude (≥30%). Consequently, AF signal decreases toward 0 values during the occurrence of these events

mean of the absolute values and power from the signal to derive a rule-based method and an ANN, respectively. It is remarkable that the rule-based method obtained a slightly higher scoring accuracy than the ANN.

In order to predict the pre-apneic and regular breathing events, the work of Ozdemir et al. (2016) extracted 39 statistical and temporal features from the AF signal and its first derivative, since the latter can contribute to reduce false apneic detections (Ozdemir et al., 2016). These features were used to train and evaluate several classifiers, being the support vector machine (SVM) model the one that showed the highest diagnostic performance.

In the case of Kim et al. (2019) and Elmoaqet et al. (2020), they focused their studies on the characterization of the changes caused in the AF signal by the presence of apneic events. They developed an algorithm based on the location of peaks (relative maximum amplitude) and valleys (relative minimum amplitude) of oronasal AF. Then, peak-to-valley amplitudes and peak-to-peak intervals were computed. The apneic event detection relied on the comparison of these metrics in a baseline window and a consecutive detection window. The optimization of this framework was carried out both manually (Kim et al., 2019) and automatically using a Gaussian mixture model (Elmoaqet et al., 2020).

Envelope analysis is also a natural way to characterize the amplitude reductions of AF signal. Hence, several studies have focused on the estimation and analysis of the envelope of AF for detecting apneic events. This is the case of Selvaraj and Narasimhan (2013), who focused on the AF envelope analysis to reflect the changes produced by the apneic events in the respiration. They extracted the amplitude of the envelope and characterized it using three parameters: variability of the respiratory instantaneous amplitudes up to 0.4 Hz, the adaptive trend to quantify the very-low-frequency variations, and the dispersion of the amplitude in a 120-s window. In the study conducted by Diaz et al. (2014), the authors applied the Hilbert transform to derive a respiratory disturbance variable (RDV) from the coefficient of variation of the envelope (Diaz et al., 2014). The RDV was then used as a predictor variable in regression models aimed at estimating the AHI. Other approaches identified the apneas and hypopneas as an amplitude modulation of the normal respiration waveform in AF signal (Ciolek et al., 2015). The apnea detection algorithm relied on the envelope extraction using the following methods: square-law and Hilbert transform. In order to minimize distortions caused by these envelope detectors, standard and recursive median filtering were proposed in substitution of classical linear low-pass filters. The empirical mode decomposition (EMD) was also applied to AF signal to extract and subsequently analyze its envelope. Wang et al. (2019) derived the intrinsic mode functions (IMFs) by means of the EMD algorithm and computed the root-sum-square of the first four (IMFs) (Wang et al., 2019). Then, they obtained the instantaneous respiratory intensity signal and extracted the respiratory fluctuation index. In a recent study conducted by Uddin et al. (2021), a novel method was proposed to detect apneic events based on the analysis of the AF peak excursion (difference between upper and lower envelopes of AF) (Uddin et al., 2021). Thus, an adaptive thresholding was applied to the drops from the maximum peak excursion to determine the presence of apneas and hypopneas. The latter were scored when a drop ≥30% in AF was accompanied to a drop ≥3% in SpO_2, or a drop >2% during at least 20 s.

Among time-domain characterization techniques applied to AF, non-linear methods have been widely used in the sleep apnea context. The study of Kaimakamis et al. (2016) focused on predicting the AHI from a linear equation of non-linear variables (Kaimakamis et al., 2016). The non-linear variables were derived from the largest Lyapunov exponent (LLE), detrended fluctuation analysis (DFA), and approximate entropy (*ApEn*). Some of these non-linear features showed significant correlation with the AHI. Rathnayake et al. (2010) and Barroso-García et al. (2020) also proposed a methodology based on the non-linear analysis of AF signal. In the first of these studies, the authors segmented the AF signal and extracted several features derived from its corresponding recurrence plots (RPs) to obtain useful apnea-related information (Rathnayake et al., 2010). After, this information was used to compute the respiratory disturbance index (RDI) and discriminate between segments of apneic events and normal breathing in adults. In the case of Barroso-García et al. (2020), the RPs from AF signal were used to characterize the behavior of the pediatric overnight AF in the presence of apneas and hypopneas (Barroso-García et al., 2020). This characterization was carried out by computing up to 9 RP-derived features: 1 from the recurrence density, 5 from the diagonal structures, and 3 from the vertical structures of the RP. The results showed that sleep apnea modifies underlying dynamics and phase space of overnight AF. Particularly, apneic events reduce the variability, stationarity, and complexity of AF, as well as the exponential divergence of its phase space. In addition, this disease also increments the dwell time in the same phase space state, the mean prediction time, and the irregularity of pediatric AF.

14.3 Analysis in Frequency Domain

As can be seen in Fig. 14.2, the recurrent behavior of apneic and hypopneic events modifies the AF spectrum. This has led several studies to focus on the automatic processing of AF signal from a frequency point of view.

Nakano et al. (2007) proposed a method to detect apneas based on the analysis of the power spectrum of 12.8 s AF segments (Nakano et al., 2007). Thus, the AF recordings from 399 subjects were automatically processed to extract the flow power by means of the fast Fourier transform (FFT). Flow power decays in the respiratory band were associated to the presence of apneic events. Once these dips were detected in the overnight AF signal, the RDI was subsequently derived.

The work conducted by Gutiérrez-Tobal et al. (2015) was the first study that applied a spectral analysis to AF signals from pediatric subjects (Gutiérrez-Tobal et al., 2015). Thus, overnight AF was investigated by means of the power spectral density (PSD), and new spectral bands of interest were specifically defined for children: 0.119–0.192 Hz and 0.784–0.890 Hz. These frequency bands were characterized by calculating the maximum and minimum amplitude and first-to-fourth statistical moments. The results indicated that the spectral power in these bands is higher in the presence of sleep apnea, suggesting that the repetitive occurrence of apneic events modifies the spectral components of pediatric AF.

In order to overcome the limitations of classical spectral analysis, such as the assumption of stationarity and linearity, the work of Barroso-García et al. (2021a) proposed the bispectral analysis of AF signal (Barroso-García et al., 2021a). They defined a frequency band adapted to the normal respiratory rate of each pediatric subject. This band was characterized by computing up to 13 features derived from bispectrum: 3 from the amplitude of the bispectral band, 4 from the entropy of distribution, 4 from the bispectral moments of the band, and 2 from the weighted center of the bispectrum. The four types of bispectral features showed complementarity with each other. In addition, the obtained results suggest that the presence of sleep apnea reduces the non-gaussianity and the non-linear interaction of harmonic components of AF, increments its irregularity, and displaces the activity to lower frequencies that are associated with apnea occurrence.

14.4 Time–Frequency Analysis

A common approach to characterize the presence of sleep apnea in AF is to conduct a time–frequency analysis employing the Hilbert–Huang transform (Fig. 14.3). This method applies an EMD process followed by the Hilbert spectrum computation. In this regard, Salisbury and Sun (2007) obtained the first and second IMFs and computed the Hilbert–Huang spectrum and its histogram in the frequency domain. Afterward, the apnea percentage was derived from the latter (Salisbury & Sun, 2007). Similarly, Caseiro et al. (2010) also employed the Hilbert–Huang transform and extracted features from the spectral histogram: frequency value in the first quarter, ratio between the first and the second halves, and ratio

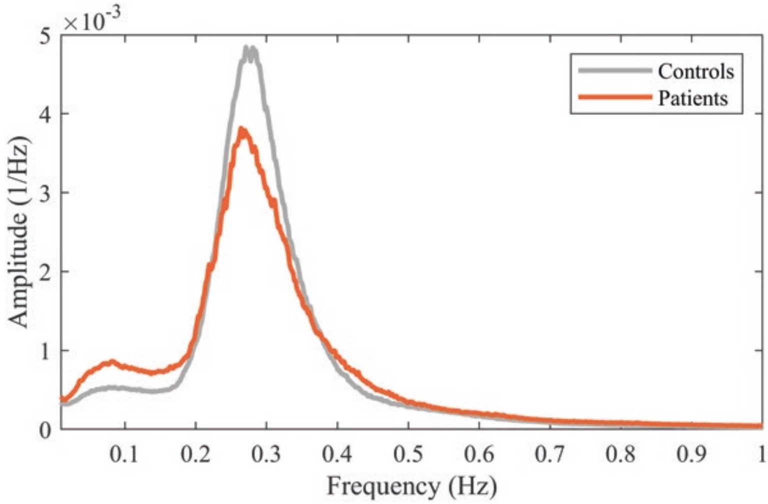

Fig. 14.2 Average spectrum of airflow (AF) signal from 974 subjects with and without sleep apnea (405 patients and 569 controls). The recurrence of apneic events leads to an AF spectrum with less power in the normal breathing band. This spectral power is redistributed in a wide range of frequency components. Particularly, the power increase at certain frequencies would be associated with the repeated occurrence of these event

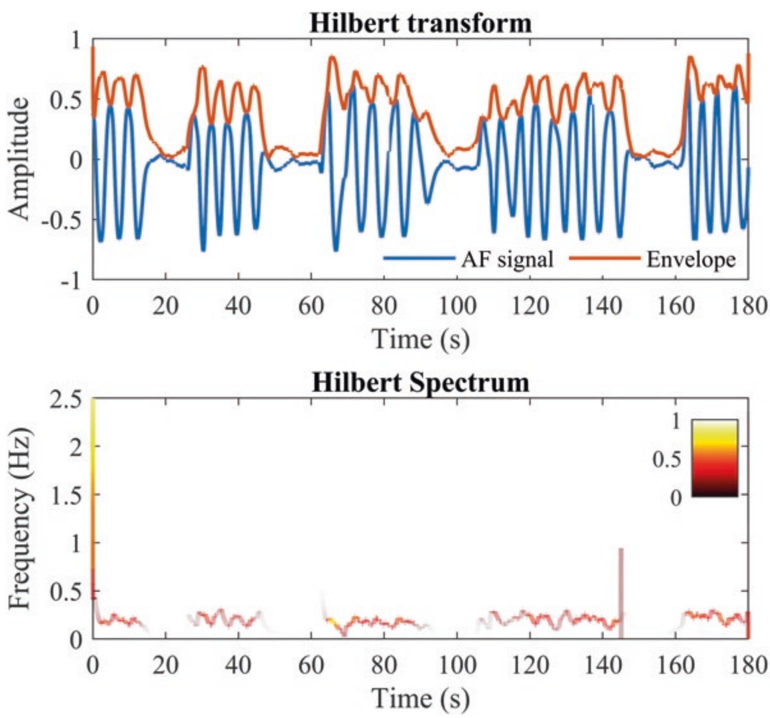

Fig. 14.3 Apneic events in the Hilbert envelope transform and spectrum of AF signal. Sleep apnea causes reductions in AF envelope. Consequently, Hilbert spectrum of AF vanishes during the occurrence of these events

between the maxima found in the first and second halves (Caseiro et al., 2010). Both methods were applied to the AF during an awake period rather than an overnight recording (Caseiro et al., 2010; Salisbury & Sun, 2007).

Another time–frequency mathematical tool is the wavelet transform. Several studies have applied this method to analyze the AF dynamics during sleep apnea. Kermit et al. (2000) applied the Haar wavelet to decompose the AF signal into

16 coefficients, which were directly used to feed a predictive model (Kermit et al., 2000). Further work from the same authors generated templates of apneas and normal respiration using a Haar wavelet decomposition. These templates were used to test the similarity of AF segments with the normal and apneic patterns (Kermit et al., 2002). Based on the continuous wavelet transform, Koley and Dey (2013a) used the cross wavelet analysis for the first time to differentiate between central, obstructive, and mixed apnea (Koley & Dey, 2013a). They assessed three pairwise combinations of signals to be analyzed via cross wavelet transform: AF, thoracic effort, and abdominal effort. The combination of the cross wavelet amplitude and phase coefficients from AF and thoracic effort showed to be more effective differentiating the apnea types. Avci and Akbaş (2015) also employed a wavelet decomposition approach to analyze respiratory signals (Avci & Akbaş, 2015). They selected the Daubechies wavelet family and extracted up to 8 features from the coefficients of 11 detail levels. In the same way, AF recordings from 946 children were analyzed by means of the discrete wavelet transform in Barroso-García et al. (2021b). They used the Haar and Daubechies mother wavelets for the AF analysis and extracted features from the eighth detail level. This detail level approximately corresponds to the normal breathing activity. Consequently, the AF reductions and cessations caused by sleep apnea modified the frequency components and the energy in this frequency band (0.195–0.391 Hz) (Barroso-García et al., 2021b).

McCloskey et al. (2018) employed wavelet spectrograms to generate graphic representations of AF that were analyzed by a convolutional neural network (CNN) for discriminating between normal breathing, apneic, and hypopneic events (McCloskey et al., 2018). The method was also compared with a 1D CNN trained with raw AF data. The 2D CNN trained with wavelet spectrograms outperformed the 1D CNN trained with raw AF data, thus highlighting the usefulness of the wavelet analysis. Similarly, Wu et al. (2021) proposed a method to detect apneic and hypopneic events from the AF signal by computing spectrograms with the short-time Fourier transform (STFT) (Wu et al., 2021). These spectrograms fed a CNN aimed at classifying 15-s segments as normal, hypopnea, and apnea.

14.5 Other Combined Approaches

In addition to the joint time–frequency analysis, other studies have shown the usefulness of combining the time and frequency domain information of the AF signal. In the study of Han et al. (2008), the mean magnitude of the second derivative (MMSD) of AF was analyzed, and an adaptive thresholding method was applied to detect apneic events (Han et al., 2008). The MMSD minimizes the contribution of baseline drifts and offset of the AF signal and, thus, is easier to interpret. The algorithm was designed and tested using the signals from 24 subjects. The normal respiration activity was also analyzed in the frequency domain between 0.2 Hz and 0.4 Hz to establish the reference behavior of the MMSD in normal respiration.

Novel time-domain features were proposed in Bricout et al. (2021), where non-periodic rate, low energy rate, and variance of the dispersion metric were analyzed along with statistical measurements, spectral power from the conventional heart rate variability (HRV) frequency bands (VLF, LF, HF), the ratio LF/HF, and the spectral kurtosis (Bricout et al., 2021). It is important to highlight that diagnostic performance of these features was higher using the AF signal from nasal pressure sensor than that obtained with a novel accelerometry sensor.

Koley and Dey (2013b, c) proposed apneic event detection models based on the analysis of short AF segments (Koley & Dey, 2013b, c). Statistical metrics were computed from the IRA and IRI signals, directly obtained from the airflow. The raw signal was also characterized by means of spectral (total and relative powers in the full spectrum, in the LF, and HF bands, respiratory frequency and its corresponding power, mean, and variance of the spectrum) and nonlinear features (*ApEn*, Lempel–Ziv complexity, LLE-derived features, Higuchi fractal dimension, and correlation dimension).

In the study conducted by Gutiérrez-Tobal et al. (2012, 2013), the authors investigated the diagnostic ability of the AF signal obtained by a thermistor and the respiratory rate variability (RRV) signal derived from AF (Gutiérrez-Tobal et al., 2012, 2013). These two signals were characterized using statistical, spectral, and non-linear features. Two spectral bands of interest were defined from AF and RRV: 0.022–0.059 Hz and 0.095–0.132 Hz, respectively. The features that obtained the highest diagnostic ability were the mean, standard deviation, peak amplitude, and power in the interest band of AF together with the central tendency measurement (*CTM*), skewness, and kurtosis of the full spectrum of RRV (Gutiérrez-Tobal et al., 2012). The combined use of AF and RRV improved the diagnostic performance reached by several classification and regression models to estimate the severity of sleep apnea (Gutiérrez-Tobal et al., 2012, 2013).

The combination of spectral and non-linear features from thermistor-recorded AF and RRV was also conducted in the pediatric sleep apnea context (Barroso-García et al., 2017). In this work, the spectral information was obtained using the first- to third-order spectral entropies (*SE*s) and the non-linear behavior by means of the *CTM*. These measurements characterized the irregularity (through *SE*) and variability (through *CTM*) of AF and RRV. The study showed the complementarity between both methodological approaches and that existing between both respiratory signals. The results suggest that the presence of apneic events reduce the variability and increase the irregularity of AF, while the variability of RRV is increased. The diagnostic ability of pediatric overnight AF was also assessed in combination with the nocturnal SpO_2 signal (Jiménez-García et al., 2020). The authors calculated time-domain statistics, spectral, and non-linear features from both AF and SpO_2, as well as the 3% oxygen desaturation index (*ODI3*). A spectral interest band of AF was obtained: 0.134–0.176 Hz, which is very similar to the low frequency band defined in the study of Gutiérrez-Tobal et al. (2015). A model combining the *CTM* of AF and *ODI3* obtained the highest diagnostic ability, suggesting that the variability of AF provides relevant and complementary information to the *ODI3* to diagnose pediatric sleep apnea.

Finally, other studies jointly employed time and frequency features from a nasal pressure signal. The work of Gutiérrez-Tobal et al. (2016) aimed to distinguish the different severity degrees of sleep apnea in adults. The authors defined a new band of interest characteristic of AF from nasal pressure sensor: 0.025–0.050 Hz, which covers the typical duration of apneic events (20–40 s) and matches the frequency band obtained using thermistor. A total of 12 features were extracted: 9 spectral and 3 non-linear features. The mean, standard deviation, minimum, and maximum from the frequency band, as well as the *CTM*, showed statistically significant differences among severity groups, suggesting that these approaches are useful to establish the severity degree of sleep apnea. Álvarez et al. (2020) combined the nasal pressure-derived AF with SpO_2 to evaluate the diagnostic ability of these two signals jointly (Álvarez et al., 2020). Both signals were characterized using time, spectral, and non-linear features, as well as clinical variables such as conventional oximetric indices and the respiratory disturbance index. The regression algorithm trained with features from both signals largely outperformed the individual diagnostic ability of these signals, suggesting that the information of AF and SpO_2 can be jointly used to diagnose sleep apnea.

14.6 Discussion

In this chapter, we have reviewed a variety of methodological approaches aimed at characterizing and extracting relevant information from the AF signal that can be used to help in the automatic diagnosis of sleep apnea. These approaches have been categorized from the four main perspectives: time domain, frequency domain, time–frequency analysis, and other combined strategies. Each of these perspectives focused on different characteristics that AF manifest in the presence of apneas and hypopneas. We have distinguished these particularities between children and adults throughout this section.

14.6.1 AF Characterization in Adults

The alterations caused by sleep apnea in the AF signal have motivated the development of algorithms for apneic event detection. Most of these algorithms were intended to obtain the localization of apneas and hypopneas by analyzing the changes of amplitude caused by respiratory cessations (Elmoaqet et al., 2020; Kim et al., 2019; Koley & Dey, 2013b). In this regard, algorithms based on the time-domain behavior of AF have been widely investigated. The reductions of amplitude in the AF signal led to the detection of apneic events in most of these algorithms (Uddin et al., 2021). In the same way, the amplitude reductions were characterized by the differences between AF peaks and valleys, as well as the differences between consecutive peaks, which are also reduced in the presence of apneas (Elmoaqet et al., 2020; Kim et al., 2019). Some authors have focused on envelope analysis (Diaz et al., 2014; Uddin et al., 2021). This is an intuitive way to track the amplitude of the AF in the time domain since it is narrowly related with the AASM manual scoring guidelines (Berry et al., 2012). A reduction of the amplitude level of the envelope with respect to the previous baseline described the presence of an apneic event (Ciolek et al., 2015; Selvaraj & Narasimhan, 2013). It is also observed that the apneas and hypopneas increase the long-term correlations of the AF and its irregularity in the time domain. Variability and complexity alterations are other particularities presented by sleep apnea in AF (Gutiérrez-Tobal et al., 2012, 2016). However, there is no consensus to it. While some studies observed a reduction in both variability and complexity, others characterized AF as more variable and more complex as severity increased, even using the same analysis techniques (Gutiérrez-Tobal et al., 2012, 2016).

Regarding frequency-domain approaches, the oscillatory pattern of the respiration and, therefore, the AF signal, have motivated the use of spectral analysis methods. The normal respiration generates activity in a narrow specific frequency band that is altered by the repeated occurrence of apneic events (Nakano et al., 2007). These respiratory bands ranges from 0.2 Hz to 0.4 Hz, which matches the normal breathing periods (every 2.5–5 s). However, the presence of sleep apnea leads to a redistribution of the spectral power, displacing the activity focus of AF to frequencies below the normal respiratory frequency (Gutiérrez-Tobal et al., 2012, 2013). This is also observed in the typical frequency range of the apneic events (around 0.04 Hz), where AF presents a higher spectral power, as well as a more asymmetric and peaked distribution of its frequency components as severity increased. In these cases, the spectral distribution of AF has higher statistical distance to the uniform distribution (Gutiérrez-Tobal et al., 2016).

These two previous approaches can be fused to exploit simultaneously their strengths in order to characterize the particularities of sleep apnea in the AF. Instantaneous variations of the respiratory activity due to apneas and hypopneas lead to changes in the spectrum of AF. The reviewed studies revealed that these changes can be analyzed using time–frequency approaches, since these can characterize spectral alterations that occur in short time intervals (Koley & Dey, 2013a). In this regard, it has been observed that the spectrogram of AF estimated by the STFT presents lower activity in the normal respiratory frequency during the occurrence of apneic events (Wu et al., 2021). This was also observed in the wavelet spectrograms, where the amplitude around the respiratory frequency is significantly reduced during the apneic/hypopneic events (McCloskey et al., 2018). Nevertheless, an exhaustive characterization of the AF signal using the wavelet transform is still lacking in adults.

14.6.2 AF Characterization in Children

The analysis of the AF signal has been much less studied in children than in adults, and some studies suggest that the diagnosis of sleep apnea in children is more challenging due to more restrictive criteria to define apneic events and severity degrees (Rosen et al., 2012). In view of the reviewed studies, apneic events reduce the variability, stationarity, and complexity of AF (Barroso-García et al., 2017, 2020; Jiménez-García et al., 2020). Moreover, when the AF was characterized in the phase space, the exponential divergence was reduced as the severity of sleep apnea increased (Barroso-García et al., 2020). This disease also increments the dwell time in the same phase space state, the mean prediction time, and the irregularity of pediatric AF in the time domain (Barroso-García et al., 2020).

The pediatric overnight AF also experiences variations in the frequency domain (Gutiérrez-Tobal et al., 2015; Jiménez-García et al., 2020). As in the case of adults, the spectral power in specific low frequency bands is higher in the presence of sleep apnea. This suggests that the recurrence of apneic events displaces the spectral power of AF to frequencies below the normal respiratory frequency (Gutiérrez-Tobal et al., 2015). By extension of the classic spectral analysis, the bispectrum also revealed that the severity of the disease localizes more activity around lower frequencies associated with apnea occurrence (Barroso-García et al., 2021a). Moreover, the pediatric AF has a more gaussian behavior as the severity of sleep apnea increases. In addition, the non-linear interaction of harmonic components of AF is reduced in the presence of apneic events, leading to lower phase coupling in the normal breathing band (Barroso-García et al., 2021a).

As far as we know, the combined time–frequency approach was only explored using the wavelet transform (Barroso-García et al., 2021b). In this case, the wavelet coefficients in the detail level related to the normal breathing are reduced as the severity degree of sleep apnea increases. At the same time, the distribution of these wavelet coefficients is more skewed and peaked around lower values. This is in accordance with the reduction of the energy in the frequency band related to normal respiration (Barroso-García et al., 2021b).

Lastly, it was observed that the AF characterization can improve using of a combination of methodological approaches both in adults and children (Álvarez et al., 2020; Barroso-García et al., 2017; Jiménez-García et al., 2020; Koley & Dey, 2013b, c). According to the reviewed studies, the joint use of different analyses is able to provide useful and complementary information to aid in the detection of sleep apnea. This combinational approach has also been applied to the analysis of AF along with other cardiorespiratory signals (Álvarez et al., 2020; Aydoğan et al., 2016; Cabrero-Canosa et al., 2004; Jiménez-García et al., 2020). These studies show that other signals can be complementary to AF and enhance its diagnostic ability.

14.7 Conclusions

In view of the results, we can conclude that the overnight AF successfully reflects the particularities caused by the occurrence of apneic and hypopneic events. The automatic signal processing methods provide useful information to define AF-based biomarkers for characterizing and helping in the diagnosis of this disease.

Regarding future research directions on the AF signal analysis in the sleep apnea context, deep-learning methods have revolutionized the automatic diagnosis of this disease in the last few years. It is true that these techniques are more focused on the classification tasks (apneic events versus normal respiration, or sleep apnea severity degree), rather than for the characterization of AF signal. However, explainable artificial intelligence (XAI) methods are expected to clarify the functional interpretation of deep-learning models, identify novel relevant information from AF signal, and thus improve the diagnosis of sleep apnea in future studies.

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