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Snoring and Arousals in full-night polysomnographic studies from Sleep Apnea-Hypopnea Syndrome patients

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"The important thing is not to stop questioning. Curiosity has its own reason for existing.
Never lose a holy curiosity."
Albert Einstein

"Curiosity is one of the most permanent and certain characteristics of a vigorous intellect."
Samuel Johnson

To the ones who have always encouraged my curious spirit.
First, I am very thankful to Prof. Raimon Jané for giving me the opportunity to work with his team and guiding me through the paths of research life these last four years. I am grateful for his advice, supervision, guidance and encouragement over the PhD years.

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During the last three months of 2010 (funding by FPI grant for temporary stays outside Spain, ref: SEST1001000958XVO) and for a month in 2011 (funding by CIBER-BBN ayudas de movilidad), I had the amazing opportunity to join the LTSI (Laboratoire Traitement du Signal et de l’Image) in Rennes. I will be forever grateful to Prof. Lotfi Senhadji for receiving me with such warm welcome in his lab and always making sure I felt at home (as well as Prof. Fabienne Porée and Prof. Guy Carrault), for providing me guidance and sharing their expertise on the EEG sleep research field. While at LTSI, I also had the chance to work in close collaboration with Xavier Navarro, Faten Mina and Jean-Yves Bansard, whom I want to thank for their patience and willingness.

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PhD has been an extremely challenging journey, in which I would surely not have been successful if I had not had the support of my family and each and every one of my dear friends.

Above all, the most special thank you goes to my parents, brother, grandpa and wonderful boyfriend who have been supportive and encouraging since the first time I waved goodbye on the “Partidas” (Departures) terminal in Lisbon airport on my way to Barcelona. Words can't even come close to expressing my gratitude and my love for you. These past four years, you have had the patience to listen to me unwearingly and not listen to me when I needed not to be listened to. You
have given me strength and motivation when I felt discouraged and insistently lifted me up while making me believe that I would achieve this goal and would become a young scientist. Obrigada!

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During my stays in Rennes I was fortunate to cross paths with the most easygoing and high spirited people with whom I shared many laughs that helped me feel less homesick. I thank Miguel Altuve, Sara Wong and Patricia Bernabe for their cheerful spirit. Likewise, I express my sincere gratitude to Rosa, Alberto, little Álvaro, David and Elo for welcoming me at their places and making me feel at home. Thank you for lifting me up and cheering me up while I was far away from home.

Finally, I express my gratitude to the reviewers and members of the committee, for their interest, attention and time devoted to this thesis.
SAHS (Sleep Apnea-Hypopnea Syndrome) is recognized to be the more prevalent and more amenable to treatment of all SDB (Sleep-disordered breathing) syndromes. The main clinical triad for SAHS is made up of 3 symptoms: apneas and hypopneas, chronic snoring and excessive daytime sleepiness (EDS). SAHS may cause a number of serious and life-threatening repercussions such as hypertension, cardiovascular and cerebrovascular diseases, metabolic syndrome, traffic accident due to sleepiness and increase risk of death. The gold standard for diagnosing SAHS is an overnight polysomnographic study performed at the hospital, a laborious, expensive and time-consuming procedure in which multiple biosignals are recorded. In the last few years, several collaborations between engineers and sleep specialists continue to offer alternative approaches and simplified methods to aid the screening of SAHS based on a reduced number of signals or even a single one.

In this thesis we offer improvements to the current approaches to diagnosis and assessment of patients with SAHS. We demonstrate that snoring and arousals, while recognized key markers of SAHS, should be fully appreciated as essential tools for SAHS diagnosis.

With respect to snoring analysis our methods were applied to a 34 subjects’ database (on a total of 74439 snores). We have used less complex approaches mostly based on time domain parameters and primarily founded on the analysis of all night snore sequence, as an alternative to the acoustic analysis of snores. We concluded that key information on SAHS severity can be extracted from the analysis of the time interval between successive snores. For that, we built a new methodology which consists on applying an adaptive threshold to the whole night sequence of time intervals between successive snores. This threshold enables to identify regular and non-regular snores and the two snoring patterns that comprise regular snores (single snoring pattern: the subject snores once per breathing cycle and double snoring pattern: the subject snores both in inhalation and exhalation). Finally, we were able to correlate the variability of time interval between successive snores in short 15 minute segments and throughout the whole night with the subject’s SAHS severity. Severe SAHS subjects show a shorter time interval between regular snores ($p=0.0036$, AHI cp: 30h$^{-1}$) and less dispersion on the time interval features during all sleep. Conversely, lower intra-segment variability ($p=0.006$, AHI cp: 30h$^{-1}$) is seen for less severe SAHS subjects. Also, we have shown successful in classifying the subjects according to their SAHS severity using the features derived from the time interval between regular snores. Classification accuracy values of 88.2% (with 90% sensitivity, 75% specificity) and 94.1% (with 94.4% sensitivity, 93.8% specificity) for AHI cut-
points of severity of 5 and 30h⁻¹, respectively. Thus, the features proved to be reliable predictors of the subjects’ SAHS severity.

In what concerns the arousal study, our work is focused on respiratory and spontaneous arousals (45 subjects with a total of 2018 respiratory and 2001 spontaneous arousals). Current beliefs suggest that the former are the main cause for sleep fragmentation. Accordingly, sleep clinicians assign an important role to respiratory arousals when providing a final diagnosis on SAHS. Provided that the two types of arousals are triggered by different mechanisms we hypothesized that there might exist differences between their EEG content. After characterizing our arousal database through spectral analysis, results showed that the content of respiratory arousals on a mild SAHS subject is similar to that of a severe one (p>>0.05). In what concerns spontaneous arousals, similar results were obtained. Our findings also revealed that no differences are observed between the features of these two kinds of arousals on a same subject (r≥0.8, p<0.01 and all points lying within the upper and lower limits of agreement of Bland-Altman analysis with p<0.05). We can affirm that based on our results: a subject having a given percentage of alpha band content on his respiratory arousals will have approximately the same alpha band content on his spontaneous arousals (weighted by the slope). Analogous conclusions can be extended to other features computed during the process. As a result, each subject has almost like a fingerprint or signature for his arousals’ content and is similar for both types of arousals. In addition, this signature has no correlation with SAHS severity and this is confirmed for the three EEG tracings (C3A2, C4A1 and O1A2). Although the trigger mechanisms of the two arousals are known to be different, our results showed that the brain response is fairly the same for both of them. The impact that respiratory arousals have in the sleep of SAHS patients is unquestionable but our findings suggest that the impact of spontaneous arousals in SAHS should not be underestimated.

Alongside and beyond the methodology wise advances we propose on SAHS diagnosis, we believe to have added new insights and further understanding on the pathophysiology and mechanisms that underlie SAHS.
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Sleep is a behavioural state that is a natural part of every individual’s life. About one-third of our lives is spent asleep. Sleep is a required activity, not an option. Even though the precise functions of sleep remain a mystery, sleep is important for normal motor and cognitive function. After sleeping, we recognize that changes have occurred, as we feel more rested and more alert. Problem sleepiness may be associated with difficulty in concentrating, memory lapses, loss of energy, lethargy and emotional instability. Sleep-disordered breathing (SDB) syndromes are an important problem of public health that affect quality of sleep and produce effects on respiratory and cardiovascular systems and daily sleepiness. SDB comprises a wide spectrum of sleep-related breathing abnormalities; those related to increased upper airway resistance include snoring, Upper Airway Resistance Syndrome (UARS), central sleep apnea syndrome with Cheyne-Stokes respiration and Sleep Apnea-Hypopnea Syndrome (SAHS). Recently, the 2nd International Classification of Sleep Disorders (10) recommended UARS to be included as part of SAHS and not considered as separate entity since the same clinical features and pathophysiological underlying mechanisms are observed in both disturbances.

SAHS involves a decrease or complete halt in airflow. Soft tissue in the back of the throat collapses and blocks the upper airway. This leads to partial reduction, hypopneas, and complete pauses, apneas, in breathing that last at least 10 seconds during sleep. The average number of apnea-hypopnea events per hour of sleep is called the apnea-hypopnea index (AHI), and the American Academy of Sleep Medicine (AASM) recently defined SAHS as the presence of more than 5 respiratory events per hour of sleep in association with the symptoms characteristic of the disorder (9),(10),(51),(117). The symptoms related with SAHS are consequence of two main fundamental physiopathological facts: on one hand, apneas, hypopneas and hypoxias, and on the other unstructured sleep. The most frequent symptoms and signs (diurnal and nocturnal) are: thunderous snoring, witnessed apneas, excessive daytime sleepiness, non-restful sleep, wide and/or short neck, obesity, episodes of nocturnal asphyxia, arousals, morning headache and arterial hypertension.
SAHS is recognized to be the most prevalent and a first-rate public health problem. Fairly recently, several studies demonstrated that undiagnosed patients double the expenditure of health care resources compared with diagnosed and treated patients. The gold standard for diagnosing SAHS is an overnight polysomnographic study performed at the hospital, a laborious, expensive and time-consuming procedure in which multiple biosignals are recorded. To overcome this issue, several authors have suggested simplified methods to aid the screening of SAHS based on a reduced number of signals—or even a single one—such as snoring sound signal.

This thesis is a result of a collaboration with the Sleep Disorders Laboratory of the Hospital Universitari Germans Trias i Pujol (HUGTP) in Badalona, Spain, in the framework of the projects TEC2007-68076-C02-01 and TEC2010-21703-C03-01. During this thesis two foreign stays on LTSI (Laboratoire Traitement du Signal et de L’Image, Rennes, France) were completed. The first one, in 2010, had a three months duration (funding by FPI grant for temporary stays outside Spain, ref: SEST1000100958XV0) and the second, in 2011, had one month duration (funding by CIBER-BBN ayudas de movilidad).

Our database (acquired in HUGTP) consists of 116 subjects and is composed of all PSG (polysomnography) nocturnal data and snoring sound signals that were acquired with a novel and pioneer system: Snoryzer Uno (Sibel SA, Barcelona, Spain).

Snoring is known to be an important clinical hallmark of SAHS (with subjects producing loud and/or harsh snores that alternate with apnea/hypopnea episodes) (10),(168). As such, it is a useful and easily accessible signal to screen this disease. With our database of snoring sound signals we were able to develop methods that provide aid on SAHS diagnosis. The robustness of methods based on the acoustic analysis of snoring episodes has proven to be effective and reliable in screening of SAHS. However, we feel that research on the study of all night snore episodes as a temporal sequence is lacking and can provide new information on SAHS disease. Thus, we focused our research on studying the relationship between breathing cycles and snoring event production. For that purpose, we proposed a new methodology for classifying two distinct types of snores: non-regular and regular snores. Our work propounds alternatives to the acoustic studies, always proposing simple and understandable methods, easy to apply, and primarily founded on the analysis of all night snore sequence, that finally can be easily integrated in any low-cost portable bedside monitor.
Bearing in mind our focus on the assessment and diagnosis improvement of SAHS, we also steered our research into the field of EEG signals, more specifically to the study of arousals during sleep. Arousals consist in short awakenings during sleep. Increased amounts of arousals result in shortening total sleep time which leads to severe sleep fragmentation (11). Increasing evidence shows that arousals are deeply involved in the pathophysiology of sleep disorders such as SAHS. Alongside with the rising controversial debate on the topic of arousal scoring and its actual role on the sleep process (whether harmful or lifesaving), there has been a rising discussing concerning the role of two types of arousals, respiratory and spontaneous arousals, in the sleep of SAHS subjects. Respiratory arousals are immediately correlated with the severity of SAHS since they occur within 3 seconds (or less) following or overlapping an apnea/hypopnea and are considered to be important markers of the morbidity of this disease. Nevertheless, spontaneous arousals have also demonstrated to lead to excessive daytime sleepiness and reduced psychomotor functioning. Respiratory arousals continue to deserve top place on the arousal research topic and very few literature can be found reporting the function, effect and consequences of spontaneous arousals in SAHS disease. Prior to our work, no authors had performed an actual comparison between the content of respiratory and spontaneous arousals in a wide range of SAHS subjects. Since both events are equally impairing and represent detrimental and harmful features for sleep we took on that task of characterizing them and trying to ascertain the differences between their contents. Further research on this matter may raise doubt towards current beliefs on respiratory arousals being the main cause for sleep fragmentation and the importance sleep clinicians assign to respiratory arousals when providing a final diagnosis.

Motivated by the will to put forward more alternatives to the diagnosis of SAHS, mainly focusing on two of the most important markers of this disease: snoring and arousal, this thesis also aims to be a guide/manual to whom may be interested in understanding its whole spectrum. For that reason, the definition, epidemiology, risk factors, clinical features, pathophysiology, clinical repercussions, treatment and most certainly the state of the art on the current diagnosis of SAHS will be reviewed on this thesis.

I.1 - Objectives

In a nutshell, this thesis proposes new alternatives to the current methods being used on SAHS diagnosis. Our achievements on snoring and arousal analysis are not likely to replace the conventional diagnosis procedure of SAHS through a polysomnographic study and a complete clinical
evaluation but they can significantly improve the management of this pathology. In depth, the main goal of this thesis is to put forward the study of new methods applied to snoring and arousal analysis with the purpose of improving the SAHS diagnosis. We aim to demonstrate that snoring and arousals, while recognized key markers of SAHS, should be fully appreciated as essential tools for SAHS diagnosis. For this reason, this doctoral thesis can be divided in two lines of work to which correspond two lines of objectives: Snoring and Arousals.

I.1.1 - Snoring

The snoring sounds signals were acquired with a novel and pioneer system: Snoryzer Uno system that is able to identify each snoring episode and define automatically its time boundaries, intensity and frequency parameters. In this way, it is possible to automatically analyse the snoring events during a sleep study on a snore-by-snore basis.

The objectives in this line of work are the following:

• Offer alternatives to the acoustic analysis of snoring episodes by taking out novel time-domain features from the analysis of the snoring sound signal that can help improving the screening of SAHS subjects.
• Put forward the study of all night snore episodes as a temporal sequence as each snore event production may be different in subjects with different levels of SAHS severity.
• Introduce the concept of regular snores (i.e. truly consecutive snores) as the ones produced in consecutive breathing cycles, since they are produced in a regular way, without interruptions.
• Propose a new methodology (such as adaptive thresholds) to identify regular and non-regular snores. Different thresholds will be proposed through adaptive estimation from the whole night sequence of time intervals between successive snores and therefore will be characteristic of each subjects’ snoring pattern.
• Propose the study of normal non-regular snores as an alternative to the study of post-apneic snores since in the latter case there are very few or sometimes even inexistent accountable episodes to carry on a feasible analysis.
• Study the correlation between temporal features of regular and non-regular snores and the severity of SAHS.
• Study the variability of snore episode features throughout all night sleep by examining the time interval between successive snores over short segments of time. Correlate the variability of time interval between successive snores in each short segment with the subject’s SAHS severity.
I.1.2 - Arousals

For the arousal study we made use of the PSG nocturnal data acquired during full-night studies. More precisely, we studied the EEG arousal signal segments from the 3 EEG tracings: C3A2, C4A1 and O1A2. Ultimately, we stored all the practical information on each arousal episode such as type of arousal, associated respiratory event (apneas and hypopneas, if any), starting time instant and duration of the episode and sleep stage, while our main focus was the study of respiratory and spontaneous arousals.

The objectives in this line of work are the following:

- To characterize and classify the two types of arousals, respiratory and spontaneous arousals, by building a set of features that is able to do so. Assess the differences between the two types of arousals given that their trigger mechanisms are different.
- Further investigate on the topic of respiratory and spontaneous arousal scoring. Discriminate and list all possible situations while scoring these two types of arousals given the existence of respiratory events (apneas or hypopneas) following or overlapping them.
- Analyse the similarity between both events through spectral analysis. Compare the shape of the PSD curves and the frequency band power values (delta, theta, alpha, sigma and beta bands) of the two events and study their correlation with each subject’s SAHS severity.
- Perform the correlation and study the agreement between the features of both types of arousals for each subject individually. This way, we will carry out an intra-subject study rather than using all arousals from all subjects at once.

I.2 - Guidelines for reading the thesis

For the sake of clarity and to improve its readability, this manuscript follows the course of the developed work itself.

Firstly, the reader should learn about the whole SAHS spectrum, including its diagnosis and treatment possibilities, in chapter II. After that, fully description not only of the instrumentation used but also of the acquired database in collaboration with HUGTP’s sleep lab is given in chapter III. In what concerns the results and achievements, our work can be divided in two themes: snoring and arousals. Our findings, among other conclusions, suggest that snoring and arousal analysis, while recognized to be key markers of SAHS, should be fully appreciated as essential tools for SAHS diagnosis. As a consequence, chapters IV and V are dedicated to the results obtained on the snoring and arousal topics, respectively. For both of the latter mentioned chapters, a conclusions and future...
prospects section is included at the end with the purpose of summarizing the bulk of findings/achievements and explaining the major contributions our work is able to provide to the field of SAHS pathogenesis and its diagnosis. Finally, on chapter VI, the reader can appreciate the final conclusions and the discussion of the relevance of our contributions to the field of SAHS and, in particular, its diagnosis. Ultimately, the publications (in the form of journal papers, indexed PubMed conference papers and seminars) that this thesis gave rise to, are listed in chapter VII.
II - The Sleep Apnea-Hypopnea Syndrome (SAHS)

II.1 - Syndrome definitions

SAHS is decidedly the more prevalent and more amenable to treatment of all SDB syndromes (228). According to the National Consensus Document on SAHS (51), the latter is a combination of “symptoms including excessive sleepiness and cognitive-behavioural, respiratory, cardiac, metabolic or inflammatory disorders secondary to repeated episodes of upper airway obstruction during sleep”. In depth, it consists on the recurrent occurrence of airflow cessation/reduction during sleep, as consequence of an anatomical-functional alteration of the upper airways (UA) that conducts to its collapse, leading to decreases on the oxyhemoglobin saturation and microarousals that cause unrefreshing sleep, excessive daytime sleepiness (EDS) and neuropsychiatric, respiratory, cardiac, metabolic and/or inflammatory disorders (117). These electroencephalographic microarousals, also called arousals, are triggered by the progressive respiratory effort made by the subject in an attempt to restore the airflow after the UA collapse and the gasometric changes produced as consequence of the airflow limitation.

In agreement with the Spanish Consensus (51) and the American Academy of Sleep Medicine (9) criteria, the airflow limitation respiratory events during sleep can be classified as follows:

- **Obstructive apnea**: Absence or reduction > 90% of the respiratory signal (thermistors, nasal cannula or pneumotachography) for >10 seconds in presence of respiratory effort detected by thoracoabdominal movement.
- **Central apnea**: Absence or reduction > 90% of the respiratory signal (thermistors, nasal cannula or pneumotachography) for >10 seconds in absence of respiratory effort detected by thoracoabdominal movement.
- **Mixed apnea**: A respiratory event that usually begins with a central component and ends with an obstructive component.
• **Hypopnea**: A discernible reduction (>30% and <90%) in the width of the respiratory signal of >10 seconds or an evident reduction in the thoracoabdominal result accompanied by desaturation (≥3%) and/or micro-arousal on EEG.

Unlike the definition of apnea, which has remained consistent over time, the definition of hypopnea has varied. This, in part, is a reflection of the fact that this event involves a more subtle reduction in airflow. A consensus conference (9) (Chicago Criteria) provided a definition of hypopnea as including one of three features: a substantial reduction in airflow (>50%), a moderate reduction in airflow (<50%) with desaturation (≥3%), or a moderate reduction in airflow (<50%) with EEG evidence of arousal. Subsequently, population studies correlating the apnea-hypopnea index (AHI) with cardiovascular disease have helped to hone the definition of hypopnea. The Sleep Heart Health Study (134), a large cohort study designed to relate cardiovascular disease with polysomnographic findings, defined hypopnea as a 30% decrease (from baseline) in airflow or chest wall movement for ≥10 s, accompanied by an oxygen desaturation of ≥4%. A high degree of interscorer reliability was shown with this definition.

The impact that arousals have on sleep immediately correlates this episodes with the SAHS. It is important to clarify that electroencephalographic arousals are commonly classified according to their origin in two types. On one hand, we have the spontaneous arousals that occur spontaneously during sleep and on the other hand, the respiratory arousals that are consequence of gasometric changes and airflow limitations events. The latter type sparks controversy around its origin and utility.

Many publications on the topic which affirm that respiratory arousals are essential to the finalization of an apnea event and have major responsibility on ensuring the reversibility of sleep (17),(28),(51),(78),(178). In contrast, Longobardo et al. (118) suggest that normal breathing can be recovered with no need to sleep stage changing and respiratory arousals will actually induce the further occurrence of apneas (101),(218),(234),(235),(231). This is founded on the premise that chronic sleep fragmentation may alter the chemoreceptor’s sensitivity which can conduct to an elevation of the awakening reaction (73). This theory is not only supported by epidemiologic studies but also by a respiration control model developed by Longobardo et al. (118) that analyses the influence of the arousal threshold on the respiratory stability. Pitson and Stradling (169) also verified that not all apneas end with arousal, although it does not give evidence that they may promote the further occurrence of apneas.

While some researchers (51),(117) propose to extend the definition of apnea and hypopnea by including arousals as a tool to evaluate its disturbing effects on SAHS, the understanding of its
origin and functionality achieves major priority, not only to allow a better mastery of SAHS’s physiopathology but also to hasten the development of new diagnosing techniques.

It should be pointed out that even if the repeated occurrence of respiratory events (apneas and hypopneas) is associated with SAHS, the production of such events to a certain extent is usual in approximately a quarter of the population, without constituting pathology itself (51). For this reason, SAHS exists if a high number of such events lead to acute and chronic consequences on the patient’s health (123). To measure that number, we define:

- **Apnea-Hypopnea Index (AHI):** Sum of the number of apneas and hypopnea per hour of sleep. An AHI<5 is considered normal but not sufficient to discard SAHS. This number needs to be combined with the number of respiratory effort related electroencephalographic arousals so that evaluation is accurate and no false negatives are discarded.

- **Respiratory Effort Related Arousal (RERA):** Period >10 seconds of progressive increase in respiratory effort (ideally detected by a progressive increase in esophageal pressure that ends with a micro-arousal. It can also be detected by short periods of flow limitation – flattening of the signal from the nasal catheter or reduction in the thoracoabdominal sum accompanied by micro-arousal). The respiratory effort increases to compensate the decrease in airflow caused by the narrowing of UA. Breathing becomes impossible and causes the respiratory control to respond in form of arousal. The RERA differs from apneas-hypopneas because the former does not produce a significant blood oxygen desaturation, nonetheless it fragments sleep, and therefore has negative repercussions on the organism.

- **Respiratory Disturbance Index (RDI):** the sum of the number of apneas and hypopnea per hour of sleep (AHI) + RERA.

Additionally, and although this thesis will focus on SAHS pathology, it is rather important to make reference to other relevant sleep breathing disorders such as:

- Central sleep apnea syndrome with Cheyne-Stokes respiration (32),(122).
- Hypoventilation syndrome in obese patients (32).

**II.2 - Disease spectrum**

According to the AASM (9), patients who have AHI greater than 15 events per hour, but do not exhibit EDS or other) sleep-related comorbidities (e.g.: repeated asphyxia during sleep, recurring arousals during sleep, perception of sleep as non-restful, tiredness and/or fatigue during the day, difficulties in concentrating) are diagnosed with SAHS. Such patients may have an increased risk of
developing hypertension (238). In contrast, other patients diagnosed with SAHS exhibit excessive sleepiness and/or have sleep-related comorbidities. The AHI is the key measure for case identification, for quantifying disease severity, and for defining disease prevalence in the population (184). In practice, however, clinicians should not rely solely on AHI for diagnosing and/or determining treatment plans, but also base their decisions on symptoms, sleep architecture, arousal indices, degree of desaturation and examination of raw PSG data. Nevertheless, the most widely used severity criteria use “cutoffs” based on the frequency of apnea and hypopnea events. By consensus, the three levels of SAHS severity: mild, moderate and severe are defined as shown in Table 1.

<table>
<thead>
<tr>
<th>SAHS severity</th>
<th>AHI “cutoffs”</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>5 ≤ AHI ≤ 15</td>
</tr>
<tr>
<td>Moderate</td>
<td>15 &lt; AHI &lt; 30</td>
</tr>
<tr>
<td>Severe</td>
<td>AHI ≥ 30</td>
</tr>
</tbody>
</table>

Table 1 SAHS severity classification criteria. AHI in h⁻¹.

These severity criteria are based, in part, on corresponding risk for the development of hypertension. Although most epidemiologic studies have used the AHI as the single polysomnographic derived measurement when testing the association between SAHS and cardiovascular complications, these definitions do not take into account important factors, such as (among others) the age, sex or the severity of oxygen desaturation. The current severity criteria also correlate poorly with symptom severity (70). Furthermore, investigators (119),(213) have questioned whether the AHI alone is the best predictor for clinically relevant outcomes such as survival, cardiovascular events, or the development of hypertension and metabolic dysfunction. Available evidence supports this doubt; for example, recurrence of atrial fibrillation among OSA patients is predicted best not by the AHI, but rather by the severity of nocturnal hypoxemia (67).

That being said, future research should focus on addressing the previously mentioned limitations and offer clinical founded SAHS definitions which include the harmful effects (acute or chronic) that cause these respiratory events in a more generalized way to patients with different ages, sex or physiological conditions (228).

**II.3 - Epidemiology and risk factors**

Despite the numerous advancements in the understanding and the pathogenesis and clinical consequences of SAHS, the great majority of patients (approximately 70%–80%) remain undiagnosed (174),(227). It is estimated that 26 percent of adults are at high risk for SAHS (236). The prevalence
of SAHS in the general population is approximately 20 percent if defined as an AHI greater than five events per hour (236). In contrast, it is 2 to 9 percent if defined as an AHI greater than five events per hour accompanied by at least one symptom that is known to respond to treatment (e.g., daytime sleepiness) (55),(97). Therefore, it is common to be minimally asymptomatic and have an AHI in an abnormal range.

Public knowledge of risk factors along with physician awareness needs to be addressed to inform appropriate diagnostic attention and case finding in the future:

- **Age**: The prevalence of SAHS increases from 18 to 45 years of age, with a plateau occurring at 55 to 65 years of age (97). If aging has an etiologic role in sleep apnea, then authors would expect the prevalence to continue to increase over the older-age range, but this does not seem to be the case. Most of the age related increases in SAHS occur before the age of 65 years and then plateaus subsequently. This is not what would be expected with continued accumulation of cases and suggests several possibilities: the incidence may decrease with age older than 65 years, a cohort effect, or perhaps an increased mortality rate among older aged patients with sleep apnea (237).

- **Ethnicity and race**: SAHS is more prevalent in African Americans who are younger than 35 years old, compared to Caucasians of the same age group (45). This observation is independent of body weight. The prevalence of SAHS in Asia is similar to that in the United States, despite having a lower mean body weight. These observations suggest that race may be an important risk factor, possibly related to differences in craniofacial structure (112).

- **Gender**: Three to 4 percent of women and 6 to 9 percent of men have SAHS, when defined as an AHI greater than five events per hour accompanied by daytime sleepiness or a cardiovascular morbidity (e.g., hypertension)(97). Some of the gender differences may be age-related, although there is little gender difference among adolescents or after the sixth decade (63). Other hypotheses for the gender differences in sleep apnea have included differences in airway caliber and compliance (145), soft tissue structure (192), genioglossal activity (170), and regional fat distribution (142) (with men more likely to have upper body fat distribution and women more likely to have lower body fat deposition).

- **Obesity**: is the best documented risk factor for SAHS. The prevalence of SAHS progressively increases as the body mass index and associated markers (e.g., neck circumference, waist-to-hip ratio) increase. Weight reduction (by any means) can improve severity of sleep apnea in many patients and may be completely curative in some. Extrapolating from pooled surgical and medical weight loss studies, a 10% to 20% weight reduction is associated with an approximately 50% reduction in AHI (237).
• **Craniofacial morphology**: Craniofacial and upper airway soft tissue abnormalities each increase the likelihood of having or developing SAHS. Examples of such abnormalities include an abnormal maxillary or short mandibular size, retroposition of the hyoid bone and maxilla, a wide craniofacial base, tongue volume, tonsillar hypertrophy, and adenoid hypertrophy (64). One could imagine that a comprehensive risk assessment in the future would include craniofacial profiling.

• **Familial/genetic factors**: Adult sleep apnea is a complex disease. A complex disease is one in which no one gene or risk factor is sufficient or required to produce a disease. This conclusion is supported by evidence that only about one-fourth of the prevalence of SAHS or an elevated AHI has a genetic basis. In addition, the inheritance of obesity and craniofacial abnormalities explains only a fraction of the two- to four-fold increased likelihood of SAHS or an elevated AHI among the family members of patients with SAHS. Each of the risk factors listed earlier are also “complex” traits, and can operate either alone or in combination to result in the initiation and propagation of various genetic and environmental factors that act and interact to produce this disease (8).

• **Others**:
  - Current smokers (but not past smokers) are nearly three times more likely to have SAHS than never smokers (113).
  - Nasal congestion confers an approximately two-fold increase in the prevalence of SAHS compared to controls, regardless of the cause of nasal congestion (45),(128),(238). This is probably related to increased resistance due to decreased nasal patency.

### II.4 - Pathophysiology

In humans, the upper airways (UA) are not a rigid structure, and its patency depends on the balance of forces acting on the walls (transmural pressure) and the resistance of the walls to collapse (wall elastance, *i.e.*, the inverse of compliance). The UA structure is composed of a collapsible segment in between two rigid segments. The proximal segment (nasal cavity) is rigid thanks to its osteocartilaginous walls, the medium segment (pharynx) has variable rigidity due to its muscle-ligamentous walls and the distal segment (trachea) which is also rigid as cause of its cartilaginous walls (Figure 1).

During inspiration, the negative intraluminal pressure tends to collapse the airway and the activity of upper airway dilating muscles (*e.g.*, the genioglossus) phasically increases to counteract this collapsing force and maintain patency. Other upper airway muscles (*e.g.*, tensor palatine) have a
more constant tonic activity and maintain a level of wall stiffness to resist collapse. Inspiratory phasic muscle activity is normally maintained during sleep after a transitory drop during the wake-sleep transition. However, tonic muscle activity appears to fall as sleep deepens. This causes a decrease in airway luminal cross-section and an increase in upper airway resistance to airflow. During wakefulness, upper airway muscles respond to a burst of negative pressure with a reflex-like increase in activity. Thus, if a more forceful inspiratory effort is made in response to a stimulus (e.g., an increased PaCO₂ or decreased PaO₂ (respectively, partial pressure of carbon dioxide or oxygen in arterial blood)) producing a more negative intraluminal pressure, a compensatory increase in dilating force occurs. This response is reduced during sleep with the loss of the wakefulness stimulus. At a given inspiratory flow rate, intraluminal pressure will be more negative if the airway crossectional area is reduced. Patients with SAHS usually have some degree of anatomic narrowing of the upper airway.

Since the subject is asleep and therefore possesses minor activity of Autonomic Nervous System (ANS), some changes in the respiratory system will immediately contribute to reduce the UA calibre, hindering the airflow while sleeping:

- Hypotonia of the UA dilator muscles: can promote a decrease in the dilator muscle tone and possibly being insufficient to compensate the negative pressure produced by the inspiratory muscles (mostly intercostals and diaphragm).
- Such hypotonia may cause an increase of pharynx resistance.
- Limited ventilatory response to hypoxia and hypercapnia, resulting in an imbalance between dilator and collapsible thoracic muscles causing fluctuations on UA’s calibre.
• Decreased ventilation: which causes a decrease in volume per minute and an increase in PaCO₂.
• Changes in reflex activity: the reflex mechanisms are mediated by mechanoreceptors or pressure sensitive receptors of the UA, at the level of the epiglottis, and are sensitive to the negative inspiratory pressure of the UA. The negative inspiratory pressure stimulates these mechanoreceptors through reflexes that activate the genioglossus. The stimulation of mechanoreceptors is the main mediator of cortical arousal and sleep-stage changing since as the UA collapsibility increases the thorax “pumps” faster and this causes the mechanical stress that stimulates mechanoreceptors of the lower respiratory tract (which activates the central nervous system - CNS) triggering respiratory arousals, muscle activation, UA opening and resumption of breathing.

Three main factors likely contribute to SAHS pathogenesis. Firstly, the anatomical abnormalities, secondly the regulation of pharyngeal dilator muscle activation, important in maintaining airway patency, is likely dysfunctional in sleep apnea patients and finally, evidence suggests that SAHS patients have intrinsically unstable ventilator control (high loop gain) that may also contribute to pharyngeal compromise.

Evidence (52),(53),(157) also suggests that patients with SAHS have variable mechanisms underlying their disease such that not all patients with SAHS acquire their disease for the same reason. Some patients have primarily an anatomic problem, and in such individuals surgery would be predicted to be an effective therapy. Other individuals have primarily unstable ventilator control, in which case efforts to stabilize ventilation (e.g., oxygen) may well be effective (217). Other patients have primarily a problem with pharyngeal dilator muscle control, which is a group of patients that should likely be targeted if effective methods to stimulate hypoglossal output are defined. Some patients have multiple underlying mechanisms, in which case several therapies may be required to eliminate disease. Thus, ongoing research is working to define various apnea phenotypes, with a view toward a therapeutic strategy in which patients with SAHS are treated individually by targeting their underlying cause (124).

• **Anatomical abnormalities:** Substantial data have demonstrated that patients with SAHS have an anatomically compromised pharyngeal airway. In some patients, this compromise is based on obesity, whereas in others soft tissues and craniofacial structure likely contribute. Multiple imaging studies (191) have demonstrated that patients with SAHS have compromised pharyngeal lumen dimensions as compared with matched controls. However, imaging studies performed during wakefulness are influenced by ongoing pharyngeal dilator muscle activity.
Thus, conventional imaging does not allow the observer to distinguish fully anatomic from physiologic contributions. Regardless, the existing data suggest that patients with SAHS have a tendency for pharyngeal collapse on a biomechanical basis, independent of other non-anatomic variables.

- **Regulation of pharyngeal dilator muscle activation:** The evolution of speech in man, which demanded laryngeal motility, left the upper airway devoid of bony support and vulnerable to pharyngeal collapse. Thus, pharyngeal dilator muscles, such as the genioglossus, are critical to the maintenance of pharyngeal patency in humans. Through protective reflex mechanisms, individuals with SAHS have increased pharyngeal dilator muscle activation compared with control subjects. This increased muscle activity serves to preserve pharyngeal patency in the face of anatomic compromise. With the onset of sleep, however, reflex mechanisms are markedly attenuated. Thus, pharyngeal dilator muscle activation falls markedly, leaving the susceptible airway vulnerable to collapse. In normal individuals without anatomic compromise, the fall in pharyngeal dilator muscle activation is well tolerated. However, in patients with SAHS, the fall in activity leads to pharyngeal collapse. The collapse generally persists until arousal occurs, which leads to reactivation of these muscles. Evidence does suggest, on the other hand, that even severe sleep apnea patients will have some periods of stable breathing without arousals from sleep. Although the mechanisms mediating these periods of stability are currently unknown, evidence (101),(102),(235) suggests that genioglossus recruitment is necessary and sufficient to stabilize the upper airway. The role of arousal from sleep has also been reported to contribute to apnea pathogenesis (101),(118),(234),(235). The ventilatory response to arousal is commonly robust and relatively independent of chemical control. The result can be a marked reduction in PaCO$_2$ once subsequent sleep is re-established. If PaCO$_2$ falls below the apnea threshold, cessation of activity from the central respiratory pattern generator activity occurs. That is, ventilatory drive will cease, even in normal individuals, if CO$_2$ levels fall below a critical apnea threshold. This fall in output to both diaphragm pump muscles and upper airway muscles can lead to central or obstructive apnea, depending on the prevailing mechanics of the upper airway. Thus, repetitive arousals (state instability) may promote breathing instability, and measures to stabilize state may be effective in stabilizing breathing, at least in some patients.

- **Loop gain:** In addition to anatomic factors and upper airway muscles, loop gain is likely important in apnea pathogenesis. Loop gain is an engineering term used to describe the intrinsic stability or instability of a negative-feedback control system (232),(233). A system with a high loop gain is intrinsically prone to instability, whereas a low loop gain system tends to be quite stable. In the case of breathing, ventilatory loop gain is defined as the propensity for periodic
breathing or cycling respirations to develop in an individual. Thus, periodic breathing would tend to develop in an individual with high loop gain in the face of a minimal perturbation, whereas stable breathing despite major perturbations would be found in an individual with low loop gain. Younes et al. (233) have reported techniques to quantify loop gain and have demonstrated an elevated ventilatory loop gain in individuals with moderate-to-severe SAHS compared with normal individuals. A propensity for development of periodic breathing may contribute to marked CO₂ fluctuations. As stated above, if CO₂ falls below the apnea threshold, this could contribute to either central or obstructive apnea, depending on the prevailing airway mechanics. 

Fluctuations in output from the central pattern generator (to both the upper airway and the diaphragm) would be predicted to yield obstructive apnea when genioglossal output is at its lowest point. However, the exact mechanism whereby elevated loop gain contributes to airway collapse remains unclear (124).

Other factors may also be important in mediating upper airway collapse. Increases in volume can have important effects on pharyngeal mechanics via longitudinal tethering (84). Recent data suggest that increases in end-expiratory lung volume lead to a more stable upper airway via caudal traction forces, whereas reductions in end expiratory lung volume yield pharyngeal collapse. Upper airway sensory impairment may be one factor contributing to altered reflex control in SAHS patients. Pharyngeal constrictor activity and altered timing of pump vs pharyngeal dilator muscles are likely less critical factors.

Summing up, SAHS pathogenesis is confirmed on anatomic compromise coupled with loss of compensatory reflexes mediating upper airway dilator muscle activity. Ventilatory control instability and longitudinal tethering of the upper airway via lung volume effects are also important factors mediating airway patency.

All the factors explained earlier promote the reduction of the UA calibre which leads to an imbalance of the pressures and to an increase on pharynx’s resistance causing the UA obstruction and airflow limitation.

The airflow reduction for a substantial period of time causes the decrease in the partial pressure of oxygen and an increase of carbon dioxide in the blood (respectively, PaO₂ and PaCO₂). This situation triggers the regulation mechanism shown in Figure 2. The CO₂ levels are controlled by peripheral chemoreceptors in the aortic and carotid body, in addition to the chemoreceptors on medulla oblongata. Different values are demanded for the PaCO₂ and PaO₂ for daytime and sleep where in the latter case the PaCO₂ is higher and PaO₂ is lower as a cause of the reduced metabolic demand. After receiving the hypoxia-hypercapnia signal, the respiratory control centre sends an
afferent response to the motoneurons of the spinal cord. This response raises the inspiratory muscles activity. When the hypoxia produces a substantial decrease in the $\text{SaO}_2$ (saturation level of oxygen in hemoglobin), the neurologic centres of the central system release an immediate response through the efferent neurons: an arousal. The arousals are also result of an enormous respiratory effort and/or hyperaemia produced. These arousals are transitory and bring the subject back to the physiologic conditions of the awake state allowing the reopening of the UA, possibly causing loud rattling. This puts an end to the apnea episode, avoiding the subject’s death but interrupts and alters the sleep process which will not reach profound and restful sleep stages.

II.5 - Clinical manifestations and repercussions

The main clinical triad for SAHS is made up of 3 signs/symptoms (33):

- Chronic snoring: this is the symptom with greatest sensitivity (its absence makes the diagnosis of SAHS improbable). However, the majority of snorers do not have SAHS (40% of men and 20% of women snore in the general population). Therefore, the presence of chronic snoring as the only symptom is not enough to carry out a sleep test with the intention of diagnosing SAHS.
- Witnessed apneas: this is the symptom with greatest specificity, which increases if the apneas are observed repeatedly over the course of the same night and if they are prolonged.
- Excessive daytime sleepiness (EDS).
Other frequent symptoms and signs that (occasionally related to patient age and sex) are: diaphoresis, nightmares, restless sleep, insomnia, gastroesophageal reflux, enuresis, decreased libido, loss of memory, difficulty in maintaining concentration, affected work/study performance, apathy, irritability, morning nausea, symptoms of depression and chronic tiredness.

No clinical parameter, either isolated or in combination with others, has demonstrated enough value to diagnose SAHS, as they may also frequently appear in healthy individuals or be absent in SAHS patients. Exhaustive clinical evaluation and physical exploration are necessary as they allow classifying the patients according to a pre-test clinical probability which is essential for later evaluating the diagnostic method to use.

SAHS can lead to a number of complications, ranging from daytime sleepiness to possible increased risk of death. Many studies have shown that apart from reducing the subjects’ quality of life as consequence of its clinical manifestations (114) SAHS can also cause hypertension, cardiovascular and cerebrovascular diseases, lead to traffic accidents and increase the risk of death. SAHS repercussions will be described in more detail in the subsequent sections.

**II.5.1 - Unrestful sleep**

Regardless of whether respiratory arousals are a cause or consequence of SAHS, it becomes rather unquestionable that its recurrent occurrence leads to unstructured sleep, shortens the total time of sleep and thus causes EDS (158).

In addition to this, 1 up to 20% of traffic accidents has proven to be related with excessive sleepiness (54).

To measure the EDS clinicians may use subjective methods (the Stanford Sleepiness Scale or the most widely used Epworth Sleepiness scale (98), where the presence of a score equal to or more than 12 points (out of 24 points) indicates pathological hypersomnia) or objective methods (the Multiple sleep latency test (MSLT) and the Maintenance of Wakefulness test (MWT)).

**II.5.2 - Respiratory repercussions**

The majority of SAHS patients seem to present normocapnia during wakefulness. The presence of hypercapnia in these patients suggests the presence of mechanical disorders of the respiratory system related to obesity or Chronic Obstructive Pulmonary Disease (COPD) (240).

Pulmonary hypertension is strongly linked to the presence of COPD, but this relationship in SAHS patients is not mandatory (155). Such obstructive sleep apnea-associated pulmonary
hypertension (without COPD) could be consequence of the cardiovascular changes that occur in SAHS.

**II.5.3 - Cardiovascular repercussions**

Together with EDS, the cardiovascular repercussions are the most evident and widely discussed disturbances caused by SAHS.

During apnea, the hypoxemia-hypercapnia stimulates chemoreceptors and the lack of breathing blocks the sympathetic inhibition afferent from the thorax. Both mechanisms increase the sympathetic outflow that at the same time is responsible for generalized vasoconstriction, increase in arterial pressure and increase in the myocardial consumption of O$_2$ (199). The obstruction of the pharynx induces inefficient inspiratory effort. This then generates very negative intrathoracic pressures that increase the transmural pressure of the left ventricle and the venous return to the right heart. Then the interventricular wall is displaced towards the left, increasing the preload of the right ventricle and the postload of both ventricles. The final consequence is the reduction in systolic volume and the absence of diastolic relaxation. The repetitive episodes of deoxygenation and reoxygenation induce the excessive production of oxygen free radicals, proinflammatory cytokines, circulating inflammatory cells, C-reactive protein and endothelial adhesion molecules. These changes promote generalized endothelial lesions and favour the development of atherosclerosis (185).

Figure 3 summarizes how hypoxemia, hypercapnia, reduction in intrathoracic pressure and cortical and sympathetic activation induce intermediate mechanisms that potentially favour the development of cardiovascular and metabolic disease and premature death.
50% of SAHS patients have hypertension and 80% of patients with resistant hypertension have SAHS. There is a direct relationship between the severity of SAHS and the probability of hypertension, and SAHS is a causal factor for arterial hypertension.

The prevalence of cardiac insufficiency (CI) in SAHS patients is higher than 10%. The studies available indicate a significant improvement in the LV (left ventricular) ejection fraction, reduction in the number of hospitalizations and increased survival in patients with CI-SAHS that tolerate and use CPAP (Continuous Positive Airway Pressure, the most common SAHS treatment technique which will be explained further ahead) (126).

The prevalence of all types of arrhythmias, especially atrial fibrillation (AF) is increasing in patients with SAHS (103).

Epidemiological studies indicate that the probability of stroke in patients with SAHS is from 1.6 to 4.3 times greater than subjects without SAHS (13).

II.5.4 - Neurological and Neuropsychological repercussions

Among the neurological complications of SAHS we should highlight the potential occurrence of seizures especially after apnea termination. The most frequent are located in predisposed territories, either on pre-existing epilepsy or ischemic areas, in which case they would be focal seizures (75).

Arousals promote a decrease on the cerebral blood flow velocity. As a result, apnea episodes have direct influence on cerebral perfusion and can potentially cause cerebrovascular disorders such as angiopathy or thromboembolic and hemodynamic events together with their consecutive ischemic injuries (77).

Patients with SAHS show increased sympathetic activity during daytime and sleep as a result of hypoxemia and other events occurring during apnea. A high sympathetic activity can lead to pathologies such as obesity, diabetes, heart failure or hypertension in addition to raising the values of platelet aggregation, fibrinogen concentration or blood viscosity (146). Furthermore, it can even cause morning headaches (240).

SAHS also has neuropsychological consequences as demonstrated in several studies (30),(108). According to Findley et al. (59) SAHS patients with hypoxemia have higher risk of cognitive deterioration than SAHS patients without hypoxemia. Bédard et al. (30) suggest that hypoxemia further affects both intelligence and psychomotor task performances while the attention deficit caused by EDS affects concentration and memory.
II.5.5 - Metabolic and inflammatory repercussions

The respiratory effort during apnea produce changes in intrathoracic pressures followed by a volume overload on the right side of the heart and thus conducts to an increase in the atrial natriuretic peptide secretion. This increase, together with the decreasing levels of antidiuretic hormone induces nocturia in SAHS patients (167).

Metabolic syndrome is defined when a subject has at least 3 of the following criteria: increased waist diameter, hypertension, insulin resistance, glucose intolerance, reduced HDL cholesterol and high triglycerides. It may also involve inflammation, endothelial dysfunction and sympathetic activation. SAHS patients present most of the previously mentioned factors and 40% of them correspond to metabolic syndrome criteria (146).

The glucose metabolic balance taking place during sleep will potentially be affected in subjects with unstructured conducting to decreased glucose tolerance and insulin sensitivity and even causing endocrine pathologies such as insulin resistance and type 2 diabetes (179).

Finally, SAHS is also associated with functional problems such as morning headaches and impotence and with the triggering of certain endocrine disorders such as hypothyroidism and acromegaly (75).

Neither blood nor hormonal analyses are during a conventional sleep study. Future studies on the metabolic effects of SAHS are encouraged to determine whether hormonal and blood test analysis are relevant and should be included in SAHS diagnosis routine.

II.6 - Diagnosis

Collaborations between engineers and sleep specialists offer substantial opportunities to improve on current approaches to diagnosis and assessment of patients with sleep problems. Such collaborations could also prove key to improved fundamental understanding of the pathophysiology that underlies sleep disorders and their adverse impact on the brain, cardiovascular system, and optimal health. Nonetheless, to this day, sleep medicine still depends heavily on neurophysiological and cardiorespiratory monitoring that have evolved only in limited ways during the past several decades (37). After physical examination, the conventional polysomnography (PSG) observed by a technician in the sleep laboratory is the reference method for the diagnosis of patients with suspicion for SAHS and other respiratory sleep disorders (51),(111). PSG is an expensive, laborious and technically complex technique that is not available at all centres, and due to the large demand
of examinations it cannot be used in all patients. In order to deal with these difficulties, within the hospital environment, portable equipment has been developed to register only the respiratory variables: respiratory polygraphy (RP). RP is considered (at the hospital as well as at home) to be an acceptable method in order to confirm diagnosis in patients with moderate or high clinical suspicion for SAHS and several sleep professionals use and frequently use this method. A flowchart of steps for SAHS suspicion supported by Durán-Cantolla et al. (51),(117) is shown in Figure 4.

Several alternatives to PSG have been proposed in the last few years such as the use of portable monitoring systems and the development of SAHS screening algorithms that require the use of a reduced set of biosignals or even a single one (123).

II.6.1 - Physical examination

The first step in SAHS diagnosing usually consists on the visual examination performed by the medical doctor. The face, neck, mouth, tongue, soft palate, uvula, nasal cavity, pharynx and oropharynx are examined. The 2D cephalometry is an x-ray imaging technique used in the search for malformations (such as retrognathia and micrognathia), mandibular retroposition, jaw disorders,
bad bites, nasal patency and obstruction and tonsillar hypertrophy. Anterior rhinoscopy can also be
efficient in detecting valve anomalies, septum deviation, hypertrophic turbinate and nasal polyposis.

In case of evidence of anatomical alteration the sleep specialist may be interested in using
3D imaging techniques (Computer Tomography (CT) and Magnetic resonance (MRI)) that will permit
visualizing the UA cross-sectional area with more detail (117).

**II.6.2 - Polysomnography**

Nocturnal PSG is the gold-standard diagnosing method on SAHS. PSG consists on a set of
established signals (neurophysiologic, respiratory and cardiac variables) recorded on a polygraph
and is performed in a sleep laboratory attended by trained personnel using a polygraph. The
polygraph is mostly a digital system and has five distinct tasks on a polysomnographic study (161):

- Amplification and monitoring of signals from different electrodes, transducers, and
  sensors during sleep for continuous signal acquisition, detection of unexpected events
  and continuous quality control. The monitoring mode displays signals in adequate time
  and amplitude resolution and must allow notes to be added to the data displayed
  online.
- Recording of signals together with notes and comments on the digital media with
  appropriate resolution for later accessibility.
- Visualization of recorded data for review and classification purposes, support of
  classification task in order to draw diagnostic conclusions.
- In order to support the evaluation of data, many computer-based polygraphs provide
  software to analyse the sleep recordings with programs to determine sleep stages,
  arousals, respiratory, cardiac, and movement-related events.
- The polygraph should support procedures for archiving recorded sleep data.

PSG requires a minimum of 12 physiological signals (163) although more than 20 variables
are frequently recorded (161). The specific selection of optional signals recorded in a sleep study
depends on the physiological function of interest. Audiovisual recording is part of PSG, using a video
camera and a room microphone in the sleep lab. The sleep lab is always under the supervision of
qualified personnel. Chesson et al. (40) encourage the development of novel techniques that allow
PSG to be the least supervised as possible.

Not only the PSG study must be monitored but also needs to be correctly evaluated. So far,
this evaluation is based on a set of rules most of which focus on a visual assessment of the traces.
This assessment is very tedious, mainly due to the large number of signals to be analysed but also
because of its nature and duration (PSG study usually lasts up to 8 hours). Thus, new automated analysis techniques should be evaluated to be applied on PSG. Penzel and Canisius (161) suggest a review on Rechtschaffen and Kales (177) criteria for the classification of EEG sleep stages towards a more procedural routine which may aid in the development of these automatic methods.

**II.6.2.1 - Sleep recording**

Sleep can be divided in different sleep stages. To recognize the sleep stages with the help of polysomnography, the recording always requires electrophysiological signals for visualization. This sleep scoring is performed for time episodes of either 20 or 30s duration which are called 'epochs'. An 8-hour sleep consists of 960 30-second epochs to be classified visually. The visual sleep stage scoring according to the rules of Rechtschaffen and Kales (R & K) (177) is regarded as the gold standard for sleep classification.

The minimum set of signals has been described in full detail in the recommendations of R & K. The minimum requires one electroencephalographic (EEG) lead with electrodes placed either at C3-A2 or C4-A1 according to the 10-20 system for placement of electroencephalography electrodes on the skull. It is well established to have at least one second EEG lead in order to have an alternative signal if one lead loses its quality during the night. For better sleep evaluation, three leads are preferable, reflecting frontal, central and occipital EEG activity (24),(183). Such signal (or signals) can show the brain activity through the frequency and amplitude of different brain waves (*delta, theta, alpha, sigma* and *beta*), certain brain activity patterns (vertex waves, spindles and K complexes) and arousals.

Two EOG (electrooculography) leads are always needed. Often they are abbreviated as ROC (right outer canthus) and LOC (left outer canthus). One EMG (electromyography) lead is required on the chin. The chin muscles present a perfect signal to record muscle tone in general.

Based on these former described signals, a visual sleep scoring can be done. According to R & K’s manual, it is possible to distinguish the sleep stages: wake, REM sleep, and NREM sleep stages 1-4. NREM sleep stages 1 and 2 are summarized as 'light sleep' and stages 3 and 4 are summarized as 'deep sleep' or 'slow-wave sleep' due to the dominance of slow delta waves in the EEG.

Besides the scoring of sleep stages, interruptions of sleep, or central nervous activations, so-called arousals from sleep are evaluated and counted (11). An arousal is an increase in EEG frequencies for at least 3s. It may occur during any sleep stage. During REM sleep there is an additional increase in EMG muscle tone. A certain number of arousals often associated with changes in body position is found during normal sleep. An excessive number of arousals does disturb sleep considerably and needs to be documented (161).
Automated sleep analysis primarily focuses on the sleep EEG signal. Several analysis algorithms restrict themselves to the analysis of one EEG only. The definition of sleep stages according to R & K's recommendations requires the interpretation of EOG and EMG in addition. Therefore, some but not all sleep analysis software also evaluate EOG and few programs evaluate EMG. The adding of EOG analysis in terms of slow and rapid eye movements improves automatic sleep analysis considerably (161).

Sleep analysis has to follow a sequence of steps listed here. The analysis of the sleep EEG first requires the removal of artefacts such as: electrode cable movements, changes in electrode impedance and interferences from other biosignals (ECG (electrocardiography), EOG and EMG). As far as possible these influences have to be removed. The analysis of background activity will quantify the amount of delta, theta, alpha, sigma and beta waves. The analysis of these waves can be any kind of spectral analysis, e.g. Fourier transform, filter banks, or time-domain wave analysis. The next step is the detection of distinct patterns (vertex waves, K complexes and spindles). After having identified waves and patterns at a high time resolution (a resolution of 1 second appears to be appropriate), the next step is to stage the sleep in five sleep stages (NREM stages 1-4 and REM) in 30-second epochs. For the reduction of resolution from 1s to 30s different rules, neural networks, or fuzzy logic approaches are used (162). All methods try to mimic the visual classification of R & K but the accuracy of the automatic sleep staging measured against the visual sleep staging comes as close as 90%.

The analysis of muscle tone in order to support sleep staging is difficult and no reliable method has been established. Only relative changes in the amplitude of the EMG can be evaluated and the EMG amplitude is often confounded by ambient noise or by ECG artefacts or other movement artefacts.

II.6.2.2 - Respiratory recording

To detect sleep-related breathing disorders such as SAHS, it is advisable to record oronasal airflow, respiratory movements with two independent signals at the ribcage and the abdomen, and the effect of respiration reflected by blood gases.

The best method of measurement of oronasal airflow is the pneumotachograph closed face mask but since it is not very comfortable and can disturb sleep, other methods are employed. Other methods include nasal cannulas connected to pressure transducers that have amplifiers which take into account the quadratic relationship between the absolute flow and pressure. This parameter is able to apneas, hypopneas or hypoventilation through the reductions in airflow.
The ribcage movements and abdominal effort produced while breathing permit differentiating between obstructive, central or mixed respiratory events. The optimal method is to measure intrathoracic pressure with an esophageal pressure transducer. Yet this is a rather invasive method and as a result the majority of studies usually measure the intrathoracic pressure through inductance plethysmography.

Tracheal microphones or less favorable alternatives such as room microphone to pick up snoring noise are also helpful on the diagnosis of SAHS and partial upper airway obstruction.

Both hypoxia and hypercapnia are parameters to be taken into account on the quantification of the harmful effects resultant from the airflow reduction during an apnea/hypopnea. This is done using pulse oximeters and capnographs.

**II.6.2.3 - Cardiovascular recording**

Usually one lead of ECG (electrocardiography) is recorded during PSG and it can be used to derive heart rate and may give hints on the presence of arrhythmias. ECG and heart rate are also used to investigate sleep-related transient tachycardia or bradycardia. Some arrhythmias may be associated with specific sleep stages, e.g. REM sleep. Heart rate changes are very characteristic for sleep apnea. Along with each apnea event, a relative bradycardia followed by a relative tachycardia is observed. This pattern has been described as a cyclical variation of heart rate (72),(106).

The recording of blood pressure has major importance on sleep recordings because elevated blood pressure presents the direct link to cardiovascular consequences of sleep disorders. During an apnea episode the blood pressure increases significantly and shows important changes associated with sleep stage. The most widely used device for this record is the sphygmomanometer cuff but it often disrupts sleep. The photoplethysmograph allows continuous measurement of blood pressure but tends to interrupt sleep as well. The most accurate measurement is the invasive recording of arterial blood pressure (161).

After the elimination of artefacts and ectopic beats the analysis of the heartbeat (where R waves are detected through the ECG lead) takes place. There are many methods for the accurate automatic detection of such waves. Once we have the RR signal, periods with high or low heart rate can be identified. Classification thresholds depend on various parameters such as age, sex, or other diseases (e.g. diabetes).

**II.6.2.4 - Movement recording**

The limb movements are recorded by two EMG on tibial muscles. They are primarily used for the diagnosis of restless legs syndrome.
The movement of the legs is considered when there is an increase in tibial EMG activity lasting longer than 0.5 s. Periodic limb movement disorder is diagnosed if at least 4 separate events are detected in a window of 5 to 90 seconds.

The movement recordings can also be used to measure seizures that occur as a result of anoxic suffering in some cases of SAHS.

**II.6.2.5 - Body position recording**

Registration of body position is essential given that many respiratory disorders during sleep only occur in certain positions, such as snoring or some cases of SAHS. Sensors are used to transform the body angle into continuous voltage signals and contact sensors are used to detect the supine position.

**II.6.2.6 - Behavioural recording**

Apart from physiological signals, audio and film recordings of subjects can be conducted during sleep study. Video recordings are useful to document episodes of apnea, movement disorders, seizures or Rapid eye movement behaviour disorder (REM sleep behaviour disorder) with uncontrolled movements during sleep. These audiovisual recordings could also serve in documenting the frequency in the patient's diuresis, which would allow the study of a possible nocturia caused by SAHS.

**II.6.3 - Portable monitoring**

Portable systems for monitoring the SAHS consist in simplifications of the gold standard PSG that permit to extend the diagnosis to a greater number of individuals using fewer resources, while improving its efficiency. Portable systems basically reduce both the supervising sleep personnel needed and the number recorded variables.

Hein (83) in accordance with the recommendations of the American Academy of Sleep Medicine, the American Thoracic Society and the American College of Chest Physicians (15), (39), (62) classified the PSG systems in four levels:

- **Level 1**: corresponds to conventional PSG performed under supervision and with a minimum of 12 signals (gold-standard reference method).
- **Level 2**: PSG performed outside the sleep lab and therefore without qualified supervision. This level must include at least sleep staging and respiratory measures. No studies have demonstrated its accuracy, so it is not recommended either for screening or for discarding of sleep-disordered breathing.
• **Level 3**: consists in supervised polygraphy in which at least three cardiorespiratory parameters plus the sleep position have to be measures. It is recommended for the detection of disorders on a subject with AHI > 15 that does not suffer from pathologies such as COPD or heart failure. Unsupervised Level 3 is not recommended for exclusion or confirmation of sleep-disordered breathing.

• **Level 4**: corresponds to the unsupervised or minimally supervised measure of SaO2 and an additional parameter. This level is neither advisable for detection nor for exclusion of sleep related respiratory disorders.

Yet, there are no studies demonstrating the recommendation of portable systems for follow-up examinations or for the diagnosis of central respiratory disorders or central hypoventilation.

Another available alternative to reduce the PSG costs is the execution of abbreviated polysomnographic studies among which we stand out: the afternoon recording (afternoon nap), early morning and the first half of sleep (7). Out of these, the AASM recommends (39) using the *Split-Night* studies in evident cases of SAHS. These studies establish the diagnosis in the first half of the night and set the optimal level of CPAP pressure for the second half of the night. In this way, the PSG does not need to be performed (160). Nonetheless, none of the portable monitoring systems is recommended by the AASM for these *Split-Night* studies.

Furthermore, all organisms agree that monitoring the use of these techniques for the diagnosis of sleep-related disorders should be performed by qualified personnel with good knowledge of the patient’s history and symptoms. Portable monitoring systems should be applied only by properly trained staff.

**II.6.4 - Acoustic systems**

The American Academy of Sleep Medicine defines *primary snoring* as loud upper airway breathing sounds produced during sleep, without episodes of apnea or hypoventilation. The primary snoring typically occurs while the patient is in the supine position and is usually continuous, present with each breath, and not accompanied by arousals or evidence of sleep disturbance (10). The sound is produced by vibration of pharyngeal tissues or any membranous portions of the airway that lack cartilaginous support (posterior base of tongue, soft palate, uvula, tonsils, posterior pharyngeal wall) on inspiration, although it can also be produce during expiration, due to turbulent air flow through a narrow oropharyngeal or nasopharyngeal space (74),(168). Hence, it considered as a partial obstruction of the UA and for this reason constitutes a major symptom of breathing disorder that will potentially worsen with time (51).
Snoring can be classified according to its origin as nasal, velum, tonsil/tongue or pharyngeal. However, if the origin is glottic or subglottic then the snore will be called stridor. Powell et al. (171) proposed the classification of snoring according to its severity. The least severe type of snoring would be simple snoring. This kind of snoring does not bother the bed partner and there is objective evidence of UA resistance. The loud habitual or social snoring bothers the bed partner but the subject still does not show resistance in the UA so, some studies classify it as simple as well. Finally, the most severe snoring is accompanied by SAHS. Another method is the classification according to the duration and is offered by Lugaresi et al. (121). This method defines *Stage 0* as isolated severe snoring that only disturbs the bed partner. *Stage 1* occurs when snoring appears to be constant during the night and daytime sleepiness symptoms start to occur. *Stage 2* happens when snoring occupies almost the whole night-sleep, and daytime sleepiness becomes unbearable causing psychosocial problems (difficulties in concentrating, lethargy, etc). Lastly, the *Stage 3* snoring is the type of snoring associated with an evidently severe case of SAHS.

Overall, for measuring the snore sounds it is common to use microphones that translate the variations of air pressure of sound waves into electrical impulses. After translation, the signal must be amplified, filtered and digitized before analysis. The snoring sound quality is dependent and varies with: the breathing route (oral, nasal, or both), the predominant site of upper airway narrowing, sleep stage, body position, the existence of sleep-disordered breathing and if sleep is natural or induced.

As previously mentioned on the II.5-Clinical manifestations and repercussions section of this thesis, snoring and SAHS are intrinsically connected given that the former constitutes a key symptom of this disease. Furthermore, snoring carries information relating to the site and degree of obstruction of the upper airway.

Pevernagie et al. (168) elaborated a review on the various physical analysis techniques, psychophysical and modelling the sound associated with snoring. The study mainly compares the various anatomic sites of snoring with its acoustic characteristics since the mono-level *soft palate* originated kind of snoring is assumed to be treated with surgery. The snore of a subject with simple snoring is stable, with little variation and little or no interruption. However, in a subject with SAHS the snore is irregular, with breathing resumption between apneas. In addition, an apnea episode is characterized by the absence of respiratory sound, while on an hypopnea episode the sound persists with an increasing sound pattern (168). The characteristics of snoring as indicators of its coexistence with SAHS cited in the study of Pevernagie et al. are summarized in Table 2. The cited studies use a vast number of parameters and techniques such as residual energy, formant frequencies, pitch,
intra-snore-pitch-jumps and variability of snore parameters to prove that snoring is a reliable indicator of SAHS.

For all above stated reasons it becomes rather evident that the acoustic signature of snoring signal has information on SAHS diagnosis. Bearing this in mind, more studies on this topic are encouraged to be published and should always try to validate the use of these snoring properties on diagnosing SAHS on large populations.

<table>
<thead>
<tr>
<th>Simple snoring</th>
<th>Snoring associated with SAHS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stable with little variation and little or no interruption (168)</td>
<td>Irregular with resumption of breathing between apneas (168)</td>
</tr>
<tr>
<td>Most power snoring noise below 2000 Hz with a peak power usually below 500 Hz (166)</td>
<td>Residual energy around 1000 Hz (166)</td>
</tr>
<tr>
<td>First snore after an episode of apnea consists mainly of white noise bandwidth with greater relative power at high frequencies (166)</td>
<td>Higher proportion of power above 800 Hz (166)</td>
</tr>
<tr>
<td>Large low-frequency peak in SPL (sound pressure level) at around 80 Hz (131)</td>
<td></td>
</tr>
<tr>
<td>Fundamental frequency with multiple harmonics (60)</td>
<td>Peak at low frequencies and narrow bandwidth without identifiable harmonics (60)</td>
</tr>
<tr>
<td>FFT: frequencies between 100-300 Hz (86)</td>
<td>FFT: high non-harmonic frequencies (86)</td>
</tr>
<tr>
<td>Intra-snore-pitch-jumps (4)</td>
<td>Higher formant frequencies, especially F1 (152), (197)</td>
</tr>
<tr>
<td>Variability of snore parameters (196)</td>
<td></td>
</tr>
<tr>
<td>Logistic regression on time and frequency domains (198)</td>
<td></td>
</tr>
</tbody>
</table>

Table 2 Characteristics of simple snoring and snoring associated with SAHS. Literature review (168).

II.6.5 - State of the art on SAHS diagnosis

Sleeping in a totally different environment like a sleep centre imposes stress and anxiety to the patients and the extensive wiring that is required during polysomnography can furthermore disrupt or impede their normal sleep. That said, it is obvious that there is a high demand for easier, cheaper and less obtrusive diagnostic approaches (37),(222). Technological advances may well be able to move evaluation of SAHS out of an artificial sleep laboratory, and into a home environment, with increased comfort, lower expense, and quicker analysis of results. In the last few years, sleep researchers have offered several alternatives to the conventional PSG. They suggest new methods/techniques that are able to identify SAHS or screen SAHS severity using only one or two biosignals. Below, we will briefly discuss the latest and the ones that stand out the most.

The rhynomanometry measures flow and nasal resistance in an active, passive, anterior or posterior way. Although UA’s degree of resistance is not instantaneously indicative of SAHS, a
sudden increase in nasal resistance leads the subject to change from nasal breathing to oronasal breathing, increasing the effort in breathing and compromising the UA. Furthermore, this technique can also measure other parameters indicative of SAHS such as allergic rhinitis, induced nasal obstruction and analysis of multiple regression nasal resistance (66).

Esophageal manometry is the standard technique used for measuring esophageal pressure allowing differentiation between central-obstructive respiratory events and the diagnosis of upper airway resistance syndrome. However, it is not commonly used because it is rather invasive (66).

The optical finger plethysmograph can measure the sympathetic nerve activity of the peripheral vasculature. Patients with SAHS have shown to have transient attenuation of this activity during apnea event. To measure changes produced in muscle sympathetic nerve activity, a peroneal microneurography is employed. This activity increases in SAHS patients both awake and asleep and a high increase in the activity is also observed at the end of an apnea event (66).

The Whole-body impedance cardigraphy ICGWB shows characteristic patterns in obstructive and central apneas and hypopneas and thus can be used in SAHS detection. Saarelainen et al. (186) demonstrated a of 89% sensitivity and of 80% specificity while ICGWB was measured simultaneously with overnight standard PSG.

SaO2 recordings can be a powerful tool for SAHS detection (90),(150). Apneic and hypopneic events occurred during sleep are frequently accompanied by oxygen desaturations. Consequently, differences between the recordings of SAHS and non SAHS subjects can be quite evident. Signals from control subjects (non SAHS) tend to present a constant value around 97% of saturation whereas patients suffering from SAHS are characterized by an increased instability. Nonetheless, some limitations can be found when relying on pulse oximetry alone as a diagnosis tool of sleep apnea. Pulse oximetry relies on pulsatile blood flow for its measurements and is vulnerable to the effects of poor peripheral arterial blood flow. Therefore, body movements, vasoconstriction, and hypotension can cause artefacts through an interruption of the pulse signal.

The ECG is probably the most feasible biosignal for SDB because it is modulated by respiration, sleep, and the autonomic nervous system. It also has the advantage of being rather easy to conduct since only 3-4 single use electrodes have to be attached to the patient. In addition, the measuring is less stressful for the patient as there is less sleep disturbance by the technical equipment. Using the ECG signal seems reasonable as sleep disordered breathing events are known to be associated with autonomic reactions such as increases in blood pressure or frequent cyclical variations in heart rate (CVHR) (72),(219). Recent advances in signal processing have shown that a reliable detection of SDB based on a single channel ECG is possible (31),(165).
Tracheal respiratory sounds convey important information about the pathology and physiology of the airway (159),(201). Yadollahi (225) and Nakano (148) pointed in that direction and concluded that the combination of both pulse oxymetry and tracheal sounds may result in higher sensitivity and specificity for sleep apnea detection.

The majority of research towards improving SAHS diagnosis is focused on the analysis of abnormal respiratory events. The analysis of snores and breath sounds deserves, undoubtedly, the top place on this research field (61),(91),(110),(209),(225).

Houdt (91) developed a robust algorithm for offline analysis of three common PSG nocturnal recordings: nasal airway pressure, thoracic and abdominal signals. He concluded that the characteristics of the half waves can be used to discriminate between normal and abnormal breathing (hypopneas and apneas). Kulkas (110) had the same purpose but he used only the tracheal sound signal and suggests a new tracheal sound feature for separating apnoea events from non apnoea time.

II.7 - Treatment

Regrettably, at present no method has shown to be able to eliminate SAHS in its whole. Nevertheless, there are various treatments that make possible to mitigate the effects of this syndrome by diminishing both its clinical manifestations and systemic repercussions. Due to the complex pathophysiology of SAHS, in which different factors may be causative, such treatments are focused on eliminating one or more of the drivers. Therefore, the choice of one treatment over another will be upon the type and severity of SAHS. In cases of mild SAHS simply reducing risk factors may be sufficient. For a moderate-severe SAHS the by far most effective treatment is the continuous positive airway pressure machine (CPAP).

It should be emphasized that the non treatment of patients with SAHS will imply resource consumption 2-3 times higher than a population without SAHS (182). The basis of any SAHS treatment is to reduce its risk factors, such as obesity, alcohol, central nervous system depressive drugs (benzodiazepine, narcotics or barbiturates), sleep deprivation, tobacco and supine position during sleep. These measurements serve as both the treatment of mild SAHS and as first step of any of the treatments that will be described further on (123).

The nasal continuous positive airway pressure therapy is currently the most important and effective treatment on suppressing apneas-hypopneas as well as their associated symptoms and potential complications. This technique consists in issuing airflow through a turbine connected to a nasal mask at a certain positive pressure (Figure 5). This increase in airflow at constant esophageal
pressure causes the UA resistance to decrease. This emitted airflow prevents the obstruction of the UA. On the other hand, lung volume also as influence on UA’s stability. A decreased lung volume causes a decrease in the pharyngeal airway calibre and an increase in both resistance and collapsibility of the UA. Therefore, the CPAP has an additional effect on the permeability of the UA (230). Despite its effectiveness, the CPAP treatment has certain problems concerning its acceptance and adhesion. Among the factors affecting adherence Yim et al. (230) emphasizes the symptomatic relief, initial experience, the side effects and social support. One of the most relevant side effects is congestion and rhinorrhea caused by the nasal dryness. Moreover, the less adaptive masks become more uncomfortable to use and cause skin lesions.

The MRAs (Mandibular Repositioning Appliances) are more the most suitable oral appliances for the treatment of mild-moderate SAHS (127). They enable shifting the mandible forward thereby increasing the space in the upper airway and preventing pharyngeal collapse. This movement stabilizes and clenches the jaw and the hyoid bone, preventing posterior rotation of these structures during supine position avoiding the obstruction of the UA (Figure 6). They can either be of fixed or adjustable. Its efficiency is higher than 50% in SAHS and between 70% and 80% in chronic snoring. MRA’s side effects are usually short term almost always disappear over time. These effects are caused by the obvious fact of introducing of a strange body in the mouth. An excessive salivation or dryness, teeth and jaw sensitivity and perception of an abnormal bite in the morning may also be common side effects.
Surgery is only applicable to very specific cases, where the collapse trigger factor is anatomic (27). There are three types of surgery: soft tissue surgery, surgery of the skeletal structure and tracheotomy. The major drawback associated with this technique is the fact that the collapse may be anywhere between the nasopharynx and the epiglottis and may occur at multiple locations depending on the sleep stage. Only 1-2% of SAHS patients have an abnormality located in a specific space so that corrective surgery can be performed. This technique is mainly used in patients with moderate-severe SAHS for whom other noninvasive techniques were not able to solve the problem.

A new technique for the treatment of obstructive sleep apnea is the electrical stimulation of the upper airway by applying periodic episodes of contraction and relaxation (reviewed by Randerath (175)). This stimulation aims to decrease the upper airway resistance based on the increased activity dilator muscles in wakefulness, on their fatigue and structural changes. Although the reduction in resistance using both surface and intraneuronal stimulators has been shown experimentally, there are adverse effects such as arousals, and therefore it is not recommended for clinical use.

Schicht and Pfeizer (206) reviewed the use of the pacemaker in SAHS patients with cardiac arrhythmias and concluded that atrial pacing is effective in patients with central SAHS and Cheyne-Stokes respiration. However, the results do not confirm its usefulness in the treatment of obstructive SAHS so far.
This thesis is a result of a collaboration with the Sleep Disorders Laboratory of the Hospital Universitari Germans Trias i Pujol (HUGTP) in Badalona, Spain, in the framework of the projects TEC2007-68076-C02-01 and TEC2010-21703-C03-01. Our database consists of a total 116 subjects and is composed of all PSG (polysomnography) nocturnal data and snoring sound signals that were acquired with a novel and pioneer system, Snoryzer Uno, which we will described with detail further on.

The organization of the database of signals had a major role on the development of the thesis. Not only it was time consuming but also demanded a regular collaboration with the sleep lab team and full knowledge of the software involved. More precisely, and in the case of the PSG visualization software, we invested great amount of time on understanding the impact it had on the medical doctors’ final diagnose and also exporting the database of signals.

**III.1 - Polysomnography**

As explained earlier on the II.6-Diagnosis section, full-night polysomnography is still recognized as the reference gold-standard for SAHS diagnosis. Patients that constitute this database underwent nocturnal PSG and were given a final SAHS diagnose. To submit the final diagnosis the medical doctor follows the next list of steps:

- Physical examination of the patient (II.6.1-Physical examination).
- Reviews, double-checks and corrects the whole night signal tracings, sleep staging and scored events already automatically performed by the PSG visualization software.
- Studies the report generated by the PSG software, paying special attention to the apnea-hypopnea index (AHI), sleep architecture, the oxygen desaturation index at 3% (3% ODI), number of respiratory arousals and the patient’s complaints of excessive daytime sleepiness and loud snoring (bed partner).
- Elaborates the final diagnose with 4 possibilities: no SAHS, mild SAHS, moderate SAHS or severe SAHS.

The Sleep Disorders Laboratory of the HUGTP used a computerized recording system (Compumedics E-Series Sleep System and ProFusion PSG 2, Melbourne, Australia) to record the full-night PSG tracings. The recordings consisted of: EEG data recorded with the symmetrical electrode positions C4, C3, A1, A2, O1 and O2 based on the standard international 10-20 system of electrode placement (183); left and right EOG; chin EMG; tibial EMG; three-lead electrocardiogram; oronasal airflow detection through a thermistor sensor and a nasal cannula/pressure transducer; oxygen saturation via pulse oximeter; thoracic and abdominal excursion (inductance plethysmography) and a microphone for the snoring signal.

The ProFusion PSG 2 (hereafter referred to as ProFusion PSG) is a software application which provides tools for the review, analysis, summary and reporting of PSG studies recorded with Compumedics Systems, thus assisting the sleep specialist in making a diagnosis regarding sleep disorders:

- **Simple Navigation and Information**: the physician can open one or more studies at the same time, visualize and edit patient’s details as well as view and edit the study information, including patient demographics (height, weight), supervising doctor, recording staff, hospital and recording parameters.

- **Views**:
  - **Rawdata**: displays representations of recorded inputs in the form of traces, events marked on the traces, and a hypnogram. It also contains a fully-featured toolbar which includes a variety of navigation aids, display configuration options, digital filtering and analysis features, as well as launching points for other views such as summary and companion applications such as digital video. The Rawdata view is divided into two distinct panes to allow for different timebase settings to be applied to different sets of traces (Figure 7).
  - **Summary**: the Summary view contains an epoch-by-epoch graphical representation of the study data, and is used for trend analysis. Using the Summary view, it is possible to quickly determine if any desaturations, snoring, leg movements or arousals have occurred during an epoch or range of epochs.
  - **Split Staging**: contains a synchronized display of both a single Rawdata pane and the Summary. It is best used for manual sleep staging.
- **SpO$_2$/TcCO$_2$:** the SpO$_2$ / TcCO$_2$ overview contains a condensed view of the SpO$_2$ / TcCO$_2$ traces, superimposed on each other. It spans the whole study, with one hour per line. This is useful for trend analysis.

- **Report:** the report that is automatically generated by the ProFusion software which includes the most important summary information, indices (IDH, AHI, etc), graphs and statistics from the current open study.

- **Scoring:** the physician may choose to manually score the events or to use the computer-assisted scoring. In the latter case, the physician has to initially enter the specific input assignments for scoring the following events: sleep staging (hypnogram), respiratory events (central, mixed, obstructive apneas, hypopneas, SpO$_2$ desaturation, respiratory artefact, etc), limb movements/PLM scoring, arousal events and arousal association (respiratory or spontaneous arousals), bradycardia and tachycardia scoring and heart rate artefact scoring. Nonetheless, the physician always has the possibility to manually add, reclassify or delete the events scored by the computer-assisted scoring before approving the final diagnosis report. And this was the routine performed on our subject’s database.

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Figure 7 Print screen of the ProFusion software. A 30 sec epoch of one of our subject’s PSG study is shown. Three panes are shown: on the upper one the hypnogram is displayed, on the middle one the EEG derivations, EOG, EMG and ECG signals are displayed and on the lower pane the SpO$_2$, cannula, thermistor, thorax, abdominal, snoring and tibial EMG tracings are displayed.
III.2 - Snoryzer

Snoryzer Uno system was developed by SIBEL S.A. (Barcelona, Spain) and by Jané et al. (94) of Universitat Politècnica de Catalunya (UPC) in collaboration with Servicio de Neumología de HUGTP (Badalona, Spain) and was used to record and analyse respiratory sounds during sleep.

The snoring sound signals were recorded using a unidirectional electric condenser microphone placed over the trachea at the level of the cricoids cartilage using an elastic band (60) thereby avoiding the recording of surrounding noise that has been reported to be fairly impairing (49), (104), (153). The sound signal was amplified and filtered using a second order Butterworth pass-band filter between 70 Hz and 2000 Hz and then digitized with a sampling frequency of 5000 Hz and a 12-bit analog/digital converter. The snoring episodes were then identified by a previously trained and validated automatic detector and analyser, developed by our research group (DLL Snore Analyser v9.52). The snoring detector was designed to identify snoring episodes from simple snorers and SAHS patients, and to reject respiratory sounds from regular inspiration and exhalation, cough, voice, and other artefacts (61), (95). The detector is composed of two components: the segmentation and the classification subsystems. The segmentation subsystem establishes the time boundaries of possible snoring episodes. The classification subsystem is based on a two-layer feedforward multilayer neural network, with 22 inputs and 50 neurons in the hidden layer. The output layer has two neurons that show presence or absence of snore. The input pattern consists of 22 temporal and spectral features of the sound segment. This pattern allows the distinction between snoring sound and the remaining respiratory sounds. Therefore, the detector identifies the snoring episode and defines automatically the time boundaries of the event (a snoring episode can have the minimum and maximum duration of 100 ms and 10 s, respectively). In this way, it is possible to automatically analyse the snoring events during a sleep study on a snore-by-snore basis. The snoring detector was validated (60), (95), (96) by means of a database of 948 episodes that were annotated by a medical doctor. This manual annotation included non-apneic snores, inspiration and exhalation sounds, voice, cough, and noise artefacts.

The analysis of respiratory sounds also enables to identify the apnea episodes through the reduction of signal’s power level, allowing therefore the calculation of the apnea index. An apnea episode is defined as the reduction of the signal power under a certain threshold for time period equal or greater than 10 s (the threshold is automatically determined in the beginning of the
recording and is thus dependent of the patient’s breathing sound level and also of the ambient surrounding noise).

The patient’s position was simultaneously captured and digitized using an abdominal sensor. The oxygen saturation in the subject’s blood was also measured by a pulse oximetry sensor. The Snoryzer Uno equipment was primarily designed for home use. The system’s setting up is easy as the patient only has to set the bands and place the sensor on himself, press a button and go to sleep. On the next morning he simply has to press the button once again to stop the recording and return the system back to the hospital (Figure 8).

![Snoryzer Uno equipment](image)

Figure 8 Snoryzer Uno equipment: A - acquisition system, B - tracheal microphone, C - chest band, D - microphone wrapping band, E - pulse oxymeter sensor, F - adhesive for fixation of the pulse oxymeter sensor (from SIBEL S.A.).

Through the number of snores, their frequency characteristics (as well as other parameters) and the detected apneas, Snoryzer Uno is able to present a diagnosis proposal indicating the subject’s probability of SAHS while it automatically generates a report containing the patient and study information as well as several parameters (snore number; total snoring time; mean and maximum snore sound intensity; peak, mean and maximum snore sound frequency; relevant power ratios; oxygen desaturation index; total number of apneas, etc) statistics and tendency plots.

In summary, Snoryzer Uno’s analysis software offers the following possibilities:

- Handles different databases of subjects in a fairly easy way.
- Registers and labels each event (snores, post apneic snores and apneas).
- Generates an output file exposing all parameters (mean, maximum sound intensity; peak, mean and maximum frequency, power ratios, etc) per event.
- Allows exporting the recorded signals with .DAT format.
Enable the visualization of the acquired snoring sound signal (and the other simultaneously acquired signals). The configuration of the signals can also be changed by using a configuration panel where the number of channels, horizontal and vertical zooming and time display can be easily altered (Figure 9).

- Enables the sound reproduction of segment of the signal.
- Generates a printed report with the alphanumerical results and the test analysis plots.
- Enables the visualization of the spectral analysis of a selected segment from the signal.

Figure 9 Example of a 2 minutes registration with Snoryzer Uno. The superior panel shows the respiratory sound signal where one can observe the labeled snores as well as 3 apnea episodes. The second panel shows the oximetry signal where the desaturations indicate that an apnea has just occurred. The third panel shows the sleeping position and the last panel shows the detected snoring episodes (the height of the bar indicates the snore episode intensity).
**III.2.1 - Snoryzer Uno (S1) on automatic snoring analysis**

Snoryzer Uno (S1) analysis system is used to monitor snoring during full-night studies and to classify subjects according to their AHI. The S1 system as recently been applied to assess whether the acoustic characteristics of snores differ in patients with and without SAHS, and to classify subjects according to their AHI (61). There were significant differences in supine position between Group 1 (AHI<5 h⁻¹) and Group 3 (AHI≥15h⁻¹) in: sound intensity; number of snores; standard deviation of the spectrum; power ratio in bands 0–500, 100–500, and 0–800Hz; and the symmetry coefficient ($p<0.03$). The 37 patients were classified with thresholds AHI=5 and AHI=15 with a sensitivity (specificity) of 87% (71%) and 80% (90%), respectively. Another study was designed to assess the utility of S1 system for screening patients with SAHS, by using mainly snoring information (94). A full PSG or RP were used as a gold standard methodology for diagnosis of SAHS patients. PSG, or RP, and S1 recording were performed on 35 subjects (11 no SAHS subjects, 7 mild, 5 moderate and 12 severe patients). Both systems (PSG/RP and S1) were used independently at the hospital and at home, respectively, and the estimation of AHI diagnosis was compared. The S1 system classified subjects on 4 SAHS severity levels (No SAHS, mild, moderate and severe). The S1 was able to correctly classify 77% of subjects in the 4 severity levels. The sensitivity and specificity of S1, based on snoring analysis and apnea detection, to identify healthy subjects from pathologic patients (mild to severe SAHS) were 83% and 100%, respectively. Besides, the apnea index (AI) obtained with S1 correlated with the obtained by PSG or PR ($r=0.87$, $p<0.05$). A novel recent work was published by our group, again using the S1 system on a database of 36 subjects (195). In this work, an accurate multiclass classification of snoring subjects, with three levels of SAHS (C1, AHI<5; C2, $\leq$AHI<30; C3, AHI≥30h⁻¹), was achieved on the basis of acoustic analysis of snoring alone, without any requiring information on the duration or the number of apneas. For that purpose, the Bayes model using a kernel density estimation method proved to be the best multiclass snore-based classification approach and allowed the early stratification of subjects according to their severity.

**III.3 - Database**

Our database consists of a total 116 subjects and is composed of PSG nocturnal data and snoring sound signals that were acquired with Snoryzer Uno. All subjects gave their informed consent to the study, which was approved by the research ethics committee of the HUGTP. The subjects were free of any upper airway infection and other diseases throughout the study. This database is different from the ones used on our groups’ previous publications (previously described on the former section: **III.2.1-Snoryzer Uno (S1) on automatic snoring analysis**).
The database of signals along with the subjects’ information was provided by the sleep lab team of the HUGTP. Unfortunately, and due to factors beyond us, for some subjects we do not dispose of their entire information, so in that case we labelled those situations as *missing values* (Table 3). In summary, our database consists of 89 males and 24 females (with 3 subjects for whom we do not have the gender info) with AHI range of 0.2h⁻¹ -122.7h⁻¹. Further detail on relevant sleep variables’ statistics is given in Table 3.

<table>
<thead>
<tr>
<th>Age</th>
<th>BMI</th>
<th>AHI</th>
<th>AI</th>
<th>HI</th>
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<tbody>
<tr>
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<td>49.5</td>
<td>28.7</td>
<td>38.2</td>
<td>22.5</td>
<td>16.1</td>
</tr>
<tr>
<td>sd</td>
<td>11.7</td>
<td>4.2</td>
<td>28.7</td>
<td>24.2</td>
<td>13.1</td>
</tr>
<tr>
<td>Miss. val.</td>
<td>3</td>
<td>14</td>
<td>3</td>
<td>2</td>
<td>3</td>
</tr>
</tbody>
</table>

Table 3 Database statistics for most relevant sleep variables. m=mean value. sd=standard deviation. Miss. val. = missing values. BMI = body mass index in kg/m²; AHI, AI (Apnea index) and HI (Hypopnea Index) in h⁻¹. N Snore = the number of snores.
IV - Snoring

IV.1 - Snoring as tool for SAHS screening and diagnosis

Snoring is a sound produced by vibration of the soft tissues of the upper airway during sleep. It usually occurs during inspiration, but can also occur during expiration (74). Habitual snoring is common, occurring in 44% of males and 28% of females who are between 30 and 60 years of age in the general population (239). Occasional snoring is almost universal (10).

Objective assessment of snoring is important not only to evaluate the effect of treatment interventions but also with the purpose of screening SAHS. Because snoring carries information relating to the site and degree of obstruction of the upper airway, comparative research of visual and acoustic assessment techniques on snoring has been incited by the belief that sound analysis by itself could disclose plenty information on SAHS disease (168).

The upper airway commences at the oral and nasal openings, while at the other end it divides into the tracheal and esophageal passageways. The upper airway has a complex geometry, and is enclosed by muscles and mobile nonmuscular structures that are able to alter airway configuration. The major respiratory function of the upper airway is to permit air movement into and out of the lungs. In addition, the upper airway heats and humidifies inspired air, and is important in the regulation of both inspiratory and expiratory airflow. Under resting conditions including sleep, air flows through the nose, pharynx and larynx to the extrathoracic trachea. When airflow increases, as during heavy exercise or with nasal obstruction, breathing occurs through the mouth in addition to the nose, and hence the oral cavity is also part of the upper airway.

Upper airway size and resistance vary dynamically throughout the respiratory cycle and are also affected by the route of breathing (oral vs. nasal) (189), lung volume, level of ventilation, hypoxia and hypercapnia and behavioural state (conscious vs. unconscious and wakefulness vs. sleep). In addition, upper airway resistance can increase the work of the inspiratory muscles in producing airflow.

The pathophysiology of the upper airway obstruction has been previously described on the II.4-Pathophysiology section. To further elucidate the mechanism for upper airway obstruction,
investigators have examined airflow dynamics during periods of obstruction, and found that pressure-flow relationships were identical to those previously described for other collapsible biologic conduits, i.e. the Starling resistor \((69), (173)\). This model provides a generalized approach for determining the critical pressure during inspiration, based on an analysis of pressure-flow relationships in the upper airway segment. A major feature of this model is that it describes the conditions leading to alterations in upper airway patency. Specifically, the model predicts that the airway would completely occlude whenever pressures both upstream (nasal, \(P_{us}\)) and downstream (hypopharyngeal, \(P_{ds}\)) fall below a critical pressure (\(P_{crit}\)). A good review on the Starling resistor model was recently published by Kirkness et al. \((107)\).

Snoring is caused by upper airway obstruction, which is largely related to an increased propensity to atonia of the upper airway dilator muscles during sleep which in turn induces narrowing and increased resistance at this level \((194)\). As a consequence, airflow becomes turbulent and the pharyngeal tissues vibrate as the air passes through. More specifically, snoring is characterized by oscillations of the soft palate, pharyngeal walls, epiglottis and tongue \((116),(120)\). Snoring is associated with conditions that narrow the upper airway, including obesity, nasal congestion, craniofacial abnormalities, hypothyroidism, acromegaly, and adenotonsillar hypertrophy. Besides these anatomic predisposing factors, alterations on the neuromuscular reflexes, pulmonary and upper airway mechanoreceptors as well as chemoreceptors may be responsible for modifying the upper airway dilator muscle activity and consequently lead to snoring \((141),(215)\).

Snoring is, obviously, not only a disturbance for the bed partner and a significant social problem, but also, definitely, a sign of pathology which can range from "of little importance", as in light and initial forms of snoring, to "extremely important" when it is continuous (every night) and heavy \((43)\). Snoring assumes particular characteristics, besides being a sign of pathology it can also be a trigger or causative factor. A recent study indicates that snoring can become a trigger or cause of carotid artery atherosclerosis \((115)\), in addition to being associated with other cardiovascular diseases that are clinical outcomes of SAHS \((229)\).

The gold standard for diagnosing SAHS is the overnight polysomnographic study performed at the hospital. Recently, several authors have suggested simplified methods to aid the screening of SAHS based on a reduced number of signals \((37),(62)\) – or even a single one– such as ECG \((1),(106)\), pulse oximetry \((225)\), breath sounds \((110),(226)\), snore sounds \((61),(195)\) or nasal airway pressure \((91)\). A more detailed review of the latest techniques being applied to SAHS diagnosis was already provided on II.6.5-State of the art on SAHS diagnosis section.
Snoring is known to be an important clinical hallmark of SAHS (10),(168). As such, it is a useful and an easily accessible signal to screen this disease. Acoustic analysis of snoring reveals information relating to the site and degree of obstruction of the upper airway. For this reason, research studies on automatic detection and classification of snore sounds have received considerable attention recently (2),(61),(95),(151),(195),(209),(226). Several acoustic markers have proven to be able to discriminate between simple snorers and SAHS patients. These markers include, but are not limited to, pitch (105); formant frequencies (152); peak frequencies (60),(151); soft phonation index and noise-to-harmonics ratio (80) and even psychoacoustic metrics in terms of loudness, sharpness, roughness and annoyance (48),(86) (see II.6.4-Acoustic systems section).

Concealed acoustic information in snoring events that points to the presence of SAHS is an ongoing line of research and was pioneering in the sleep medicine field. But sometimes the question, however, is not the presence or absence, but the degree of SAHS (168). We believe that other less complex approaches mostly based on time domain parameters, as an alternative to the aforementioned acoustic analysis of snores, may provide answers to this question.

Pevernagie et al. (168) stated that by convention, a distinction is made between steady snoring, which shows little variation and little or no interruptions, and the irregular snoring that characterizes the resumption of breathing in between obstructive apneas. The first hint for acoustic differences between these two phenomena was provided by Perez Padilla et al. (166) and followed by Xu et al. (224). They found that the spectrum of this first snoring immediately after an apnea was most distinct from that of all other snoring episodes. In more detail, Perez-Padilla et al. (166) affirms that the first post-apneic snore consists mainly of broad-band white noise with relatively more power at higher frequencies, so that the ratio of power above 800 Hz to power below 800 Hz can be used to separate snorers from patients with SAHS. Xu et al. (224) found differences, for some frequency and spectral parameters, between first snores after upper and lower soft palate level obstructive sleep apneas. They have shown that the mean of peak frequencies, central frequencies, and proportions of energy from 800 Hz to 2000 Hz and above 2000 Hz of the first snoring sounds after lower level obstructive apneas were higher and the proportion of energy below 800 Hz was lower than those after upper level obstructive apneas.

IV.1.1 - A new approach on SAHS diagnosis

Motivated by the former studies, we decided to further investigate on this notion that different types of snoring can be observed on a same subject during a night sleep. The abovementioned works reported significant differences between post-apneic (snores that are
produced immediately after an apnea) and all remaining snores. Nevertheless, we consider the separation in these two groups to be insufficient. For that reason we proposed a new methodology for classifying two distinct types of snores: non-regular and regular snores. Non-regular snores are the ones separated by an apnea event and/or by non-snoring breathing cycles. Regular snores are truly consecutive snores, i.e., snores that are produced in consecutive breathing cycles, without interruptions.

Cavusoglu et al. (36) and our group’s previous work (196) had tried to identify these two kinds of snores through studying snore episode separations (SES) between successive snoring episodes in the same snoring state. However, they did not succeed in finding a proper criterion because they considered a separation of less than 10 seconds to be sufficient. According to their methods, the analysis of regular snores included successive snores that are interrupted either by normal breathing cycles or by apneas that last less than 10 seconds. Even though their results shown the strong potential of SES on distinguishing simple snorers from SAHS patients, no classification results were reported for their database of subjects.

It is important to note that snoring does not have a fixed and constant occurrence, since it is subject to many influences such as body position, sleep stages, route of breathing (oral, nasal, or both) and the degree and site of upper airway narrowing (168). Not all snoring episodes have the same characteristics and trigger mechanisms during sleep, akin to what happens with the breathing pattern, which changes and shows irregularities during the lighter sleep stages (19). In this way, it is crucial to make a distinction between regular snores and non-regular snores. We overcame the issues found by Cavusoglu et al. (36) and our group’s previous work (196) by proposing the application of an adaptive threshold to the all night sequence of time interval between snores. The adaptive threshold is able to identify regular and non-regular snores and also the two snoring patterns that comprise regular snores: SP1 and SP2. The first is the single snoring pattern: when the subject snores once per breathing cycle and the second is the double pattern: when the subject snores both in inhalation and exhalation.

After having developed the adaptive threshold method and subsequently identifying the two different kinds of snores we were able to show that they enclose key information on SAHS severity. Furthermore, to do so, we propose more simplified methods than the ones currently being used in the field of acoustic analysis of snoring episodes. For instance, the results we obtained with the features derived from the time interval between regular snores suggest that the method can be a helpful aid for the early screening and severity estimation of subjects suspected of having SAHS. In addition, it can be easily integrated in any portable and low-cost bedside monitor since it only requires the recording of the snoring sound signal.
IV.2 - Classification of subjects with and without SAHS by means of a single-channel device for respiratory sounds analysis

Our first preliminary studies (136) were performed on database of 73 subjects and results showed that snoring sound intensity and its variability were able to discriminate 13 simple snorers (AHI ≤ 10) from 60 SAHS patients (AHI > 10) (Table 4). Results obtained with snoring sound intensity values show, for patients with AHI ≤ 10, the mean sound intensity was 47.6±4.03 dB-SPL, whereas for patients with AHI > 10, the mean sound intensity achieved was 53.7±6.72 dB-SPL (p=0.00026). Results also showed significant increasing tendency of the mean sound intensity and its variability with increasing AHI of the subject (Figure 10).

<table>
<thead>
<tr>
<th></th>
<th>13 simple snorers (8F, 5M)</th>
<th>60 SAHS subjects (7F, 53M)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>41.5±12.7</td>
<td>51.3±10</td>
</tr>
<tr>
<td>BMI</td>
<td>25.6±2.8</td>
<td>29±3.4</td>
</tr>
<tr>
<td>AHI</td>
<td>5.5±3.2</td>
<td>45.5±27.4</td>
</tr>
<tr>
<td>I Mean</td>
<td>47.6±4.03</td>
<td>53.7±6.72</td>
</tr>
<tr>
<td>N Snore</td>
<td>1049±1080</td>
<td>2211±1191</td>
</tr>
<tr>
<td>Tot Snores</td>
<td>13645</td>
<td>132667</td>
</tr>
</tbody>
</table>

Table 4 Database statistics for the 73 subjects database with a total of 146312 snores: 13 simple snorers (with AHI ≤ 10) and 60 SAHS subjects (with AHI > 10). F=female. M=male. Results are in m±sd=mean ±standard deviation. BMI = body mass index in kg/m²; AHI in h⁻¹. I Mean = mean sound intensity in dB-SPL. N Snore = number of snores. Tot Snores= sum of total number of snores per group.

Figure 10 Mean snore sound intensity of each snoring episode over all night recording. Two SAHS subjects: a) and b) with 2641 and 4011 snores, respectively. Simple snorer,c) with 1014 snores.
**IV.3 - Regular and non-regular snores**

As an alternative to the aforementioned, widely used acoustic analysis of snoring episodes Cavusoglu et al. (36) and our group’s previous work (196) proposed the study of snore episode separations (SES) between successive snoring episodes in the same snoring state. Since they did not succeed on automatically identifying the snoring states, they suggested overcoming this issue by considering only separations less than 10 seconds.

Snoring does not have a fixed and constant occurrence, since it is subject to many influences such as body position, sleep stages, route of breathing (oral, nasal, or both) and the degree and site of upper airway narrowing (168). Not all snoring episodes have the same characteristics and trigger mechanisms during sleep, akin to what happens with the breathing pattern, which changes and shows irregularities during the lighter sleep stages (19). In this way, it is crucial to make a distinction between two different types of snores: the ones that are successive and produced in consecutive breathing cycles –*regular snores*– and the ones that are separated by non-snoring breathing cycles and/or apneas –*non-regular snores*. Given that neither Cavusoglu et al. (36) nor our group’s previous work (196) identified these two kinds of snores we felt propelled to develop a method that was able to do so. Furthermore, we were convinced that underlying information on these two kinds of snores could help on the diagnosis and screening of SAHS severity.

In this part of the work we were essentially interested in showing that relevant information on the severity of SAHS can be estimated by the simple analysis of the time interval between regular and non regular snores, without the need to resort to any complementary and likely more complex, acoustic analysis of snores.

**IV.3.1 - Adaptive threshold**

According to the previously mentioned methods (36),(196), that tried to introduce the concept of regular snores, the analysis of regular snores included successive snores that are interrupted either by normal breathing cycles or by apneas that last less than 10 seconds. This 10-second threshold \(TH_{10}\) is based in the accepted convention that an airflow cessation that lasts more than 10 seconds is scored as an apnea (9). Nonetheless, the HUGTPs’ sleep lab team, supported by other recent publications such as Otero et al. (156), highly recommends the scoring of airflow cessations of more than 6 seconds as apneas as well.

In Figure 11 an excerpt of snoring sound signal is shown. According to the former regular snore definition \(TH_{10}\) all snores except S3 would be classified as regular snores. However, we believe that S5 should also be identified as a non-regular snore since it is not produced in the
consecutive breathing cycle. Thus, as our definition of these two episodes goes beyond the 10-second threshold we wanted to be able to identify and correctly distinguish regular snores from non-regular snores. So, for that purpose we build two different thresholds (137): the median threshold ($TH_{\text{median}}$) and the adaptive threshold ($TH_{\text{adaptive}}$).

Figure 11 Excerpt of snoring sound signal. TI is the time interval between successive snores. Green boxes indicate snores episodes and the red box indicates an apnea episode.

**IV.3.1.1 - Database**

Snoring sound signals were acquired simultaneously with PSG using the S1 system. Snoring episodes and their time boundaries were identified by the previously trained and validated automatic detector and analyser developed by our research group for the S1 system (described in detail on the *III.2-Snoryzer* section).

The database used on the validation of the thresholds consisted of 34 subjects (8 females and 26 males) with age range of 37–72 years, AHI range of 3.7–109.9 h$^{-1}$ and a total of 74439 snores. This database is part of the 116 subjects’ database previously described on *III.3-Database* section. All subjects were free of any upper airway infection and other diseases throughout the study, and none had undergone treatment for snoring or were taking any medication at the time of data collection. The study was approved by the research ethics committee of the HUGTP and informed consent was obtained from all patients. The characteristics of the database are described in Table 5.

<table>
<thead>
<tr>
<th></th>
<th>Age</th>
<th>BMI</th>
<th>AHI</th>
<th>N Snore</th>
<th>Nr Subj</th>
</tr>
</thead>
<tbody>
<tr>
<td>$m$</td>
<td>50</td>
<td>28.5</td>
<td>37.6</td>
<td>2190</td>
<td>34</td>
</tr>
<tr>
<td>$sd$</td>
<td>10</td>
<td>3.9</td>
<td>30.1</td>
<td>937</td>
<td>(8F, 26 M)</td>
</tr>
</tbody>
</table>

Table 5 Database characteristics.
IV.3.1.2 - Threshold definition and application

Let $T_I$ be the time interval between successive snores, calculated as the time interval between the onset of a snore and the onset of its previous one (Figure 11):

$$ T_I(i) = S_{\text{onset}}(i) - S_{\text{onset}}(i-1) \quad i = 1, ..., NSn $$

(1)

where $S_{\text{onset}}(i)$ is the onset of the detected $i$th snore $S(i)$ and $NSn$ is the total number of detected snores.

The median threshold is a fixed threshold and is defined as follows (Figure 12):

$$ T_{I10}(i) = \{ T_I(i) | T_I(i) < 10 \} $$

(2)

$$ TH_{\text{median}}(i) = \text{Median}(T_{I10}) + \text{Std}(T_{I10}) $$

(3)

The adaptive threshold ($TH_{\text{adaptive}}$) is able to identify snoring episodes that are truly consecutive, i.e., two snores that are neither separated by an apnea event nor separated by non-snoring breathing cycles. This threshold is adaptively estimated from the whole night sequence of time intervals between successive snores. As a result, it is characteristic of the particular snoring pattern of each subject. To compute the threshold only one initial condition is set: the threshold is initialized with value 10 ($\Theta = 10$ seconds) because the first few snores produced during sleep are not descriptive of the subjects’ snoring pattern during the night and could introduce initial bias. The 10 seconds choice is justified by the accepted convention that the airflow cessation that lasts more than 10 seconds is scored as an apnea (9),(36),(196). As such, the adaptive threshold is defined as follows:

$$ TH_{\text{adaptive}}(i) = \begin{cases} \theta, & i < 10 \\ A, & \text{otherwise} \end{cases} $$

where

$$ A = H[TH_{\text{adaptive}}(i-1) - T_I(i)] \times B(i) + (1 - H[TH_{\text{adaptive}}(i-1) - T_I(i)]) \times TH_{\text{adaptive}}(i-1) $$

$$ B(i) = (1 - \delta) \times \frac{\sum_{k=1}^{i-1} T_I(k)}{i-1} + \delta \times \frac{\sum_{k=1}^{i} T_I(k)}{i} $$

(4)

$\delta$ is the significance assigned to $i$th $T_I$ for computing the adaptive threshold $TH_{\text{adaptive}}(i)$ at the $i$th snore with value 0.1, and $H[\beta]$ is the Heaviside step function, whose value is 0 for $\beta < 0$ ($T_I(i) > TH_{\text{adaptive}}(i-1)$) and 1 for $\beta \geq 0$ ($T_I(i) \leq TH_{\text{adaptive}}(i-1)$).

On our first results’ publication (137) we proved that $TH_{\text{adaptive}}$ outperformed $TH_{\text{median}}$ on that purpose of identifying regular and non regular snores. This is illustrated in the example given in Figure 12, where $TH_{\text{adaptive}}$ is able to identify S4 as a non regular snore. In addition to this, features extracted from the regular snores identified by the adaptive threshold showed to be able to distinguish between subjects with opposite levels of SAHS severity and this situation was not seen for the case of $TH_{\text{median}}$ (IV.4-Regular and non-regular snore features as markers of SAHS section).

This was not surprising given that the former takes into account the evolution of $T_I(i)$ through all night sleep as it is based on the concept of an adaptive estimation.
Figure 12. Performance a) (and zoom b)) of $TH_{\text{adaptive}}$ and $TH_{\text{median}}$ on an excerpt of snoring sound signal shown in c).
The results obtained in this first publication exposed what Rappai et al. (176) had suggested a few years ago when affirming that although snoring is mostly seen in the inspiratory phase it can also be present in the exhalation phase. Thus, within regular snores two kinds of snoring pattern are enclosed:

- **SP1**: single pattern, when the subject snores once per breathing cycle, while inhaling or while exhaling;
- **SP2**: double pattern, when the subject snores both in inhalation and exhalation of the same breathing cycle.

Figure 13 shows five breathing cycles. SP1 is present on the two first breathing cycles and SP2 is present on the last three. S7 and S8 correspond, respectively, to inhaling and exhaling snores of the same breathing cycle. Hence, they constitute the snoring pattern SP2, where S7 has a longer time interval (TIL) and S8 has a shorter time interval (TIS).

This propelled us to create two different thresholds (from our previously described $TH_{\text{adaptive}}$)

- **LoTHadaptive**: where the significance assigned to the $i$th TI is $\delta=0.1$;
- **HiTHadaptive**: where the significance assigned to the $i$th TI is $\delta=0.5$.

We tested $\delta$ values until optimization was achieved. For all subjects the best performance of both thresholds ($LoTH_{\text{adaptive}}$ and $HiTH_{\text{adaptive}}$) on identifying the two snoring patterns was achieved with the values 0.1 and 0.5, respectively.

Regular snores are defined as the ones for which $\text{TI}(i) < HiTH_{\text{adaptive}}(i)$. Consequently, non-regular snores are defined as the ones for which $\text{TI}(i) \geq HiTH_{\text{adaptive}}(i)$.

Figure 14 shows an example of a short segment of a snoring sound signal with 9 detected snores. The performance of $LoTH_{\text{adaptive}}$ and $HiTH_{\text{adaptive}}$ on this segment is shown in Figure 15, where the asterisk markers under the solid line ($HiTH_{\text{adaptive}}$) and above the dashed line ($LoTH_{\text{adaptive}}$) correspond to snores that are selected by the combination of both thresholds. The dot markers under the dashed line ($LoTH_{\text{adaptive}}$) are the snores selected by this lower threshold.
The time intervals between the successive snores T1, T5 and T8 correspond to: snoring pattern SP1, snoring pattern SP2 and non-regular snore, respectively. S(i) and S(i+1) occur on two consecutive breathing cycles, so S(i+1) corresponds to the pattern SP1. S(i+4) and S(i+5) occur, respectively, on the inhalation and exhalation events of the same breathing cycle and thus compose the pattern SP2. S(i+7) is a post-apneic snore, so it is classified as a non-regular snore. Normal breathing cycles (non-snoring) occur between snores S(i+7) and S(i+8), hence S(i+8) is a non-regular snore.

Figure 14 Example of an excerpt of a snoring sound signal from a subject in our database. The small boxes correspond to snore episodes. The two wider boxes correspond to two apnea episodes. T1, T3, T5 and T8 are the time intervals between the snores: S(i) and S(i+1), S(i+2) and S(i+3), S(i+4) and S(i+5), S(i+7) and S(i+8), respectively.

Figure 15 Performance of LoTH\textsubscript{adaptive} and HiTH\textsubscript{adaptive} on the time interval between successive snores Ti(i) of the short segment signal shown in Figure 14.
Chapter IV - Snoring

IV.4 - Regular and non-regular snore features as markers of SAHS

In this part of the work we introduced the concept of regular and non-regular snores alongside with the development of the adaptive threshold (137). Furthermore, the purpose was also to study the characteristics of these two kinds of snores and investigate their potential on screening subjects with SAHS.

We applied $TH_{\text{adaptive}}$ and $TH_{\text{median}}$ to the TI($i$) (eq. (1)) of each of the 34 subjects.

Let $R_{TI}(i)$ be the time interval between successive regular snores:

$$R_{TI_{\text{adaptive}}}(i) = TI(i) | TI(i) < TH_{\text{adaptive}}(i)$$

$$(5)$$

$$R_{TI_{\text{median}}}(i) = TI(i) | TI < TH_{\text{median}}$$

$$(6)$$

where $TH_{\text{adaptive}}$ (defined in eq. (4)) has $\delta$ value of 0.1.

Let $A_{\text{Snores}}$, $R_{\text{Snores}}$ and $NR_{\text{Snores}}$ be all snores, the selected regular snores and non-regular snores, respectively:

$$A_{\text{Snores}}_{\text{adaptive}} = \{S(i)\}$$

$$(7)$$

$$R_{\text{Snores}}_{\text{adaptive}} = \{S(i) | R_{TI_{\text{adaptive}}}(i)\}$$

$$(8)$$

$$NR_{\text{Snores}}_{\text{adaptive}} = \{S(i) | S(i) \notin R_{\text{Snores}}_{\text{adaptive}}\}$$

$$(9)$$

IV.4.1 - Parameters and features of snores

The parameters studied were: $R_{TI}(i)$, the time interval between successive regular snores, and $IMean(i)$(dB SPL), the mean snore sound intensity of $S(i)$. The features computed from each parameter are shown in Table 6.

<table>
<thead>
<tr>
<th>Name</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>M</td>
<td>Mean value</td>
</tr>
<tr>
<td>Std</td>
<td>Standard Deviation</td>
</tr>
<tr>
<td>CV</td>
<td>Coefficient of Variation</td>
</tr>
<tr>
<td>p25</td>
<td>25th percentile</td>
</tr>
<tr>
<td>p50</td>
<td>50th percentile</td>
</tr>
<tr>
<td>p75</td>
<td>75th percentile</td>
</tr>
<tr>
<td>Mode</td>
<td>Mode</td>
</tr>
<tr>
<td>sIQ</td>
<td>Semi-Interquartile Range</td>
</tr>
<tr>
<td>Kurt</td>
<td>Kurtosis of the probability distribution</td>
</tr>
<tr>
<td>Skew</td>
<td>Skewness of the probability distribution</td>
</tr>
<tr>
<td>Max</td>
<td>Maximum value</td>
</tr>
<tr>
<td>RMS</td>
<td>Root mean square</td>
</tr>
</tbody>
</table>

Table 6 Features derived from each parameter.
Chapter IV - Snoring

The database used has been properly described in IV.3.1.1-Database section. However, the results we will describe below demand a more detailed description of the subjects. Namely, with the 34 subjects divided according to two cut-points of severity: 10h⁻¹ (Table 7) and 30h⁻¹ (Table 8).

![Table 7 Database characteristics divided in two groups with opposite levels of severity (above and under 10h⁻¹). G AHI = group of subjects with AHI under and above 10h⁻¹.](image)

<table>
<thead>
<tr>
<th></th>
<th>Age</th>
<th>BMI</th>
<th>AHI</th>
<th>N Snore</th>
<th>Nr Subj</th>
</tr>
</thead>
<tbody>
<tr>
<td>G AHI &lt; 10</td>
<td>47</td>
<td>26.12</td>
<td>5.0</td>
<td>1547</td>
<td>7 (4 F, 3M)</td>
</tr>
<tr>
<td>m</td>
<td>6</td>
<td>2.8</td>
<td>1.9</td>
<td>880</td>
<td></td>
</tr>
<tr>
<td>G AHI ≥ 10</td>
<td>52</td>
<td>29.11</td>
<td>46.1</td>
<td>2357</td>
<td>27 (4 F, 23M)</td>
</tr>
<tr>
<td>m</td>
<td>11</td>
<td>4.0</td>
<td>28.1</td>
<td>892</td>
<td></td>
</tr>
</tbody>
</table>

![Table 8 Database characteristics divided in two groups with opposite levels of severity (above and under 30h⁻¹). G AHI = group of subjects with AHI under and above 30h⁻¹.](image)

<table>
<thead>
<tr>
<th></th>
<th>Age</th>
<th>BMI</th>
<th>AHI</th>
<th>N Snore</th>
<th>Nr Subj</th>
</tr>
</thead>
<tbody>
<tr>
<td>G AHI &lt; 30</td>
<td>50</td>
<td>26.3</td>
<td>11.8</td>
<td>1752</td>
<td>16 (7 F, 9M)</td>
</tr>
<tr>
<td>m</td>
<td>12</td>
<td>2.8</td>
<td>8.3</td>
<td>877</td>
<td></td>
</tr>
<tr>
<td>G AHI ≥ 30</td>
<td>52</td>
<td>30.4</td>
<td>60.5</td>
<td>2580</td>
<td>18 (1 F, 17M)</td>
</tr>
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**IV.4.2 - Results**

In the case of TH<sub>adaptive</sub> the M, p75, Skew and RMS features were significantly different in subjects with AHI<30h⁻¹ and in subjects with AHI≥30h⁻¹, with statistical significance p<0.001 in the Mann-Whitney U test (Table 9a). Moreover, the results were also favourable for the Std and sIQ features when distinguishing between groups of subjects with AHI above and under 5h⁻¹ and 10h⁻¹ (p<0.05).

For the R_Ti(i) selected after applying TH<sub>median</sub>, the features did not perform such good results (Table 9b). The p-values obtained for all features while differentiating between subjects with AHI of 5, 10 and 15 h⁻¹ did not have statistical significance (p>0.05). The only significant differences (p<0.05) were obtained for seven features when comparing the groups of subjects with AHI above and under 30h⁻¹.
Chapter IV - Snoring  J.M.G. Mesquita

<table>
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Table 9 Statistical significance of a) \( R_{TI_{adaptive}}(l) \) and b) \( R_{TI_{median}}(l) \) features on distinguishing subjects from opposite levels of SAHS severity. \( p_X \): Statistical Significance in Mann-Whitney U Test. Subjects with AHI under \( X \) from subjects with AHI above \( X \). G AHI < 30: group of subjects with AHI under 30h\(^{-1}\), G AHI ≥ 30: group of subjects with AHI above 30h\(^{-1}\).

To observe in what extent the \( TH_{adaptive} \) offered better results, we computed the histograms of the \( R_{TI_{adaptive}} \) for all 34 subjects. The average of the histogram envelopes were calculated and drawn for two groups with different levels of severity: AHI<10h\(^{-1}\), AHI<15h\(^{-1}\) and AHI<30h\(^{-1}\) (Figure 16 a), b) and c), respectively). We can observe clear differences between the shape of the envelopes of subjects with AHI above and under 15h\(^{-1}\) and 30h\(^{-1}\), which also confirm the \( p \)-values obtained. Moreover, we can observe that the number of \( R_{TI} \) events under 1 second is much higher for subjects with AHI greater than 15h\(^{-1}\) or 30h\(^{-1}\). This indicates that most severe patients tend to snore in consecutive breathing events, i.e. they snore in consecutive inspiration and exhalation events.

Since \( TH_{adaptive} \) performed better than \( TH_{median} \) we decided to analyse \( R_{Snores_{adaptive}} \) and \( NR_{Snores_{adaptive}} \). In the case of \( R_{Snores_{adaptive}} \), there was only one \( Imean \) feature for which the \( p \)-value was under 0.05 significance level, Mode, and uniquely for 5, 10 and 15 h\(^{-1}\) cut-points of severity (Table 10 a)). On the other hand, there are 6 \( Imean \) features derived from non-regular snores that show high statistically significant differences (\( p<0.001 \)) between subjects from contrasting groups of AHI severity (Table 10 b)).
Figure 16 Average histogram envelopes of $R_{TI \text{adaptive}}$. a) for subjects with AHI above and under 10h$^{-1}$, b) for subjects with AHI above and under 15h$^{-1}$ and c) for subjects with AHI above and under 30h$^{-1}$.

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<td>p50</td>
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<td>0.1405</td>
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Table 10 Statistical significance of a) $R_{Snores_{adaptive}(i)}$ and b) $NR_{Snores_{adaptive}(i)}$ features on distinguishing subjects from opposite levels of SAHS severity.
We computed the $I_{mean}$ histograms for the regular and non-regular snores (Figure 17 and Figure 18). With respect to regular snores (Figure 17) the shape of the histograms is very similar for the two groups with contrasting AHI values. Conversely, the results obtained for non-regular snores (Figure 18) show utterly different shapes for the two groups of subjects. All 3 plots shown in Figure 18 make evidence that subjects with higher AHI produce non-regular snores with mean sound intensity values predominantly between 42 and 55dB SPL (creating a plateau effect in the case of $30h^{-1}$ cut-point of severity). On the other hand, less severe SAHS subjects have mean sound intensity values around 38 and 50dB SPL.
**IV.4.3 - Conclusions**

The application of the adaptive threshold to the time interval between successive snores of 34 subjects was essential to properly select regular snores from all-night snore episode sequences. $TH_{\text{adaptive}}$ outperformed $TH_{\text{median}}$ on that purpose which is intuitively explained since the former takes into account the evolution of TI($i$) through all night sleep as it is based on the concept of an adaptive estimation (137).

We observe that the time interval between successive regular snores has distinct distribution for subjects with high and low levels of AHI. The $R_{TI}$ events under one second are much more frequent for subjects with higher AHI suggesting that they have propensity to snore in consecutive inspiration and exhalation events (SP2 pattern, Figure 19). Conversely, subjects with lower AHI tend to snore once per breathing cycle (SP1 pattern, Figure 19). In addition to this, several $R_{TI_{\text{adaptive}}}$ features allowed the statistical distinction of subjects with high and low levels of AHI.

![Figure 19 Average histogram envelopes of $R_{TI_{\text{adaptive}}}$](image)

Regular snores have very similar mean intensity values for all 4 levels of AHI severity considered: AHI<5h$^{-1}$, AHI<10h$^{-1}$, AHI<15h$^{-1}$ and AHI<30h$^{-1}$. On the other hand, in the case of non-regular snores we can observe very different shapes on the mean intensity histograms for subjects with opposite AHI degrees of severity, which were confirmed by statistically significant differences between populations. Furthermore, we found that non-regular snores from more severe SAHS subjects present very frequently mean intensity values above 55dB-SPL whereas less severe SAHS subjects have mostly mean sound intensity values around 38 and 50dB-SPL. This makes evidence
that non-regular snores carry a large extent of information with respect to the screening of SAHS based on sound intensity.

Once we classify, from a whole sequence of snores, the ones that are regular and the ones that are non-regular, we can study these two groups of snores separately and explore their potential to screen subjects with SAHS. In this section, we showed that simple time features such as M (mean), Std (standard deviation) and RMS (root mean square) enabled to differentiate subjects with different levels of severity. The concept of regular and non-regular snores is a new and promising approach to study the snore mechanism production and can be a useful new tool to screen SAHS disease.

IV.5 - Normal non-regular snores as a tool for screening SAHS severity

One of the conclusions drawn out of the previous section was the fact that mean sound intensity of non-regular snores is different in less and more severe SAHS subjects. Thus, on this section we will assess the actual potential of non-regular snores features on screening SAHS subjects (138).

As explained earlier, two successive snores are non-regular snores if they are separated by normal breathing cycles and/or apneas. Perez-Padilla et al. (166) and Fiz et al. (60) studied the snores emitted at the end of apneas: post-apneic snores. They found that the spectrum of this first snoring immediately after an apnea was most distinct from that of all other snoring episodes. In more detail, Perez-Padilla et al. (166) affirms that the first post-apneic snore consists mainly of broad-band white noise with relatively more power at higher frequencies, so that the ratio of power above 800Hz to power below 800Hz can be used to separate snorers from patients with SAHS. Recently, Xu et al. (224) found differences, for some frequency and spectral parameters, between first snores after upper and lower soft palate level obstructive sleep apneas. They have shown that the mean of peak frequencies, central frequencies, and proportions of energy from 800Hz to 2000Hz and above 2000Hz of the first snoring sounds after lower level obstructive apneas were higher and the proportion of energy below 800Hz was lower than those after upper level obstructive apneas.

Patients with severe SAHS produce greater number apnea events during the night than mild SAHS subjects and simple snorers. Consequently, the latter may sometimes present very few or even nonexistent post-apneic snore episodes. This situation hinders further investigation of post-apneic on simple snorers and least severe SAHS subjects. In this section we address this issue by analysing separately both groups that constitute all non-regular snores: post-apneic snores and normal non-regular snores (168). We will investigate the information enclosed in both groups for the set of 34
subjects. And, more specifically, we will examine the possibility of normal non-regular snores carrying information about SAHS severity that up until now was only found in post-apneic snores.

**IV.5.1 - Non-regular snores identification**

The 34 subjects’ database used is described in detail on the [IV.3.1.1-Database](#) section.

We applied $TH_{adaptive}$ (eq. (4)) to the TI (eq. (1)) of each of the 34 subjects. Since our purpose is to study non-regular snores we applied $HiTH_{adaptive}$ (where the significance assigned to the $i$th TI is $\delta=0.5$). The non-regular snores are defined as the ones for which $TI(i) \geq HiTH_{adaptive}(i)$. After selecting all non-regular snores (GANR) we divided them into 2 subgroups:

- **GP**: group of snores that are produced immediately after an apnea episode, i.e. post-apneic non-regular snores;
- **GN**: group of snores that are separated by normal breathing cycles, i.e. normal non-regular snores.

A short segment of a snoring signal is shown in Figure 20, where S(1) is the snore produced forthwith after the apnea event: post-apneic snore. All S(2)-S(7) snores are regular snores because they are produced in consecutive breathing cycles. Given that S(7) and S(8) are separated by normal breathing cycles, then S(8) is a normal non-regular snore.

![Figure 20 Excerpt of a snoring sound signal. The dashed line box corresponds to an apnea episode and the solid line boxes correspond to snore episodes. S(1) is a post-apneic non-regular snore. All S(2) - S(7) snores are regular snores. S(8) is a normal non-regular snore.](image)

**IV.5.2 - Parameters and features of non-regular snores**

Several snore parameters from the 3 groups of snores, GANR, GP and GN were calculated. In time domain, the parameters studied were the Mean and Maximum Sound Intensity. In frequency domain, the snore parameters calculated were Peak, Mean, Center and Maximum Frequency and parameters that describe the shape of spectrum like the Standard Deviation, Symmetry coefficient.
and Spectral Flatness (95). Mean, standard deviation and 75th percentile of the previously described parameters were computed, with p-value (Mann-Whitney U test) obtained to assess the independence of the populations with AHI cut-points of 5, 15 and 30 h⁻¹.

IV.5.3 - Results

After applying \( TH_{\text{adaptive}} \) to the snore sequences of our set of 34 subjects we were able to select non-regular snores (GANR). Table 11 summarizes the number of snores analysed in each group for the set of 34 subjects. Given that for our group of mild to moderate subjects (AHI range: 3.2-12.1 h⁻¹) we had very few and in some cases inexistent post-apneic snores, we built two subsets of subjects. The SUBSET17 comprises 17 moderate to severe SAHS subjects that present both GP and GN groups of snores (Table 12) and SUBSET11 is composed of 11 mild to moderate subjects that almost uniquely produce normal non-regular snores (Table 13).

<table>
<thead>
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<tr>
<td>GN</td>
<td>20400</td>
</tr>
<tr>
<td>GP</td>
<td>804</td>
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</table>

Table 11 SET of 34 subjects (AHI range: 3.2-109.9 h⁻¹). GANR: group of all non-regular snores. GN: group of normal non-regular snores. GP: group of post-apneic non-regular snores. Total NS: total number of snores in each group. NS per subject: mean ± standard deviation of the number snores for each subject.

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<th>NS per subject</th>
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<tr>
<td>GN</td>
<td>11930</td>
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<tr>
<td>GP</td>
<td>782</td>
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Table 12 SUBSET17; SET of 17 subjects (AHI range: 15.1-109.9 h⁻¹).

<table>
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<td>GN</td>
<td>5170</td>
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<td>GP</td>
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</tbody>
</table>

Table 13 SUBSET11; SET of 11 subjects (AHI range: 3.2-12.1 h⁻¹).

For the whole set of 34 subjects we studied the acoustic parameters for GANR and GN (Table 14 and Table 15, respectively). Results obtained for the frequency domain parameters (Peak, Mean, Center and Maximum frequency) and Spectral Flatness were not significant either for GANR or for GN.

For all non-regular snores, GANR, (Table 14) we observed that \( Imax \) and \( Imean \) (maximum and minimum sound intensity) were significantly higher for more severe SAHS patients in all 3 AHI
cut-points considered (5, 15 and 30h⁻¹). Mean, standard deviation and 75th percentile of different spectral parameters that consider frequency energy distribution obtained significant results. Among them, Std. Dev, measure of dispersion of the energy in frequency (second moment of the spectrum) and the symmetry coefficient (third moment of the spectrum) were significantly different ($p<0.05$) in patients with opposite levels of severity in AHI cut-points of 15 and 30h⁻¹.

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<td>61.09 ± 4.7</td>
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<thead>
<tr>
<th>S AHI</th>
<th>Std Dev</th>
<th>CSymm</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;5</td>
<td>M ± SD</td>
<td>pC75</td>
</tr>
<tr>
<td>183.64 ± 36.6</td>
<td>59.07 ± 18.7</td>
<td>228.83 ± 38.9</td>
</tr>
<tr>
<td>≥5</td>
<td>198.92 ± 40.3</td>
<td>55.80 ± 13</td>
</tr>
<tr>
<td>$p_5$</td>
<td>0.3778</td>
<td>0.8099</td>
</tr>
</tbody>
</table>

The same noteworthy results were obtained for normal non-regular snores, GN (Table 15). Statistical significance obtained for GN is less prominent when compared to GANR because post-apneic non-regular snores are excluded from this group but, nonetheless, the results showed that normal non-regular snores enclose notable information on the severity of SAHS subjects.

Table 14 Features for SET of 34 subjects: GANR (all non-regular snores). Features a) $I_{max}$ and $I_{mean}$; b) Std Dev and CSymm. GN (normal non-regular snores). Values are mean ± standard deviation. M: mean. SD: standard deviation. pC75: 75th percentile. S AHI: Subjects with AHI above or under the cut-points 5, 15 and 30h⁻¹. * significance obtained using Mann-Whitney U test. $p_X<0.05$ was considered statistically significant.
With SUBSET17 and SUBSET11 our goal was to study the effect of the presence/absence of post-apneic non-regular snores on two sets of subjects with opposite levels of SAHS severity. The results for the most significant parameters are depicted using bar graphs in Figure 21. Noticeable differences between the mean, standard deviation and pC75 values of all 3 parameters (Imax, Imean, CSym) (Figure 21 a), b) and c)) of GP and GN of SUBSET17 are supported by p-values under 0.05, which confirms statistically significant differences. Fairly remarkable results were obtained when comparing GN from both subsets: SUBSET17 and SUBSET11. We can observe that all GN features (mean, SD and pC75) of SUBSET17 have significantly higher value than GN features of SUBSET11 (p<0.05). This suggests that there are prominent differences between the acoustic characteristics of normal non-regular snores of mild (SUBSET11) and severe (SUBSET17) SAHS subjects. Therefore, Imax, Imean and CSym parameters of normal non-regular snores prove to be key parameters for distinguishing mild from severe SAHS subjects.
IV.5.4 - Conclusions

A new method for a prompt screening of SAHS was validated in 34 snoring subjects and consists on studying parameters of normal non-regular snores (138). The time domain parameters include maximum and mean sound intensity. In the frequency domain, the parameters are Peak, Mean, Center and Maximum frequency and the ones used to describe the shape of the spectrum like the Standard Deviation of the spectrum, Symmetry coefficient and Spectral Flatness.

The novelty in this method is that it uses a group of snores produced by every snoring subject: normal non-regular snores. They consist of successive snores that are separated by normal breathing cycles, i.e., snores that are neither produced in consecutive breathing cycles (regular snores) nor emitted immediately after an apnea episode (post-apneic non-regular snores). Various studies have already proven the effectiveness of post-apneic snore characteristics on the purpose of distinguishing mild from severe SAHS patients. However, we quite often face the fact that for simple snorers and mild SAHS subjects there are very few or sometimes even inexistent post-apneic snores to carry on any feasible analysis. With our method we were able to overcome this issue while we have proven that remarkable information on SAHS severity is enclosed in normal non-regular snores.

Moreover, we also found significant differences between the characteristics of post-apneic non-regular snores (GP) and normal non-regular snores (GN). This fact suggests that the comparison of these two types of snores may be a promising tool for stratifying a population composed of...
moderate to severe SAHS subjects. Finally, we observed that normal non-regular snore parameters of severe SAHS subjects have significantly higher values than those of mild SAHS subjects. Once again, this suggests that normal non-regular snores can be used for prompt screening of SAHS severity.

**IV.6 - All night analysis of time interval between snores in subjects with SAHS**

In this part of the thesis we will show that relevant information on the severity of SAHS can be estimated by the simple analysis of the time interval between regular snores, without the need to resort to any complementary and likely more complex, acoustic analysis of snores (140).

Once again, the database of subjects used to generate the following results was the same as described on the **IV.3.1.1-Database** section and, in this case, the 34 subjects were divided in two groups with opposite levels of severity (3 cut-points of severity: 5, 15 and 30h⁻¹. Table 16, Table 17 and Table 18, respectively). These three different levels are proposed by physicians and clinical experts as criteria for SAHS definition (111).

| Table 16 Database characteristics divided in two groups with opposite levels of severity (above and under 5h⁻¹). G AHI = group of subjects with AHI under and above 5h⁻¹. |
|---|---|---|---|---|
| Age | BMI | AHI | N Snore | Nr Subj |
| m | 48 | 24.8 | 3.9 | 953 | 4 (2 F, 2 M) |
| sd | 4 | 2.9 | 0.7 | 547 |
| m | 51 | 29 | 42.1 | 2355 | 30 (6 F, 24 M) |
| sd | 11 | 3.8 | 22.8 | 854 |

| Table 17 Database characteristics divided in two groups with opposite levels of severity (above and under 15h⁻¹). G AHI = group of subjects with AHI under and above 15h⁻¹. |
|---|---|---|---|---|
| Age | BMI | AHI | N Snore | Nr Subj |
| m | 51 | 26.5 | 7.3 | 1681 | 11 (6 F, 5 M) |
| sd | 11 | 2.9 | 3.5 | 835 |
| m | 51 | 29 | 52.1 | 2434 | 23 (2 F, 21 M) |
| sd | 10 | 4.1 | 25.9 | 900 |

| Table 18 Database characteristics divided in two groups with opposite levels of severity (above and under 30h⁻¹). G AHI = group of subjects with AHI under and above 30h⁻¹. |
|---|---|---|---|---|
| Age | BMI | AHI | N Snore | Nr Subj |
| m | 50 | 26.3 | 11.8 | 1752 | 16 (7 F, 9M) |
| sd | 12 | 2.8 | 8.3 | 877 |
| m | 52 | 30.4 | 60.5 | 2580 | 18 (1 F, 17M) |
| sd | 8 | 3.9 | 22.8 | 828 |
Once more, regular snores are defined as the ones for which $T_I(i) < HiTH_{\text{adaptive}}(i)$ (see IV.3.1.2-Threshold definition and application section). Consequently, non-regular snores are defined as the ones for which $T_I(i) \geq HiTH_{\text{adaptive}}(i)$. This work is focused on the study of regular snores.

IV.6.1 - Parameters and features of regular snores

In this study we analysed a total of 74439 snores from the whole database of 34 subjects. The method consisted in applying $LoTH_{\text{adaptive}}$ and $HiTH_{\text{adaptive}}$ to the all night $T_I(i)$ sequences to obtain the RLo_TI(i) and RMid_TI(i) sequences. These two sequences are defined as follows:

$$RLo_TI(i) = T_I(i) | T_I(i) < LoTH_{\text{adaptive}}(i)$$

$$RMid_TI(i) = T_I(i) | LoTH_{\text{adaptive}}(i) < T_I(i) < HiTH_{\text{adaptive}}(i)$$

From the total of 74439 snores, after applying $HiTH_{\text{adaptive}}$ to all 34 $T_I(i)$ sequences, 21204 snores were classified as non-regular snores and 53235 were classified as regular snores. After applying $LoTH_{\text{adaptive}}$ to regular snores, 26129 TI were classified as RMid_TI and 27106 TI were classified as RLo_TI.

We calculated the mean, standard deviation and coefficient variation for 15 minute segments of the time interval sequence of regular snores. This allowed us to examine the time interval between regular snores within each 15 minute segment and also during all night. Our method is similar to what is done in the field of Heart Rate Variability (HRV), which measures time domain features of the time interval between consecutive heartbeats in small segments of a recording period (56). In the case of HRV, the task force indicates that 5 minutes segments are advisable to investigate the physiological and clinical potential of HRV. The heart rate of healthy resting adults is around 60-80 beats per minute, so one can expect 300-400 beats on a 5 minute recording. On the other hand, the respiratory rate in adults ranges from 12 to 20 breaths per minute (210). Furthermore, unlike the heartbeat, snoring may not be present in each breathing cycle. As a result, a 5 minute segment is very short and not effective as it will have very few snoring episodes. Conversely, with 30 minute segments we will have fewer segments during the night (13 segments for a 6.5h night sleep) and consequently the dispersion of the parameters will result much more smoothed, which would prevent us from drawing any conclusions. Bearing this in mind, we decided to apply our study to 15 minute segments. This enabled us to track the changes of the snore parameters per segment and over all night.

For each $k$ 15 minute segment of the all-night recording, we calculated three parameters both in the RLo_TI(i) and RMid_TI(i) sequences: average $\mu(k)$, standard deviation $\sigma(k)$ and coefficient of variation $cv(k)$ (ratio of the standard deviation $\sigma(k)$ to the average $\mu(k)$). Thereafter, we computed
the average and standard deviation of $\mu$, $\sigma$ and $cv$ obtained for all $k$ segments (Table 19). Features $A\mu$, $A\sigma$, $Acv$, $SD\mu$, $SD\sigma$ and $SDcv$ were calculated for each subject, for both $RLo\_TI(i)$ and $RMid\_TI(i)$ sequences.

<table>
<thead>
<tr>
<th>Feature</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>$A\mu$</td>
<td>Average of parameter $\mu_x$ over all $k$ segments</td>
</tr>
<tr>
<td>$A\sigma$</td>
<td>Average of parameter $\sigma_x$ over all $k$ segments</td>
</tr>
<tr>
<td>$Acv$</td>
<td>Average of parameter $cv_x$ over all $k$ segments</td>
</tr>
<tr>
<td>$SD\mu$</td>
<td>Standard Deviation of parameter $\mu_x$ over all $k$ segments</td>
</tr>
<tr>
<td>$SD\sigma$</td>
<td>Standard Deviation of parameter $\sigma_x$ over all $k$ segments</td>
</tr>
<tr>
<td>$SDcv$</td>
<td>Standard Deviation of parameter $cv_x$ over all $k$ segments</td>
</tr>
</tbody>
</table>

Table 19 Features derived from the parameters. $X= RLo\_TI(i); RMid\_TI(i)$

**IV.6.2 - Statistical analysis and classification**

For each feature, the Mann-Whitney $U$ test was used to assess the independence of the respective populations. Kolmogorov-Smirnov test was previously performed to confirm that the two samples had different continuous distributions (76).

We applied the Bayesian classification algorithm for supervised learning to evaluate the performance of the features on classifying the subjects according to the three abovementioned cut-points of SAHS severity (93). The Bayesian classifier is a classification algorithm for supervised learning that stores a single probabilistic summary for each class, and assumes conditional independence of the attributes given the class. The assumption of class independence allows the classifier estimate the parameters required for accurate classification while using less training data than many other classifiers. The classification is based on estimating the probability or probability density of features $X$ given class $Y$. We have used the normal distribution approximation. To ensure the statistical validity of the classification results, we used the leave-one-patient-out cross validation process, where the training set is build by taking at each round all patients except the one used for testing.

**IV.6.3 - Results**

**IV.6.3.1 - Screening SAHS severity using time interval between regular snores**

As an illustrative example, Figure 22 and Figure 24 show parameters $\mu$, $\sigma$ and $cv$ of $RMid\_TI$ and $RLo\_TI$, respectively, for each $k$ 15 minute segment from 4 subjects with different values of SAHS severity: a) $AHI=3.2h^{-1}$, b) $AHI=5.3h^{-1}$, c) $AHI=25.6h^{-1}$ and d) $AHI=82.9h^{-1}$. Figure 23 and Figure 25
both display the results obtained for features $A_{\mu}$, $A_{\sigma}$, $A_{cv}$, $SD_{\mu}$, $SD_{\sigma}$ and $SD_{cv}$ of the RMid_TI and Rlo_TI, respectively, sequence for all population. The bar graphs depict the mean and standard deviation values of the features for every 2 groups of subjects with opposite levels of AHI severity. Features $A_{\mu}$, $A_{\sigma}$ and $A_{cv}$ allow us to investigate the average of the time interval between regular snores within each $k$ short segment, whereas features $SD_{\mu}$, $SD_{\sigma}$ and $SD_{cv}$ give evidence of the dispersion during all night sleep.

When examining Figure 22 a) we observe that the least severe subject (AHI of 3.2 h\(^{-1}\)) presents the highest values of $\mu$ in each $k$ segment. Contrarily, the two most severe SAHS subjects (Figure 22 c) and d) present the lowest $\mu$ values. Figure 23 shows that less severe SAHS subjects have higher values of RMid_TI within each 15 minute segment ($A_{\mu}$) than more severe SAHS subjects. These differences are highly statistically significant for AHI=15 h\(^{-1}\) ($p=0.0136$) and AHI=30 h\(^{-1}\) ($p=0.0036$) cut-points of severity. The variability of RMid_TI within each $k$ segment, given by the feature $A_{cv}$, is always higher for severe SAHS subjects. This feature permits distinguishing between subjects with opposite levels of severity (Figure 23 b) and c), $p=0.0167$, 0.006 for AHI cp: 15h\(^{-1}\), 30h\(^{-1}\); respectively).

Figure 22 Parameters for RMid_TI($i$) sequence. Parameters $\mu$ RMid_TI, $\sigma$ RMid_TI and $cv$ RMid_TI obtained for all $k$ segments for 4 subjects with AHI: a) 3.2h\(^{-1}\), b) 5.3h\(^{-1}\), c) 25.6\(^{-1}\) and d) 82.9h\(^{-1}\).
Standard deviation of parameters $\mu$, $\sigma$ and $cv$ enables to interpret the dispersion of time interval between consecutive snores along all night sleep. Higher variability in all three parameters is observed for the least severe subject, as compared to the same parameters in the most severe subject (Figure 22 a) and d), respectively). The two most severe subjects present almost the same value for all 3 parameters in all night short $k$ segments. Results obtained for the whole database confirm lower values of $SD\sigma$ and $SDcv$ for more severe SAHS subjects (Figure 23), in agreement with the four individual cases shown in Figure 22.

The results obtained for parameters and features of sequence RLo_TI exhibited similar behaviour as the one seen for RMid_TI sequence. For the RLo_TI sequence, features $A\mu$ ($p=0.0429$, 0.0025; AHI cp:15$h^{-1}$, 30$h^{-1}$) and $Acv$ ($p=0.0032$, 0.0025; AHI cp: 15$h^{-1}$, 30$h^{-1}$) enabled to distinguish between subjects with opposite levels of severity with statistical significance. Once again this is easily observed in Figure 24 a), where the least severe subject (AHI of 3.2$h^{-1}$) presents the highest values of $\mu$ in each $k$ segment, as opposed to the most severe subject which presents very low $\mu$ in all $k$ segments (Figure 24 d)). For all 34 subjects and all AHI cut-points considered, $SD\mu$, $SD\sigma$ and $SDcv$ features presented higher values for less severe subjects than for more severe subjects (Figure 25). This fact suggests a greater dispersion on the value of time interval between snores during all night for less severe SAHS subjects.
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Figure 24 Parameters for RLo_TI(i) sequence. Parameters μ RLo_TI, σ RLo_TI and cv RLo_TI obtained for all k segments for 4 subjects with AHI: a) 3.2 h⁻¹, b) 5.3 h⁻¹, c) 25.6 h⁻¹ and d) 82.9 h⁻¹.

Figure 25 Bar graphs for features Aμ, Aσ, Acv, SDμ, SDσ and SDcv of RLo_TI for 34 subjects with three cut-points of severity: 5h⁻¹, 15h⁻¹ and 30h⁻¹. Features Aσ, Acv and SDcv appear scaled by a factor of 10 only for the sake of a better presentation.
IV.6.3.2 - Classification of subjects

Classification results obtained with the Bayesian classifier with leave-one-patient-out cross validation process are displayed in Table 20. All 6 features: $A\mu$, $A\sigma$, $Acv$, $SD\mu$, $SD\sigma$ and $SDcv$ were used in the classification as our purpose is to evaluate their reliability on predicting the subjects’ SAHS severity. Both RMid_TI and RLo_TI sequences obtained the best results in terms of diagnostic accuracy for $5h^{-1}$ and $30h^{-1}$ AHI cut-points (RMid_TI: accuracy=88.2% for AHI cp:5h$^{-1}$ and 73.5% for AHI cp:30h$^{-1}$, RLo_TI: accuracy=91.2% for AHI cp:5h$^{-1}$ and 94.1% for AHI cp:30h$^{-1}$). These high accuracy classification results are accompanied by a good balance of sensitivity (S) and specificity (Sp) (RMid_TI: S (Sp)=90% (75%) for AHI cp:5h$^{-1}$, RLo_TI: S (Sp)=94.4% (93.8%) for AHI cp:30h$^{-1}$). Even though a good accuracy value of 73.5% was obtained for the 15h$^{-1}$ cp of AHI, the specificity value appears to be more compromised in the case of RLo_TI sequence (45.5%).

<table>
<thead>
<tr>
<th>AHI cut-points</th>
<th>$5h^{-1}$</th>
<th>$15h^{-1}$</th>
<th>$30h^{-1}$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>S</td>
<td>Sp</td>
<td>Ac</td>
</tr>
<tr>
<td>RMid_TI</td>
<td>90</td>
<td>75</td>
<td>88.2</td>
</tr>
<tr>
<td>RLo_TI</td>
<td>96.7</td>
<td>50</td>
<td>91.2</td>
</tr>
</tbody>
</table>

Table 20 Classification results for the Bayes classifier with leave-one-patient-out cross validation. S: sensitivity, Sp: specificity, Ac: accuracy (all in percentage)

IV.6.4 - Conclusions

In this section, we used uniquely the snoring sound signal collected by one microphone attached to a band around the neck. The development of simple methods such as ours, based solely on snoring sound signal analysis, should be continuously encouraged in the field of SAHS diagnosis due to the simplicity of the tracheal sound measurement and the significant information about the physiology and pathology of the airways that it contains (201).

Some research studies have already reported significant differences between post-apneic snores (snores that are produced immediately after an apnea) and all remaining snores (60),(166),(224). Nevertheless, we consider the separation in these two groups to be insufficient. For that reason we proposed a new methodology for classifying two distinct types of snores: non-regular and regular snores. Non-regular snores are the ones separated by an apnea event and/or by non-snoring breathing cycles. Regular snores are truly consecutive snores, i.e., snores that are produced in consecutive breathing cycles, without interruptions.

Cavusoglu et al. (36) and our group’s previous work (196) had tried to identify these two kinds of snores, but they did not succeed in finding a proper criterion because they considered a
separation of less than 10 seconds to be sufficient. According to their methods, the analysis of regular snores included successive snores that are interrupted either by normal breathing cycles or by apneas that last less than 10 seconds. We overcame this issue by applying an adaptive threshold to the all night sequence of time interval between snores of each subject.

By applying a higher \( \text{HiTH}_{\text{adaptive}} \) and a lower \( \text{LoTH}_{\text{adaptive}} \) threshold we can appraise the time intervals on the two snoring patterns that comprise regular snores: the single pattern (SP1) and the double pattern (SP2). Examining the two kinds of snores classified by the application of both thresholds (RMid_TI snores and RLo_TI snores) was of major importance since it enabled to study the behaviour of each feature for both kinds of snores. If we had only applied our study to regular snores altogether, we would have faced confusing and misleading outcomes that would have been much more difficult to interpret (140).

Results obtained for feature \( \text{Acv} \) on both sequences suggest that there is more variability in each short 15 minutes segment for the more severe SAHS subjects. This can be understood as intra-segment variability. This finding is in agreement with previously reported studies (196) where, in spite of not having focused on regular snores, SAHS patients showed higher snore to snore variability on intensity and frequency domain snore features (AHI cp:10h\(^{-1}\)). We must emphasize that our study has achieved similar results with no need to perform any acoustic analysis of snore episodes.

Regarding the evolution of both snoring patterns along the night, we observe that the dispersion of \( \mu \) and \( \sigma \) (SD\( \mu \) and SD\( \sigma \)) is much higher for less severe patients. This fact suggests that there is more variability during all sleep on this kind of patients. In addition, when examining the progress during the night of the time interval (TI) between successive regular snores, we observe less dispersion in more severe patients. This makes evidence that those patients present a steadier and shorter TI during sleep than less severe patients.

In the method proposed by Ng. et al (151), where peak frequency components via wavelet bicoherence analysis were used, the sensitivity and specificity values were reported to be 85% and 90.7%, respectively, for differentiating between apneic and non-apneic snorers. Another fairly recently published work on multi-feature snore analysis using pitch and total airway response features (105) reported classification results of 89.3% sensitivity with 92.3% specificity and 90% accuracy. One of our group’s latest published works (61) obtained performance results of 80% sensitivity and 90.9% specificity using a model that included intensity and frequency domain snore parameters. In contrast, using only 6 features derived from the analysis of time interval between snores, we achieved the best performances of 94.1% accuracy (with 94.4% sensitivity and 93.8% specificity) for AHI cp of 30h\(^{-1}\) and 88.2% accuracy (with 90% sensitivity and 75% specificity) for AHI cp of 5h\(^{-1}\). Furthermore, it should be emphasized that the complexity of the proposed method is
fairly low since only the analysis of the time interval between snores is involved whereas the algorithms used in (61),(105),(151) require complex acoustic analysis of snore parameters.

Even though we used a substantial amount of snores (74439 snores) to perform this study, an important next step will be to apply this new methodology on a wider database in order to confirm the results obtained in this paper. Apart from the sample size, another limitation of this study is the fact that it is only applicable to snoring subjects. Nonetheless, according to the latest publications, the non snoring SAHS patients comprise a very small percentage of the overall spectrum of SAHS (117). On the other hand, although the implementation of our method on a portable low-cost bedside snoring sound analyser may be easily integrated and this constitutes a major strength on itself, it requires an automatic detection of the time boundaries of each snoring event, and we are aware that not all of the available devices have this option implemented.

In conclusion, we designed a method that allows the identification of non-regular and regular snores. The results obtained with the features derived from the time interval between regular snores suggest that the method can be a valuable aid for the early screening and severity estimation of subjects suspected of having SAHS. In addition, it can be easily integrated in any portable and low-cost bedside monitor that performs automatic analysis of snoring episodes.

IV.7 - Conclusions and future prospects

The prevalence of SAHS is increasing and it is becoming a rather serious and complex public health problem (37),(117),(222). Taking the high prevalence of this disorder into account, there is a high demand for easier, cheaper and less obtrusive diagnostic approaches. In this part of the thesis, we used uniquely the analysis of the snoring sound signal collected by one microphone attached to a band around the neck. The development of simple methods such as ours, based solely on snoring sound signal analysis, should be continuously encouraged in the field of SAHS diagnosis due to the simplicity of the tracheal sound measurement and the significant information about the physiology and pathology of the airways that it contains (201).

Snoring is a central sign, around which various factors and disorders can be found as causes and effects. In particular, loud continuous (every night), intermittent (during the night) snoring are constant in patients suffering from SAHS. Early diagnosis of SAHS is not easy, but important for therapeutic intervention. For an accurate diagnosis, polysomnography obviously represents a gold standard. This technique is, however, very laborious, time-consuming and expensive; and the rather small number of sleep laboratories available at hospitals cannot admit all suspected patients. The recording of tracheal sounds allows monitoring of the snoring and breath sounds, and also of sleep
apnea (61),(140),(195). For that reason, and the fact that snoring is recognized to be the clinical hallmark of SAHS (10),(168) snoring is the constant phenomenon to be recorded. We are aware that in some rare cases of SAHS, snoring may not always be present. Nonetheless, according to the latest publications, the non snoring SAHS patients comprise a very small percentage of the overall spectrum of SAHS (117).

Several systems based on the acoustic analysis of snoring (see II.6.4-Acoustic systems section) have been developed and have already proven they can be applied to home monitoring of sleep, to screen and/or select patients for more complex investigations. The availability of these portable small compact systems offers great advantages for the specialized physician and patients. These devices fill the big gap in the screening of SAHS. They are, in particular, developed for outpatient use, and enable the physician to make a prompt diagnosis of SAHS, and decide if patients should be submitted to PSG or advised for CPAP treatment. These snoring based acoustic systems make it possible to avoid the time-consuming, expensive and sometimes unnecessary PSG, which can be reserved for problematic cases. Furthermore, long-term surveillance of patients, who are not at acute risk, can be accomplished at home (43). Another important point is the application of snoring portable monitoring devices to epidemiological studies. These systems will also facilitate accurate estimation of prevalence of SAHS, that may substantially modify the epidemiological data so far reported in the literature by the AASM (10), Yaggi et al. (227) and Lloberes et al. (117).

The robustness of methods based on the acoustic analysis of snoring episodes has proven to be effective and reliable in screening of SAHS. However, we felt that research on the study of all night snore episodes as a temporal sequence was lacking and could provide new information on SAHS disease. We focused our research on studying the relationship between breathing cycles and snoring event production. Prior to our work, some publications had suggested the existence of two different types of snoring, stating that by convention a distinction is made between steady snoring, which shows little variation and little or no interruptions, and the irregular snoring that characterizes the resumption of breathing in between obstructive apneas (166),(168),(196),(224). In this sense, we decided to give continuity to the formerly mentioned works. Nevertheless, we considered the separation of all snores produced during the night in post-apneic snores (snores that are produced immediately after an apnea) and all remaining snores to be insufficient. For that reason we proposed a new methodology for classifying two distinct types of snores: *non-regular* and *regular* snores. Non-regular snores are the ones separated by an apnea event and/or by non-snoring breathing cycles. Regular snores are truly consecutive snores, i.e., snores that are produced in consecutive breathing cycles, without interruptions. For that, we developed a threshold that is adaptively estimated from
the whole night sequence of time intervals between successive snores and therefore is characteristic of each subjects’ snoring pattern.

We wanted to offer alternatives to the acoustic studies, always proposing simple and understandable methods, easy to apply, and primarily founded on the analysis of all night snore sequence, that finally could be easily integrated in any low-cost portable bedside monitor.

The major achievements methodology wise we attained were the following:

- The development of an adaptive threshold that is able to identify regular and non-regular snores on the whole night snore episode sequence.
- The development of a higher and lower adaptive threshold that are able to identify two snoring patterns that comprise regular snores: SP1, the single snoring pattern and SP2, the double snoring pattern, respectively.
- Study of the variability of snore episode features throughout all night sleep by examining the time interval between successive snores (TI) over short segments of time. This time-scale study on short segments of time was found to be suitable with 15 minute size segments. This enabled us to track the changes of the snore parameters per segment and over all night.
- Using the features derived from the time interval between regular snores ($A_{\mu}, A_{\sigma}, A_{cv}, SD_{\mu}, SD_{\sigma}$ and $SD_{cv}$) to classify subjects according to 3 cut-points of severity: $5h^{-1}$, $15h^{-1}$ and $30h^{-1}$.

The former methods were applied to our 34 subjects’ database (on a total of 74439 snores) and the most important findings/conclusions we achieved are the following:

- That non-regular snores from more severe SAHS subjects present very frequently mean intensity values between 42 and 55dB-SPL whereas less severe SAHS subjects have mostly mean sound intensity values around 38 and 50dB-SPL (137).
- That Normal non-regular snores are an alternative to the study of post-apneic snores since in the latter case there are very few or sometimes even inexistent accountable episodes on simple snorers and mild SAHS subjects carry on any feasible analysis (138).
- Maximum ($p=0.038$) and mean ($p=0.024$) sound intensity and symmetry coefficient ($p=0.013$) features of normal non-regular snores are significantly higher for more severe SAHS patients in all 3 AHI cut-points considered (5, 15 and $30h^{-1}$) (138).
- Severe SAHS subjects show a shorter time interval between regular snores ($p=0.0036$, AHI cp: $30h^{-1}$) and less dispersion on the time interval features during all sleep (140).
- Conversely, lower intra-segment variability ($p=0.006$, AHI cp: $30h^{-1}$) is seen for less severe SAHS subjects (140).
- Features derived from the analysis of time interval between regular snores achieved classification accuracies of 88.2% (with 90% sensitivity, 75% specificity) and 94.1% (with 94.4%
sensitivity, 93.8% specificity) for AHI cut-points of severity of 5 and 30 h⁻¹, respectively. The features proved to be reliable predictors of the subjects’ SAHS severity (140).

**IV.7.1 - Future prospects**

The sleep stage and sleep position data was not taken into account in our work because we were only interested in the analysis of the whole night sleep independently of these sleep variables. Nonetheless, we are aware that some studies have been published on that topic (88),(89) and given that it represents an interesting research line we believe that our methods can be applied on that scope and could provide new inputs on the occurrence of the two types of snoring during the night progress.

Another future development may be the investigation of the possible relationship between harsh snoring and the subsequent production of sleep disruptive events such as arousals. The majority of the research in the field of SAHS and sleep fragmentation addresses mostly the analysis of EEG and apnea-hypopnea events (20),(46),(47),(71),(205). Other authors started studying the relationship between sleep disturbance and snoring (12),(88),(147). However, these studies are still very preliminary as they only analyse very simple parameters such as the number of snores per hour of sleep, maximal and mean nocturnal sound intensity and snore related short arousals per hour of sleep. A natural evolution of the work we developed with snoring in this thesis can be the investigation of arousals, sleep architecture disruption and their correlation with snoring events. Moreover, understanding the evolution of snoring (whether regular or non-regular snores) characteristics throughout sleep may provide new insights on the possibility of snoring episodes being another cause, besides apnea and hypopnea events, of disruptive events such as arousals.

The investigation and analysis of regular and non-regular snores is indeed a work in progress and the future prospects on research in this topic can include the study of their correlation with the source of snoring. Different trials have compared anatomical locations of snoring and found the acoustic spectrum of palatal vs nonpalatal snoring (6),(87),(100),(143) to be clearly different. Knowing the source of snoring may provide further knowledge on the production of regular and non-regular snores.

We strongly believe that if snoring carries information on the site and degree of obstruction of the upper airways (168), the degree of SAHS severity is strongly linked with the triggering of regular and non-regular snores. We foresee that the further investigation of these two kinds of snoring episodes will provide further understanding on the underlying mechanisms of SAHS disease, which will surely lead to new developments on its diagnosis.
Finally, we should emphasize that an exclusive and ultimate conclusive study on SAHS, to confirm diagnosis, can only be made with a system such as the polysomnography, to which we must refer for difficult or undetected cases. Snoring analysis is not likely to replace the conventional diagnosis procedure of SAHS through a polysomnographic study and a complete clinical evaluation, but it can significantly improve the management of this pathology (61). Automatic snoring analysis and the application of methods such as ours could also be helpful for the follow-up of snorers without SAHS before and after application of medical and surgical therapies.
V.1 - Sleep and the EEG signal

Sleep is not a passive event, but rather an active process involving characteristic physiological changes in the organs of the body. During sleep all activity of the Somatic Nervous system is suspended (SoNS, in charge of voluntary control, conscious control) and therefore all voluntary movement is suspended, along with a poor response to external stimuli. Although several features of the Autonomic Nervous System (ANS responsible for involuntary control, unconscious) are associated almost exclusively to this period, the ANS also reduces its activity to meet the metabolic needs of organism. The low ANS activity is measured by Somers et al. (200) in the peroneal nerve showing that sympathetic ANS activity progressively decreases during sleep except in REM sleep phase whose activity intersperses with periods where activity is inexisten with short periods of intense activation. This explains the decrease during sleep in functions such as salivation, digestion, intestinal activity, glucose release from the liver, urinary bladder release, heart rate acceleration, relaxation (dilatation) of the airways or peripheral vascular resistance. This leads to a decrease in metabolic rate between 5-17% during the sleep period (164). ANS functions during sleep can be physical: physical recreation (resting state of the cardiovascular system), endocrine (glucose metabolic balance), immunologic functions, contribution to the growing process and protein synthesis, or mental: mental restoration, memory and/or behaviour consolidation, elimination of irrelevant memories, brain maturation, motivation regulation and adaptation to emotional conflict.

Scientists study sleep by measuring the electrical changes in the brain using electroencephalograms (EEGs), which can be acquired during an all-night polysomnographic study. In conventional scalp EEG, the recording is obtained by placing 10-20 electrodes on the scalp with a conductive gel or paste (II.6.2.1-Sleep Recording section). The electrodes measure very small voltages caused by synchronized activity in very large numbers of synapses (areas of near contact between two neurons) in the brain’s outer layers (cerebral cortex). Scalp EEG activity shows oscillations at a variety of frequencies. Several of these oscillations have characteristic frequency
ranges, spatial distributions and are associated with different states of brain functioning (e.g., wakefulness and various sleep stages). These oscillations represent synchronized activity over a network of neurons.

Other than its use in sleep-analysis, as for example in the assessment of the quality of sleep, in diagnosis, monitoring and managing sleep-related disorders, EEG is also an important clinical tool in general, as for example in epilepsy (localized or generalized convulsion waves), in judging the degree of maturity of the brain, in monitoring anesthesia, and in the diagnosis of brain death (220).

The EEG typically has amplitudes from 10 to 100 µV and a frequency content from 1 to 30Hz. Signals of 10-30µV are considered as low amplitude and potentials of 80–100µV are considered as high amplitude. An alert adult displays a low amplitude EEG of mixed frequencies in the 16-25Hz range (beta), while a relaxed adult produces large amounts of sinusoidal waves, in the 8-12 Hz range (alpha), which is particularly prominent at the back of the head. In many disease states, EEG activity tends to be either in the 1-4Hz range (delta) or the 4-8Hz range (theta). Sleep is composed of a periodic sequence of states during which the organism displays physiological characteristics radically different from wakefulness. These include both transient and long-term changes in brain activity, body movement, cardiac function and respiration (81). In the context of sleep analysis, we assume that the relevant frequency content of the EEG signal is in the 1–25Hz range (14). Below we summarize the content of each of the frequency bands in sleep analysis. There is not a universally accepted standard for the definition of these frequency bands. However, various schemes that appear in the literature differ only slightly, hence we may assume that our analysis will not be significantly influenced by the particular choice of the frequency band definitions:

- **Delta band** (δ, 1-4Hz): Tends to be the highest in amplitude and the one that has the slowest waves. It is seen normally in adults in slow wave sleep, corresponding to deep sleep.

- **Theta band** (θ, 4-8Hz): May be seen in drowsiness or arousal in adults; it can also be seen in meditation. Also very present while falling asleep.

- **Alpha band** (α, 8-12Hz): Generally corresponds to (although not as much as beta band) alertness or awake state.

- **Sigma band** (σ, 12-16Hz): Occurs mostly in light sleep and consists mostly of patterns of sleep spindles and K complexes. Spindles and K complexes can last at least 0.5s of duration. The spindles, also called sleep spindles are high frequency discharges in the frequency range of 12-14Hz, having oscillatory amplitude with many ups and downs. The K complexes are slow discharges, negative (upward) and with high amplitude that continue immediately to a positive slower deflection (downward).
- **Beta band** ($\beta$, 16-25Hz): Beta activity is closely linked to alertness and motor behaviour. Generally appears when the nervous system is active, during periods of sensory input and mental activity.

An illustrative example of amplitude and frequency of the previous bands is shown in Figure 26.

![Illustrative example of brain waves and activity patterns observed in sleep analysis. From http://alleydog.com/topics/consciousness_sleep.php](http://alleydog.com/topics/consciousness_sleep.php)

Sleep fluctuates cyclically between two fundamentally distinct neurophysiological states referred to as Non-Rapid Eye Movement (NREM) and REM, or active sleep. NREM sleep is further divided into four stages, namely stages 1, 2, 3, and 4, which are distinguished from each other principally on the basis of EEG. NREM sleep is slower and usually of higher voltage than that of wakefulness. As sleep gets deeper, the brain waves get slower and have greater amplitude.
An interesting summary of the most important physiological changes the individual suffers during each sleep stage is shown in Table 21. On the next sections we will provide a more detailed description of the sleep stages as well as a characterization of the polysomnographic signals in each stage according to Rechtschaffen & Kales rules (164),(177) and as recommended by the AASM (10) prior to its new revision in 2007 (92).

<table>
<thead>
<tr>
<th></th>
<th>NREM</th>
<th>REM</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Time</strong></td>
<td>Stage 1: 4-5%</td>
<td>Stage 2: 45-55%</td>
</tr>
<tr>
<td></td>
<td>Stage 3: 15-20%</td>
<td>Stage 4: 20-25%</td>
</tr>
<tr>
<td><strong>Level of conscience</strong></td>
<td>Response to external stimuli.</td>
<td>Difficult to awaken. Wakes up confused and disoriented. Unable to remember dreams.</td>
</tr>
<tr>
<td><strong>Function</strong></td>
<td>Physical restoration</td>
<td>Mental restoration</td>
</tr>
<tr>
<td><strong>Memory</strong></td>
<td>Improvement of declarative memory</td>
<td>Improvement of procedural memory</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>EEG</strong></td>
<td>Low amplitude α and θ waves and vertex waves</td>
<td>Low amplitude θ waves, spindles and K complexes</td>
</tr>
<tr>
<td></td>
<td>High amplitude: θ, δ &gt;20% and &lt;50% (&gt;75µV)</td>
<td>High amplitude: θ, δ &gt;50% (&gt;75µV)</td>
</tr>
<tr>
<td><strong>EOG</strong></td>
<td>Slow eye movements</td>
<td>Occasional eye movements</td>
</tr>
<tr>
<td></td>
<td>No eye movements</td>
<td>Rapid opposite phase eye movements</td>
</tr>
<tr>
<td><strong>EMG</strong></td>
<td>Muscle tone reduce: medium-low amplitude</td>
<td>Low amplitude</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Lowest amplitude</td>
</tr>
<tr>
<td><strong>ANS</strong></td>
<td>Low sympathetic activity</td>
<td>Very low sympathetic activity</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Short duration but intensive sympathetic activity</td>
</tr>
<tr>
<td><strong>Ventilation per minute</strong></td>
<td>Reduced by 13%</td>
<td>Reduced by 15%</td>
</tr>
<tr>
<td><strong>Respiratory Rate</strong></td>
<td>Stable</td>
<td>Very stable</td>
</tr>
<tr>
<td><strong>Heart rate</strong></td>
<td>Stable and following the respiratory rhythm.</td>
<td>Increases with the ANS</td>
</tr>
<tr>
<td><strong>HRV</strong></td>
<td>Expressed by short-term correlations</td>
<td>Expressed by long-term correlations</td>
</tr>
<tr>
<td><strong>Arterial Pressure</strong></td>
<td>Reduced up to 10-15%</td>
<td>Increases with ANS</td>
</tr>
<tr>
<td><strong>Temperature</strong></td>
<td>Core temp. reduces</td>
<td>Core temp. reaches minimum</td>
</tr>
<tr>
<td></td>
<td>Pheripheral temp. increases</td>
<td>Core temp. increases progressively</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Thermoregulation inhibited</td>
</tr>
<tr>
<td><strong>Hormonal</strong></td>
<td></td>
<td>Growing hormone secretion</td>
</tr>
</tbody>
</table>

Table 21 Changes produced in physiological variables classified according to sleep stage. (29), (164), (167).
**V.1.1 - Wakefulness**

The first phase of the study is wakefulness, which corresponds to the awake state. The characteristics of polysomnographic signals are:

- **EEG:** Low amplitude and high frequency bands mainly alpha and beta. The beta band appears in mental effort activities, so that in studies where the patient may be awake but in a resting state, it is considered that the wakefulness includes only the alpha band (8-12Hz) and mixed frequencies (2-7Hz). Any of the previous representing more than 50% of the epoch.
- **EMG:** Amplitude relatively high as a result of the patient's movements while awake.
- **EOG:** The EOG of the right and left eye has large amplitude peaks with opposite phases, at the same time instant.

**V.1.2 - Slow wave sleep or NREM**

The following phases are included in NREM sleep. They consist of four sleep stages numbered from 1 to 4 according to greater sleep depth.

- **Stage 1:** Stage 1 occurs at the onset of sleep or sometimes after an awakening event occurred after NREM stages 2, 3, 4 or REM. This stage lasts only a few minutes constituting 4-5% of total sleep time. Sleep is light and external stimuli are perceived, making it easily interruptible and consequently unrestful sleep. Muscle activity slows down (although some individuals experience sudden muscle contractions), breathing is calm and heart rate drops slowly.
  - **EEG:** low amplitude and mixed frequencies (2-7Hz), mainly in the theta range (4-8Hz), over 50% of the epoch and less than 50% of alpha frequency (8-12Hz). Fairly often vertex waves appear (waves with high amplitude and frequency peaks), but no spindles nor K complexes.
  - **EMG:** low amplitude, but higher than in the subsequent sleep stages, except for wakefulness.
  - **EOG:** eye movements are slow (called SEMs). As in REM, the electrooculogram of left and right eye present opposite phase peaks, but in this stage they have much lower amplitude and last longer.

- **Stage 2:** Stage 2 usually appears after stage 1 and represents between 45-55% of total sleep time. This stage corresponds to the beginning of sleep itself.
Chapter V - Arousals

J.M.G. Mesquita

- EEG: Low amplitude and frequencies mostly in the theta range, which makes it somewhat slower than Stage 1. It is characterized by the presence of spindles and K complexes of more than 0.5 s. This stage can also have up to 20% of high-amplitude delta waves.
- EMG: Lower amplitude than in the previous stage.
- EOG: Eye movement disappears but occasionally SEMs appear.

• **Stages 3 and 4:** The set of 2 stages is called slow wave sleep, delta or deep, and constitutes 15-20% of total sleep. Stage 3 usually appears only in the first third of the sleep cycle and constitutes 4-6% of it. Stage 4 constitutes 12-15%. Because these stages correspond to deeper sleep, it is very difficult to wake someone while at it and, when able to do so, the subject would wake up confused and disoriented. Apart from sleep itself being the most restful during these stages (especially in stage 4) it is usually in these stages that non reported dreaming take place, nightmares, in the case of children, and sleepwalking. Muscle activity and heart and respiratory rate decrease with respect to the other NREM stages.
  - EEG: Large number of high amplitude waves (greater than 75µV) and very slow, i.e. with very low frequencies, in the delta range (1-4Hz). The difference between stage 3 and 4 lies in the amount of delta waves. Thus, the subject is in stage 3 if, for a given signal period, more than 20% but less than 50% are waves with amplitude greater than 75 µV and frequency between 1 to 2 Hz (this range is called slow delta). If that percentage is more than 50% then the subject is at stage 4, in which case the brain produces delta waves almost exclusively.
  - EMG: low amplitude.
  - EOG: No eye movements.

**V.1.3 - Rapid sleep or REM**

This stage differs fundamentally from the others in the fact that consists of a multitude of rapid eye movement (REMs), as in wakefulness. It is also in this stage where vivid and emotional dreaming is reported, in many cases, containing colourful and eccentric events which the subject is able to describe with detail (in 80% of cases). During REM breathing becomes more rapid and irregular and heart rate increases, arterial blood pressure rises, males experience erection and the body loses the ability to regulate its temperature. There is an increase in cerebral blood flow and metabolism. The limb muscles become temporarily paralyzed (muscle atonia) which prevents the
subject from theatricalising the dream. In a healthy subject, the first REM episodes episode should appear within the first 60-90 minutes of sleep. Most subjects should undergo three to five episodes of REM sleep each night, although the duration of REM sleep decreases progressively with age. Thus, children spend almost 50% in REM sleep, while adults spent only a 20-25% of time in this sleep stage. This is why this stage is believed to be strongly correlated related to brain maturation.

- EEG: Low amplitude and frequencies in the alpha-theta range, similar to stage 1. Sawtooth waves may be present (the wave ramps upward and then sharply drops, resembling to the teeth on the blade of a saw) with slow activity (3-5 Hz).
- EMG: Very low amplitude, because REM stage is characterized by muscle atonia. In truth, it is the stage with lower amplitude level.
- EOG: The electrooculogram of the right eye and left often have large amplitude peaks with opposite phases, at the same time instant. These sparks are called REMs, which also appear in the awake stage.

Normal sleep progresses from light to deeper stages and returns to light stages typically in the following order: 1 → 2 → 3 → 4 → 3 → 2 → REM. Figure 27 shows an hypnogram that graphically depicts the pattern of cycling we experience. It consists on a simple way to represent the stages of sleep as a function of time.

![Figure 27](http://science.education.nih.gov/supplements/nih3/sleep/guide/info-sleep.htm)

The cycles, lasting 90–120 min, are present in the first portion of the night and may repeat 2 to 4 times over the night, with the REM episodes tending to increase in length. Periods of wakefulness during the night may also be observed. Wakefulness and REM sleep correspond to cortical activation whereas NREM sleep corresponds to quiescence. Wakefulness is distinguished from sleep by awareness of the environment, capacity to develop meaningful responses to external stimuli, and ability to perform complex, coordinated sensorimotor tasks. In NREM sleep, mental activity is minimal, if any, and sensorimotor responses to external stimuli are generally limited to
simple reflexes, such as withdrawal from pain. In addition, the threshold for eliciting response is increased compared to its wakefulness level. However, sleep differs from other states of diminished consciousness, such as anesthesia and coma, by the ability to awake quickly in response to sufficient stimulation.

**V.2 – Arousals**

**V.2.1 – Definition and scoring**

According to the American Sleep Disorders Association (ASDA), the term ‘arousal’ conventionally indicates a temporary intrusion of wakefulness into sleep (11). Frequent arousals result in fragmented sleep and lead to increased daytime sleepiness. The transition from sleep to wakefulness is characterized by abrupt changes in electroencephalographic (EEG) and skeletal muscle activity (177). This response is triggered by the brainstem reticular activating system (RAS). The RAS receives input from sensory systems, and has projections via the thalamus, hypothalamus, subthalamus, and basal forebrain of the cortex (154).

Arousals are identified by labour-intensive, extensive and expensive polysomnography performed in sleep laboratories. They may take the form of abrupt changes in EEG rhythm, suggestive of an awake state (often termed desynchronization), brief increases in electromyographic (EMG) amplitude and/or visible behavioural awakening. Although somewhat contested, the ASDA rule for scoring arousals, still gathers relative consensus and is the most widely used (11). The ASDA criteria recommends arousals to be scored from either central or occipital derivation and defines arousal as an abrupt shift in EEG frequency of 3s or more in duration, which may include theta, alpha and/or frequencies greater than 16Hz but not spindles, subject to the following rules and conditions:

- Subjects must be asleep, defined as 10 continuous seconds or more of the indications of any stage of sleep, before an EEG arousal can be scored. A minimum of 10 continuous seconds intervening sleep is necessary to score a second arousal.
- The EEG frequency shift must be 3s or greater in duration to be scored as an arousal.
- Arousals in NREM sleep may occur without concurrent increases in sub-mental EMG amplitude.
- Arousals are scored in REM sleep only when accompanied by concurrent increases in submental EMG amplitude.
- Artefacts, K complexes or delta waves are not scored as arousals unless accompanied by an EEG frequency shift (as previously defined) in at least one derivation. If such activity precedes an EEG
frequency shift, it is not included in reaching 3s duration criteria. When occurring within the EEG
criteria. artefacts or delta wave activity are included in meeting the duration criteria.

- Non-concurrent, but contiguous, EEG and EMG changes, which were individually less than 3s in
duration, are not scored as arousals.
- Intrusion of alpha activity of less than 3s duration into NREM sleep at a rate greater than one
burst per 10s is not scored as an EEG arousal. Three seconds of alpha sleep is not scored as an
arousal unless a 10s episode of alpha-free sleep precedes.
- Transitions from one stage to another are not sufficient of themselves to be scored as EEG
arousals unless they meet the criteria indicated above.

From the above criteria, it is clear that the arousal scoring criteria are based on the EEG
signal alone with only one exception: scoring of arousal during REM sleep requires the presence of a
simultaneous increase in the EMG amplitude. The presence of bursts of alpha or theta activity in
REM sleep EEG is a common phenomenon; however, not all of these events reflect physiological
arousal from REM sleep. Therefore, to reliably score arousal from REM sleep, we need the additional
requirement of EMG amplitude increase.

The principle of defining an arousal as being 3s or greater in duration is a methodological
decision rather than a physiological one, as the identification of events of shorter duration may be
difficult to achieve practically. Nonetheless, some authors choose to apply a shorter arousal duration
definition by proposing the study of frequency shifts greater than 1 second (132),(144),(190). The
latter works all refer to criteria being applied in the context of children sleep fragmentation analysis.
However, several authors, while working with adult databases, have also opted to modify the time
threshold to 1s or 1.5s (38),(47),(68),(129),(172). Their choice is founded on the premise that it
allows improving detail in the analysis (130).

Apart from the event duration itself, other suggestions have been made to refine arousal
scoring to include or focus on other physiological responses such as heart rate or blood pressure
changes. Studies have found that autonomic signs of arousal (i.e., blood pressure changes, heart rate
changes) always accompany EEG arousal (ASDA definition) and strongly support the idea of including
information on this autonomic activity in a new arousal scoring definition (34),(44),(79),(169),(208),(221). Other studies have suggested that other events such as K complexes
or bursts of delta waves may also be forms of arousal that need to be considered, although there is
continuing controversy concerning whether K complexes and delta-bursts could reflect a
“disruption” or a “protection” of sleep (41),(78).

Thus, in the last few years, several researchers have questioned the reliability of the
currently used ASDA definition for scoring arousals and agree that it needs to be reviewed as it may
be causing the underestimation of its impact in daytime sleepiness and sleep fragmentation (24),(78),(154),(203),(208),(211). Since several studies continue to support EEG arousals as an important component of the sleep process, the improvement on the scoring reliability of EEG arousals is essential in clinical PSG as a means of determining the extent to which daytime compromise is specifically related to sleep disturbance and to give treatment response guidelines to practitioners.

V.2.2 - Role of arousals in sleep

For some authors (17),(78),(187) arousals have an essential role on the regulation of the sleep process, ensuring the reversibility of sleep, without which it would be identical to coma. Although sleep is characterized by decreased conscious perception, tasks such as control of the autonomic, metabolic and hormonal changes are accomplished nevertheless during sleep through a partial activation confined to some cerebral areas. In the mentioned authors’ perspective, such activation is stimulated by the arousal system. Arousals are therefore, responsible for connecting the sleeper with the surrounding world maintaining the selection of relevant information; adapting the organism to the dangers and demands of the outer world, and most importantly, restoring homeostasis during respiratory and cardiovascular failure during sleep providing an excitation drive to vital processes (78).

Nevertheless, several empirical studies in animals, humans, and clinical populations have shown links between the frequency of EEG arousals, sleep fragmentation and daytime sleepiness, supporting the idea that the former represents a detrimental and harmful feature on sleep (25),(35),(202). Increasing the frequency of arousals and the number of nights during which arousals are induced increases residual sleepiness, and this effect is independent from reduction in EEG sleep stage amounts. In addition to sleepiness, sleep fragmentation produces numerous effects such as decreased psychomotor performance, degraded mood, altered hormone secretions, decreased pulmonary function, altered metabolic rate, increased arousal thresholds, and alteration in EEG evoked responses similar to that seen after total sleep deprivation. Sleep fragmentation may also result in sleep stage rebounds. Finally, patients with sleep fragmented by respiratory or movement disorders have been shown to have improved alertness and psychomotor function when arousals during sleep have been reduced (181).

In what concerns sleep-related breathing disorders, arousal from sleep is believed to be an important, if not crucial, mechanism for reestablishing airway patency in sleep apnea episodes (178). This notion was reinforced over the years by the everyday observation that apneas and hypopneas
end abruptly and almost invariably with arousal. Fairly recently, efforts are being made towards understanding the actual role of arousal during sleep in subjects with SAHS, understanding the mechanisms for their occurrence and also determining if they are needed to initiate opening of the UA (or obtain adequate flow) and promote recurrence of the obstruction or not (42),(101),(234),(235),(231). The major findings were firstly introduced by Younes (234) who concluded that arousals are incidental events that occur when thresholds for arousal and for arousal-independent opening mechanisms are close. That said, arousals are not needed to initiate opening or to obtain adequate flow and they likely increase the severity of the disorder by promoting greater ventilatory instability. Later on, and consistent with Younes’ achievements, Jordan et al. (101) demonstrated that respiratory events that are terminated with an ASDA arousal are associated with greater hyperventilation and are more likely to be followed by a secondary respiratory events. They extended the findings of Younes by assessing dilator muscle activity on both initial and secondary respiratory events. More specifically, studies such as Younes’ (234), Longobardo et al. (118) and Jordan et al. (101) suggest that normal breathing can be recovered with no need of arousal and respiratory arousals will actually induce the further occurrence of apneas. This is founded on the premise that chronic sleep fragmentation may alter the chemoreceptor’s sensitivity which can conduct to an elevation of the awakening reaction (73). This theory is not only supported by epidemiologic studies but also by a respiration control model developed by Longobardo et al. (118) that analyses the influence of the arousal threshold on the respiratory stability.

In addition to the former discussions that continue to spark the debate on the controversial topics of arousal scoring and its actual role on the sleep process, there is also a rising debate concerning two types of arousals: *respiratory* and *spontaneous* arousals. This debate makes sense after recognizing that the arousal phenomenon is a key mediator of sleep fragmentation in SAHS subjects and the main responsible for daytime impairment in areas such as alertness/wakefulness and psychomotor functioning. We strongly believe that understanding the mechanisms behind the two types of arousals will offer new insights on the prominent role arousals play in the SAHS pathogenesis.

*Respiratory arousals* are immediately correlated with the severity of SAHS since they occur within 3 seconds (or less) following or overlapping an apnea/hypopnea (21). Being a mechanism of recovery from respiratory events during sleep, arousals are nonetheless considered to be important markers of the morbidity of this disease (169),(181). Besides the effects of recurrent hypoxemia, the surges in heart rate and blood pressure observed with arousal terminating an obstructive apnea are
implicated in the cardiovascular morbidity of SAHS, such as hypertension and myocardial infarction (44),(180),(193). Furthermore, the presence of arousal results in enhanced hyperventilation on termination of disruptive respiratory events (101),(234). Nevertheless, spontaneous arousals have also demonstrated to lead to excessive daytime sleepiness and reduced psychomotor functioning (26),(30),(154),(172),(241). Spontaneous arousals can result as an activation of an organic trigger such as intestinal passage, excessive bladder loading, organ dysfunction, harsh episodes of bruxism and other unknown causes.

Given its patent correlation with SAHS, respiratory arousals continue to deserve top place on the arousal research topic (42),(58),(101),(169),(204). Moreover, the majority of works that take in the study of both events (respiratory and spontaneous) are mainly focused on studying the reliability of proposed methods to detect both types of events or rather in attaining the effectiveness of others to treat them (133),(172). Tauman and co-workers (207) studied the indices of respiratory and spontaneous arousals and their correlation with the AHI, the sleep pressure score (SPS) and the Epworth sleepiness scale (ESS) whereas Dingli et al. tried to correlate them with sleep staging (47). However, neither of them has truly focused on characterizing them nor on trying to ascertain the differences between the content of these two types of arousals.

To the best of our knowledge an actual comparison between the content of respiratory and spontaneous arousals has not yet been performed in a wide range of SAHS subjects. Thus, on our work we aim to assess their differences through feature analysis and also to correlate them with the SAHS severity level of the subjects. Bonnet et al. (24) bluntly point out that the scoring of arousals and the controversial discussions around its role in sleep may have added much to our understanding of the sleep process but significant work on the neurophysiology of arousal still needs to be done. We are convinced that additional knowledge on respiratory and spontaneous arousals will provide an improved awareness on how the trigger mechanisms influence the brain response of the two different types of arousals and this may offer new insight into their effect on SAHS pathology.

V.3 - Polysomnographic EEG database and pre-processing

For the arousal study we made use of the PSG nocturnal data of 47 subjects with AHI range of 0.2-109.9h⁻¹. This database is part of the 116 subjects’ database previously described on III.3- Database section. More precisely, we used the C3A2, C4A1 and O1A2 EEG tracings and the ECG signal. With respect to EEG tracings, the ASDA task force on scoring arousals (11) recommends the scoring to be performed on the C3A2 and C4A1 tracings although it also advises the use of an
occipital referential EEG derivation. Finally, the criteria recommend arousals to be scored from either the central or occipital derivation EEG. More recently in 2007, AASM published a revised manual on scoring sleep and associated events (92) and reinforced that arousal scoring should incorporate information from both the occipital and central derivations. Given the previous recommendations we decided to expand our study to the O1A2 derivation rather than using only the central derivations as it is common procedure in the majority of works published on the EEG arousal research topic (46),(211),(223),(234).

As previously stated on the III.1-Polysomnography section, the polysomnographic signals were acquired using the computerized recording system: Compumedics E-Series Sleep System (Figure 28).

Figure 28 a) Profusion PSG 2 software printscreen with a respiratory arousal event marked on the C3A2 tracing and corresponding obstructive apnea marked on the cannula signal. b) Electrode placing positions for EEG acquisition.
In the context of sleep analysis the relevant frequency content of the EEG signal is in the 0.3-30Hz range, so we applied (to the 3 EEG derivations with 256Hz sampling frequency) a seventh order zero-face Butterworth filter with cut-off frequencies set at 0.3 and 30Hz and a 50Hz-notch filter for power line noise reduction (Figure 29).

EEG is expected to be a recording of the brain electrical activity but it may contain electrical activities arising from sites other than the brain (artefacts). HUGTP sleep physicians manually checked the EEG tracings searching for eventual impairing artefacts and reported them throughout the study. Nonetheless, we also performed visual inspection of the EEG tracings and observed that the ECG component was rather present throughout the whole signal tracings. Thus, we decided to apply an adaptive filter to minimize that ECG component that might be contaminating the EEG signals (Figure 29). We applied a recursive least square (RLS) adaptive filter where the primary input was the EEG signal and the reference input was the ECG signal (82). The adaptive filter was designed according to a previous application to cancel ECG in the EEG signal (149). The order of the adaptive filter was set to 10, the forgetting factor and the regularization factor on the weighted least squares cost function were set to 0.999 and to 0.01, respectively. A 15 second short segment of signal is shown in Figure 30 for the 3 EEG tracings, where the contaminated signals are shown in red and the final clean tracings are shown in blue.

Figure 29 EEG filter application scheme.

**Figure 29 EEG filter application scheme.**
Consequently, for each of the 47 subjects we had 3 clean EEG tracings (C3A2, C4A1 and O1A2) and the next step consisted in extracting the excerpts of arousal signal from the whole night EEG tracings (Figure 31). So, finally, we obtained a structure that included the arousal signals from the 3 EEG tracings together with practical information on each arousal event such as type of arousal, associated respiratory event (if any), starting time instant and duration of the event, sleep stage, etc. A summary of the most important database variables and characteristics is shown in Table 22.
Figure 31 Example of resulting clean EEG arousal.

Table 22 Database characteristics on the EEG arousal study. 

<table>
<thead>
<tr>
<th>N Subj</th>
<th>BMI</th>
<th>Age</th>
<th>AHl</th>
<th>AROUSAL Nr</th>
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<td>100</td>
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<td>(8 F; 39 M)</td>
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<td>10.7</td>
<td>28.5</td>
<td>50</td>
<td>38</td>
<td>50</td>
<td></td>
</tr>
</tbody>
</table>

Table 22 Database characteristics on the EEG arousal study. n=total number. m=mean value. sd=standard deviation. BMI = body mass index in kg/m²; AHl = Apnea-Hypopnea Index in h⁻¹. AROUSAL Nr = arousal number. Ev. Dur = mean and sd duration of the arousal events in seconds. RESP AR Nr = number of respiratory arousals. SPONT AR Nr = number of spontaneous arousals.

V.4 - Scoring of sleep data

All PSG subjects’ recordings were scored using Profusion PSG 2 software. The recordings were scored in accordance with Rechtschaffen and Kales rules (177) for sleep staging and the Task Force of the ASDA (11) criteria for arousal scoring, respectively. Respiratory events (central, mixed and obstructive apneas and hypopneas) were also scored according to the American Academy of Sleep Medicine (AASM) rules for scoring respiratory sleep disordered breathing events (9). Final scoring was performed and double checked by a human expert, blinded to the subject.

V.4.1 - Respiratory and spontaneous arousals scoring

As explained on the preceding section, arousals were scored as recommended by the ASDA task force criteria and manually checked afterwards by a HUGTP sleep physician in order to identify possible false positives and false negatives. The annotations of arousals events were exported (with
Profusion PSG 2 software) simultaneously with the sleep tracings and consisted in two different tags: respiratory and spontaneous arousals (Table 22 on V.3-Polysomnographic EEG database and preprocessing section).

To our knowledge there is still no consensus on the duration of the time interval between a respiratory event and an arousal event so that the latter is scored as respiratory arousal. Our respiratory arousals’ annotations are in agreement with Dingli et al. (47) and Tauman et al. (207) definitions: occurring within three seconds (or less) following or overlapping an apnea or hypopnea. Nonetheless, we decided to further investigate the arousal annotations and the respiratory events. We came across with different types of spontaneous arousals and we labeled them as situations: starting on 1 and ending in 9 (Figure 32 b)). Without further thinking, one would immediately expect spontaneous arousals to be labeled as such only if they obeyed to situation 4. However, by the time we recognized this, we were not preoccupied in giving an answer to it but rather in identifying all situations properly. Although we anticipate that all spontaneous labeled situations (except situation 4) may arguably be seen as spontaneous arousals, given that in some cases they are on the verge of being tagged as respiratory arousals. With respect to respiratory arousals the tagging was in agreement with the previously mentioned definition (Figure 32 a)).

Figure 32 Respiratory and spontaneous arousal tagging. a) Respiratory arousal tagging. b) Spontaneous arousal tagging. RESP stands for respiratory arousal, SPONT stands for spontaneous arousal and RE stands for respiratory events.
V.5 - Characterizing respiratory and spontaneous arousals

Motivated by the former argumentations (V.2.2-Role of arousals in sleep section) we wanted to properly characterize both arousal types: respiratory and spontaneous arousals. Our first step consisted in building a set of features that were able to do so. We computed a set of features for each arousal event. The whole set of features can be divided in three groups: T) Temporal, M) Marginals and S) Spectral.

T) Temporal:

The temporal feature set is composed of the following temporal features: t1) mean, t2) standard deviation, t3) median, t4) kurtosis, t5) skewness and t6) maximum value of each arousal signal segment.

M) Marginals:

An important field of EEG research is devoted to the study of brain activities that are transient and “localized” in space and time. Wavelet is an effective time-frequency analysis tool for analysing transient signals. Its feature extraction and representation properties can be used to analyse various transient events in biological signals (5),(16),(57),(212). More precisely, the wavelet transform is an effective tool in signal processing due to its attractive properties such as time-frequency localization (obtaining a signal at particular time and frequency, or extracting features at various locations in space at different scales) and multi-rate filtering (differentiating the signals having various frequencies). Discrete wavelet transform (DWT) projects a signal into a set of basis functions that are scaled and delayed versions of a prototype function (mother wavelet). The projection coefficients are obtained by multiresolution analysis (MRA) through the application of a bank of digital filters (125). We were interested in using wavelet decomposition on our arousal study, given that we aimed to characterize arousals according to their content. The DWT marginals reflect the average signal intensity over dyadic subbands. The marginals (can be seen as signal intensity) were previously proposed by Farina et al. and Vautrin et al., also in the context of EEG signal analysis, to represent a signal over the frequency bands (57),(212). They are an example of transformation of the wavelet coefficients and are calculated at each node of the decomposition and defined as follows:

\[
m_x(j) = \sum_{k=0}^{2^j-1} c_x(j,k), \quad j = 1, \ldots, J
\]

\[
c_x(j, k) = \frac{|d_x(j,k)|}{\sum_{j=1}^{J-1} \sum_{k=0}^{2^j-1} |d_x(j,k)|}
\]

\[
m_x(j) = \sum_{k=0}^{2^j-1} c_x(j,k), \quad j = 1, \ldots, J
\]

\[
c_x(j, k) = \frac{|d_x(j,k)|}{\sum_{j=1}^{J-1} \sum_{k=0}^{2^j-1} |d_x(j,k)|}
\]
The N coefficients $dx(j,k)$ of the decomposition of a discrete signal $x$ of length N are computed using $h$ and $g$ filters (125). $J$ is the deepest level of the decomposition $J = \log_2 N$. The features that will represent the signal $x$ are the components of the vector $M_x = [m_x(1), \ldots, m_x(J)]$. The vector $M_x$ contains information on the distribution of the wavelet coefficients over J bands. It allows the representation of the signal by the contributions of each frequency band (derived from a dyadic scale) computed with the orthogonal Daubechies order 4 wavelet. Daubechies wavelet was the chosen analysing wave because it has previously proven to be appropriate to apply to EEG analysis due to its orthogonality property and efficient filter implementation. Higher orders Daubechies have more oscillations which are not required to our analysis and are computation costly. The range of our physiological interest is between 0.3 and 30 Hz. This range is classified approximately in a number of frequency bands: delta, theta, alpha, sigma and beta. The dyadic scale decomposition allows our signal (sampling frequency= 256Hz) to be decomposed in 7 levels (Figure 33). The wavelet decomposed components, $d_7$ and $d_6$ are within the delta EEG band (1–4Hz), $d_5$ within theta band (4–8Hz), $d_4$ contains both alpha and sigma bands (8–1 Hz) and $d_3$ within the beta band (16-25Hz). The lower level decompositions $d_1$ and $d_2$, corresponding to higher frequencies have negligible magnitudes in normal EEG.

Our set of marginal features consists in the vector $M_x$. $M_x$ vector contains five features: m1) marginal of level 3, corresponding to component $d_3$ (16-32Hz); m2) marginal of level 4, corresponding to component $d_4$ (8-16Hz); m3) marginal of level 5, corresponding to component $d_5$ (4-8Hz); m4) marginal of level 6, corresponding to component $d_6$ (2-4Hz) and m5) marginal of level 7, corresponding to component $d_7$ (1-4Hz).

Figure 33 Wavetree for fs=256Hz, with all decomposed components. Our vector of features $M_x$ is composed of: m1) detail coefficient $d_3$, m2) detail coefficient $d_4$; m3) detail coefficient $d_5$; m4) detail coefficient $d_6$ and m5) detail coefficient $d_7$. 

\[ Fs = 256Hz \]
5) **Spectral**

The representation of power distribution as a function of the EEGs constituent frequencies (power spectral density, PSD, curve) is a usual method used on signal processing. For the PSD calculation, the nonparametric Fast Fourier Transform (FFT) algorithm was applied, using the technique as described by Welch et al.: the Welch periodogram (216). The Welch periodogram with a 128 length Hamming window and 50% overlap was used to generate the power spectral density (PSD) curve (Figure 34).

The following features were computed out of the PSD:

s1) the median frequency of the PSD.

s2) EBW, the equivalent statistical bandwidth (eq. 14) is the bandwidth of a hypothetical rectangular filter which would pass a signal with the same mean square value statistical error as the actual filter when the input is white noise:

\[
EBW = \frac{\int_{0}^{\infty} |\text{PSD}(f)|^2 df \cdot \int_{0}^{\infty} |\text{PSD}(f)|^4 df}{\left(\int_{0}^{\infty} |\text{PSD}(f)|^4 df\right)^{2/3}}
\]  

(14)

s3), s4), s5), and s6): the normalized power values as a fraction of the total power of the frequency bands: delta (1-4Hz), theta (4-8Hz), alpha (8-12Hz) and beta (16-25Hz) bands, respectively. We opted not to include the sigma band in this set of features since some literature has suggested this band should be excluded from sleep analysis because it is mostly composed of sleep spindles and k complexes (11),(14). The area under the spectral curve that corresponds to the power of delta, theta, alpha and beta frequency bands was calculated using the Trapezoidal Integration Method.

s7) the maximum peak spectrum within the frequency range of 4-25Hz (FMaxPeak).

s8) the ratio of the power around the maximum peak (FMaxPeak±2Hz) over the total power of the spectrum.

s9) the skewness of FMaxPeak band.

s10) the kurtosis of FMaxPeak band.
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We should point out that these set of features were calculated for each arousal event and for the 3 derivations because we wanted to study the information given by the 3 tracings. That is, if all 3 performed equally and obtained the same results or similar results were only obtained for the C3A2 and C4A1 tracings given that they correspond to central derivations.

V.6 - Classifying respiratory and spontaneous arousals with the set of features

V.6.1 - Methodology. Statistical feature analysis

The next step consisted in using our previously described set of features to discriminate and classify the two types of arousal: respiratory and spontaneous. The database we used consists on the same 47 subjects previously described on the V.3-Polysomnographic EEG database and preprocessing section. The only difference was the exclusion of 92 arousal events since after computing the PSD curves we observed that those events did not present the peak on frequency range of 4-25Hz which prevented us from calculating some of the features (Table 23).
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Table 23 Database characteristics. RESP AR Nr = number of respiratory arousals. SPONT AR Nr = number of spontaneous arousals. SPONT_RE = number of spontaneous arousals that are overlapped by one or more respiratory events. SPONT_TRU = number of spontaneous arousals that are not overlapped by respiratory events. (see Figure 32).

Provided that our set of features consists on a total of 21 features per arousal and we have an arousal signal for each derivation, we have a total set of 63 features (Table 24). As recommended, before moving on to the classification we applied the Mann-Whitney U test in order to obtain the most significant features on discriminating between respiratory and spontaneous arousals. We decided to apply this test to the whole number of arousals, i.e., testing the effectiveness of the 63 features on discriminating between the two types of arousals: 2392 respiratory arousals versus 4640 spontaneous arousals.

The results showed that in the case of derivation O1A2 only 8 features were able to discriminate between the two types of arousals ($p<0.05$) (Table 25). On the other hand, in the case of derivation C3A2, 12 features succeeded on that task. For the sake of maintaining the same set of features for each derivation and also to include features from the 3 groups of features we decided to use the 12 features that achieved the discrimination between the two groups of arousals.

<table>
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</table>

Table 24 Summary of the feature set. a) Temporal features. b) Marginal features c) Spectral features.
Table 25 \( p \) Mann-Whitney U test values for statistical significance in discriminating between 2392 respiratory arousals and 4640 spontaneous arousals. 12, 11 and 8 features obtained statistical significance for derivations C3A2, C4A1 and O1A2, respectively.

### V.6.2 - Arousal classification

As we recognized the existence of what we considered to be different distinct kinds of arousals within spontaneous arousals, we decided to apply our classification study to distinct opposite groups of arousals. On the V.4.1-Respiratory and spontaneous arousals scoring section we identified the list of situations within spontaneous arousals and here we opted to make a distinction between: spontaneous arousals that are overlapped by one or more respiratory events, SPONT_RE (situations 1, 2, 3, 5, 6, 7, 8 and 9), and spontaneous arousals that are not overlapped by respiratory events (situation 4), SPONT_TRU (Figure 32). So, we are interested in classifying the following groups of arousals:

- **G1)** RESP (2392 arousals) versus SPONT (4640 arousals);
- **G2)** RESP (2392 arousals) versus SPONT_TRU (2076 arousals);
- **G3)** SPONT_RE (2564 arousals) versus SPONT_TRU (2076 arousals);
- **G4)** SPONT_TRU of subjects with AHI\(<15\text{h}^{-1}\) (567 arousals) versus SPONT_TRU of subjects with AHI\(\geq 15\text{h}^{-1}\) (1509 arousals);
- **G5)** SPONT_TRU of subjects with AHI\(<30\text{h}^{-1}\) (917 arousals) versus SPONT_TRU of subjects with AHI\(\geq 30\text{h}^{-1}\) (1159 arousals).
The two last groups (G4 and G5) were created with the purpose of investigating whether there were any marked differences between the SPONT_TRU arousals of subjects with opposite levels of SAHS severity.

For each of the previous groups we built 8 feature matrices to which we would apply our classification problem:
- **AAD**: Matrix with all arousals from the group and all 36 features (12 per derivation).
- **AD1**: Matrix with all arousals from the group and the 12 features from derivation C3A2.
- **AD2**: Matrix with all arousals from group and the 12 features from derivation C4A1.
- **AD3**: Matrix with all arousals from group and the 12 features from derivation O1A2.
- **AADmatPC**: Matrix with all arousals from the group and the 2 first Principal Components (PCA analysis of AAD data matrix)
- **AD1matPC**: Matrix with all arousals from the group and the 2 first Principal Components (PCA analysis of AD1 data matrix)
- **AD2matPC**: Matrix with all arousals from the group and the 2 first Principal Components (PCA analysis of AD2 data matrix)
- **AD3matPC**: Matrix with all arousals from the group and the 2 first Principal Components (PCA analysis of AD3 data matrix)

Principal component analysis (PCA) is a statistical feature extraction/selection technique that is often used with the purpose of dimensionality reduction (3),(50),(99). Principal components can be used to summarize the data in two or three dimensions instead of using all variables that compose the initial data matrix. PCA transforms the featured data onto a new coordinate system along which variance of the featured data matrix is maximized. If the original data matrix contains $p$ uncorrelated variables, then we obtain $p$ principal components (PCs) in the new coordinate system. We performed the PCA on our 4 initial data matrices (AAD, AD1, AD2 and AD3) with the purpose of feature reduction. Since the first few PCs accounted for most of the variance in the original data matrix we calculated the percentage amount of variance explained by the 2 first principal components and obtained an average of $43.3\pm3.2\%$ for the first PC and $19.7\pm1.8\%$ for the second PC. As these two components together explained about 63% of the total variance of the data (for each the 4 data matrices: AAD, AD1, AD2 and AD3) we decided to build the other 4 new matrices: AADmatPC, AD1matPC, AD2matPC and AD3matPC. These latter matrices consist on the two first columns (2 first PCs) of the PC scores matrix, which roughly contains the coordinates of the original data matrix in the new coordinate system.
For each group of arousals (G1, G2, G3, G4 and G5) we followed the classification workflow depicted in Figure 35. The aforementioned feature matrices were employed on some of the most relevant classifiers described in the literature, including AdaBoost (65),(188), Bayes classifier with kernel smoothing density estimate (93) and Discriminant analysis (with linear and quadratic discriminant functions)(109). Bayes and Discriminant analysis classifiers were applied using the Matlab Statistics toolbox (The MathWorks Inc., version 2010b). AdaBoost was also chosen as a classifier given its proven reliability in many areas and also its simplicity. The AdaBoost implementation (GML AdaBoost Matlab Toolbox, MSU Graphics & Media Lab, Computer Vision Group, Moscow, Russia) uses classification and regression trees as weak classifiers with 2 splits and 50 iterations (214). Moreover, evaluation of the classification performance was carried out using N-fold cross-validation. In this strategy, the whole set of arousals is split in N equal parts, where N-1 is used to train the classifier and the remaining fold is used for testing. This is repeated for the N-folds and the classification performance is averaged. In this experiment setting validation was carried out with 5 and 10 folds.

Figure 35 Classification workflow scheme. For the 8 feature matrices the 3 types of classifiers with 2 types of cross-validation

Figure 36 and Figure 37 summarize the classification results. For each group, we selected the combination of classifier and validation that provides the highest performance for each of the 8 feature matrices. As it is depicted in the bar plots we can attain 3 main observations: no good performance results were obtained for none of the 5 groups (for neither of the 8 feature matrices), none of the classifiers stood out in the classification task and there was no improvement on the classification performance when dimensionality reduction was applied.
Figure 36 Best classification performance results for groups G1, G2 and G3 and for all features matrices. AdaB = AdaBoost. DA lin = Discriminant analysis with linear discrimination function. DA quad = Discriminant analysis with quadratic discrimination function. By = Bayes. NF10 = 10 fold cross-validation.
V.6.3 - Conclusions

With the set features we attempted to classify a total of 7032 arousals in two types: respiratory and spontaneous arousals. Four of the most relevant classifiers described in the literature (AdaBoost, Bayes and Discriminant analysis (with linear and discriminant function)) with 5-fold and 10-fold cross validation were employed with that purpose. However, we did not succeed on that task. Moreover, the outcomes were still poor after improving our arousal definition in order to ensure that we were actually classifying events that were truly respiratory and truly spontaneous (group G2). On the other hand, the appliance of dimensionality reduction (using PCA) also showed no significantly different results from the ones obtained using the whole matrices of features.

We may argue the fact that the set of features may not be appropriate to characterize these two types of arousals but to our knowledge no works have been published on this matter neither using this set of features nor any other.

Results obtained for groups G4 and G5, where we attempted to observe differences for opposite levels of severity, led us to question even more the inability to discriminate these two
events given that their trigger mechanisms are thought to be different. Hence, we decided to centre our study on the analysis of the power spectrum of the two events as we believed that the power of the frequency response on each arousal may differ in respiratory and spontaneous arousals. Additionally, we also concentrated our efforts in applying that analysis on each subject individually. Further understanding on the two types of arousals may be underlying on the SAHS severity of the subject.

V.7 - Spectral analysis of EEG arousals

V.7.1 - Database

Driven by the results obtained in the former section we decided to focus our work on the analysis of power spectrum of arousals. In the context of arousal analysis we assume that the relevant frequency content of the EEG signal is in the 4-25Hz, since according to the ASDA criteria (11) and as suggested by other published works (47),(78), the delta frequency band (1-4Hz) corresponds to deep sleep and constitutes an artefact on EEG arousal episodes and should be therefore excluded from this analysis. Bearing that in mind, we applied a high pass filter of fifth order with the stopband at 3Hz and passband at 5Hz (stopband attenuation of 20dB and passband ripple of 3dB) to the arousal signals’ from the 3 EEG tracings.

For this study we worked with 45 subjects (with AHI range of 3.7-109.9h⁻¹) of the previously described database (V.3-Polysomnographic EEG database and pre-processing section). We have excluded two subjects from our study as they presented very few respiratory arousals to carry on a feasible analysis. Following the observations stated on the scoring of respiratory and spontaneous arousal events we decided to reduce our set of arousals to a total of 3980: 1996 respiratory (m±sd=10±2secs duration) and 1984 spontaneous (9±1.2secs). In detail, we included in this study uniquely the respiratory arousals that occurred within 3 seconds (or less) following or overlapping an apnea or hypopnea (Figure 32 a)). From this group we made sure we excluded the respiratory arousals that were associated with scored unsure respiratory events while we wanted to assure we would work with actual respiratory arousals. With respect to spontaneous arousals, we defined spontaneous arousals as the ones that did not overlap with any respiratory events (situation 4 on Figure 32 b)). These spontaneous arousals were formerly defined as SPONT_TRU on the previous Arousal classification section. From now onward whenever we use the term respiratory and spontaneous arousals we will be referring to the preceding definitions. Table 26 depicts the database characteristics for the 45 subjects and also with subjects divided according to AHI cut-point of severity of 30h⁻¹, which will be of interest later on.
Table 26 Database characteristics on the spectral analysis of EEG arousal study. SAHI: subjects with AHI above and under the cut-point of severity of 30h⁻¹.

<table>
<thead>
<tr>
<th></th>
<th>NSUB</th>
<th>BMI</th>
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</table>

Inevitably and as expected, less severe SAHS subjects present a smaller number of respiratory arousals since they produce fewer apneas/hypopneas. Yet, the least severe SAHS subject of our database (AHI=3.7h⁻¹) produced a minimum of 6 respiratory arousals which enabled us to compute the mean PSD curve. For this database, a positive correlation between the number of respiratory arousals and the AHI was obtained and is demonstrated in Figure 38 ($r=0.626$, $p=4.18\times10^{-1}$). Conversely, the number of spontaneous arousals and the AHI show negative correlation ($r=-0.47$, $p=6.87\times10^{-4}$). Furthermore, the corresponding arousal indices were calculated as a function of total sleep time and expressed as per hour of TST (Figure 39, TOTAL=total arousal index, RAI=respiratory arousal index; SAI=spontaneous arousal index). In agreement with Tauman et al.’s results (207), we also observed that the TOTAL was significantly higher in the severe SAHS subjects compared to less severe (Figure 39 a); $r=0.36$, $p=0.015$). Similarly, the RAI showed a significant linear correlation with AHI (Figure 39 b); $r=0.649$, $p=1.429\times10^{-6}$). In contrast, the SAI showed an inverse relationship with AHI (Figure 39 c); $r=-0.402$, $p=0.0062$.)
Chapter V - Arousals

Figure 38 Correlation between the number of respiratory and spontaneous arousals and the AHI of the 45 subjects.

Figure 39 Correlation between a) TOTAI, b) RAI and c) SAI and the AHI of the 45 subjects. TOTAI=total arousal index. RAI=respiratory arousal index. SAI=spontaneous arousal index.
V.7.2 - Spectral analysis. PSD curves

The next step consisted in computing the mean normalized PSD curves of both types of arousals for the 3 EEG tracings (Figure 40, Figure 41, Figure 42). As we were interested in examining the power content of the frequency bands, we also computed the theta, alpha, sigma and beta band power expressed as a fraction of the total normalized power for the resulting mean PSD curve of each type of arousal. These results are presented in Table 27.

Here again, the visual inspection of the mean PSD curves of both respiratory and spontaneous arousals enables us to conclude that there shapes are quite similar and this is verified in the arousals of all 3 derivations. Additionally, the power of frequency bands values for both types are consistent with the visual inspection of the mean PSD curves (Table 27). However, this may be justified by the fact that we are including all arousals from all 45 subjects in the attempt to uncover differences between the two types of arousals. This is rather evident on the right column figures a2) and b2) (Figure 40, Figure 41 and Figure 42), where we acknowledge the existence of very different shapes in the PSD curves.

Figure 40 Derivation C3A2: a1) RESP, respiratory and b1) SPONT, spontaneous mean and mean±sd PSD curves. a2) PSD curves of all 1996 respiratory arousals. b2) PSD curves of all 1984 spontaneous arousals.
Figure 41 Derivation C4A1: a1) RESP, respiratory and b1) SPONT, spontaneous mean and mean±sd PSD curves. a2) PSD curves of all 1996 respiratory arousals. b2) PSD curves of all 1984 spontaneous arousals.

Figure 42 Derivation O1A2: a1) RESP, respiratory and b1) SPONT, spontaneous mean and mean±sd PSD curves. a2) PSD curves of all 1996 respiratory arousals. b2) PSD curves of all 1984 spontaneous arousals.
These latter findings led us to change our strategy while applying spectral analysis (139). Further to not being able to uncover the differences between the two types of arousals when considering arousals altogether, the next step consisted in studying the shapes of the PSD curves for all arousals of each subject (per derivation) and ascertain the differences between the power band values. The purpose was not only to characterize and scrutinize differences between the two groups of scored arousals - respiratory and spontaneous arousal - but also to analyse the changes on the spectral content of these two groups of arousals on subjects with different levels of SAHS severity.

Results for the mean and mean±sd PSD curves of the 3 EEG derivations for a mild (12.1h⁻¹), a severe (47.9h⁻¹) and a very severe SAHS subject (103.8h⁻¹) are shown in Figure 43, Figure 44 and Figure 45, respectively. The visual inspection of both respiratory and spontaneous mean PSD curves allows us to ascertain that their shapes are quite similar and this is confirmed for all 3 derivations. This similarity is observed not only in less severe SAHS subjects but also in more severe ones.
Figure 43 For derivation C3A2 (Der1). a) respiratory and b) spontaneous arousals mean and m±sd PSD curves for a) mild SAHS subject (12.1h⁻¹), b) severe SAHS subject (47.9h⁻¹) and c) very severe SAHS subject (103.8h⁻¹). The mean PSD curves were computed out of a total of a) 16 respiratory arousals and b) 64 spontaneous arousals; b) 65 resp and b) 44 spont; c) 106 resp and c) 37 spont.
Figure 44 For derivation C4A1 (Der2), a) respiratory and b) spontaneous arousals mean and m±sd PSD curves for a) mild SAHS subject (12.1 h⁻¹), b) severe SAHS subject (47.9 h⁻¹) and c) very severe SAHS subject (103.8 h⁻¹). The mean PSD curves were computed out of a total of a) 16 respiratory arousals and b) 64 spontaneous arousals; b) 65 resp and b) 44 spont; c) 106 resp and c) 37 spont.
Figure 45 For derivation O1A2 (Der3), a) respiratory and b) spontaneous arousals mean and m±sd PSD curves for a) mild SAHS subject (12.1h⁻¹), a) severe SAHS subject (47.9h⁻¹) and a very severe SAHS subject (103.8h⁻¹). The mean PSD curves were computed out of a total of a) 16 respiratory arousals and b) 64 spontaneous arousals; a) 65 resp and b) 44 spont; a) 106 resp and b) 37 spont.

For the second part of the analysis, the average band powers (for theta, alpha, sigma and beta bands) of all 45 subjects mean PSD curves were computed for the two types of arousals (Table 28). Results attain what we had already foreseen with visual inspection of PSD curves: no statistically significant differences are observed when comparing spectral content of respiratory and spontaneous arousals.
Finally, the whole set of 45 subjects was divided in two groups according to the cut-point of AHI of 30h⁻¹ (Table 26) and once again the average band powers were calculated for those two groups of subjects (Table 29). The variation of the frequency band powers with respect to SAHS severity shows the same pattern of changes for the two groups: RESP AR and SPONT AR (in all 3 derivations). That is, alpha and sigma band powers values decrease for the more severe SAHS subjects, but no significance is observed in any case. Beta band power values also appear to have no correlation with SAHS severity since no significance is seen comparing subjects with opposite levels of SAHS severity. Theta band power increases with SAHS severity and this increase is only significant (p<0.05) and consistent for spontaneous arousals of derivations C3A2 and C4A1 (Table 29 a) and b)). Correlation between the theta band power of spontaneous arousals (C3A2 derivation) and the AHI is shown in Figure 46 (r=0.366, p=0.013).
**Table 29** Mean and standard deviation band power values for SAHI: subjects with AHI above and under the cut-point of severity of 30 h\(^{-1}\).  
\(p\) = significance obtained using Mann-Whitney U test. Derivations a) C3A2, b) C4A1 and c) O1A2.

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<td>20</td>
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**Figure 46** Correlation between the AHI and the mean normalized theta band power of spontaneous arousals (for derivation C3A2).
V.7.3 - Conclusions

In this section, we performed the EEG spectral analysis on a total of 3980 arousals composed of both respiratory and spontaneous arousals (139). Our goal was to determine if any differences could be found between these two kinds of arousals through the analysis of their spectral content. The visual inspection of the shapes of the mean PSD curves for respiratory and spontaneous arousals allows us to attain the similarity for all levels of SAHS severity and on all 3 derivations. Furthermore, the computed band power values showed no difference between respiratory and spontaneous arousals. Regarding the changes in the bands power values with respect to different levels of SAHS severity, we observed the same behaviours for respiratory and spontaneous arousals: theta and beta power increased with increasing SAHS severity and alpha and sigma powers decreased with increasing SAHS severity. However, the only significant results were obtained for the theta band power, where fairly good correlation was obtained with the AHI. This outcome is in agreement with the findings made by Dingli et al. (46).

Respiratory arousals are generally defined as the ones following, overlapping or adjacent in a small window of time (usually 3 seconds) to apneas/hypopneas. However, there is no widely approved agreement and there are hardly any studies reporting the value of that window of time. The chosen value of that window of time may be crucial on the accurate classification of the arousals and may cause a respiratory arousal to be scored as spontaneous arousal and vice-versa. Moreover, spontaneous arousals may be caused by undetected respiratory events, severe snoring episodes or even upper-airway intermittent obstruction. Thus, these latter spontaneous arousals would have to be included in an exceptionable group of respiratory-driven arousals since they should be distinguished from the spontaneous arousals that result as an activation of an organic trigger such as intestinal passage, excessive bladder loading or organ dysfunction and other unknown causes (78).

We are aware that more efforts can be put on the task of uncovering the differences between the two types of arousals. Applying more robust methods and techniques may succeed on that purpose. Overall, the results obtained provide evidence that respiratory and spontaneous arousals have alike spectral contents. These findings may challenge the current beliefs regarding the underestimation of the importance of spontaneous arousals and their contribution to sleep fragmentation in patients suffering from SAHS.
V.8 - Feature analysis of respiratory and spontaneous arousals in subjects with Sleep Apnea-Hypopnea Syndrome

Tauman and co-workers (207) studied the indices of respiratory and spontaneous arousals and their correlation with the AHI, the sleep pressure score (SPS) and the Epworth sleepiness scale (ESS) whereas Dingli et al. tried to correlate them with sleep staging (47). However, neither of them has truly focused on characterizing them nor on trying to ascertain the differences between the content of these two types of arousals. Dingli et al. (46) and Xavier et al. (223) studied the electroencephalographic changes, through the analysis of the spectral content of different frequency bands, during and at the termination of apneas and hypopneas.

In this section, we will also perform, in addition to studying other features, the spectral analysis of EEG arousal signals with the purpose of characterizing the two kinds of arousals: respiratory and spontaneous arousals. The results obtained in the latter section suggested the similarity between the two kinds of arousals. In this section we will perform the correlation and study the agreement between the features of both types of arousals for each subject. This way, we will be able to carry out an intra-subject study rather than using all arousals from all subjects at once. For that purpose we will use the Bland-Altman analysis (135).

To the best of our knowledge an actual comparison between the content of respiratory and spontaneous arousals has not yet been performed in a wide range of SAHS subjects. Thus, on our work we aim to assess their differences through feature analysis and also to correlate them with the SAHS severity level of the subjects.

V.8.1 - Database

In the context of arousal analysis we assume that the relevant frequency content of the EEG signal is in the 4-25Hz since the delta frequency band (1-4Hz) corresponds to deep sleep and constitutes an artefact on EEG arousal episodes. On that note, we applied a high pass Butterworth filter of eighth order with cut-off frequency at 4 Hz (stopband at 2 Hz and passband at 4Hz; stopband attenuation of 40 dB and passband ripple of 1dB ) to the arousal signals’ from the 3 EEG tracings.

For this study we worked with 45 subjects (with AHI range of 3.7-109.9h⁻¹) previously described on the former V.7.1-Database section. A total of 4019 arousals: 2018 respiratory (10±1.6 s in duration, m±sd) and 2001 spontaneous (9±1.2 s) were used. Since one of our goals is to
investigate the relationship between the characteristics of both respiratory and spontaneous arousals with the subjects’ SAHS severity, we divided the whole set of 45 subjects in two groups, according to the $30h^{-1} \text{AHI}$ cut-point (cp) of severity. Detailed anthropometric, AHI and arousal information on the database is displayed in Table 30.

<table>
<thead>
<tr>
<th>NSUB</th>
<th>BMI</th>
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<th>AHI</th>
<th>RESP AR</th>
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<tr>
<td>n</td>
<td>14</td>
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<tr>
<td>m</td>
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<td>16.5</td>
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<tr>
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<td>8.2</td>
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<td>9.3</td>
<td>24.2</td>
<td>57</td>
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</table>

Table 30 Database characteristics on the spectral analysis of EEG arousal study. SAHS: group of subjects with AHI above and under and above the cut-point of severity $30h^{-1}$.

V.8.2 - Methodology

This section was motivated by our previous findings (139) where we performed the visual inspection of the PSD curves and calculated the average band power values (for theta, alpha, sigma and beta bands) for all 45 subjects’ respiratory and spontaneous arousals. The results obtained introduced the notion of the similarity between the spectral content of those two kinds of arousals. Hence, we decided to further investigate on this line by adding new features to the analysis, correlating the features with the subjects’ SAHS severity and studying the correlation and agreement between the features of respiratory and spontaneous arousals. For this last stated goal, we used the Bland-Altman analysis.

Here again, we computed a set of features for each arousal of the 45 subjects for the 3 derivations: C3A2, C4A1 and O1A2. The set of features includes, but is not limited to, some of the features previously described on V.5-Characterizing respiratory and spontaneous arousals section. In this section we do not include results for the marginal set of features as they performed poorly. The following set of features is divided in two groups, T) temporal and S) spectral:

T) Temporal: mean (t1), standard deviation (t2), median (t3), kurtosis (t4), skewness (t5) and maximum value of each arousal signal (t6).

S) Spectral: median frequency of the PSD (s1); the frequency band power expressed as a fraction of the total normalized power: theta (4-8Hz, s2), alpha (8-12Hz, s3), sigma (12-16Hz, s4) and
beta (16-25Hz, s5) bands; the (theta+alpha+sigma)/beta ratio (s6) and the (theta+alpha)/beta ratio (s7). Location of the maximum peak spectrum within the frequency range of 4-25Hz (s8). Ratio of the power around the maximum peak over the total power of the spectrum (s9) and its skewness (s10) and kurtosis (s11). The exact location (whether in theta, alpha, sigma or beta band) of the maximum peak (s12).

After calculating the previously described features for each arousal we computed the mean value of each feature per subject.

**V.8.3 - Results**

Our previously published findings suggested the existence of marked similarity not only between the shapes of the PSD curves but also the average power values of the frequency bands (theta, alpha, sigma and beta) of both respiratory and spontaneous arousals (139). Additionally, it was also demonstrated that no signature differences were observed on the spectral content of both kinds of arousals for a severe SAHS subject when compared to a milder one. In this section, we have obtained alike results for our enlarged set of features.

Table 31 shows the comparison between the features of the two groups of arousals for our whole 4019 arousal database (2018 respiratory and 2001 spontaneous). The results are shown for a subset of 7 features (out of the total 18 features) that obtained the lower \( p \) values, for the sake of better readability. Confirmation on the similarity of both types of arousals is given by the similar values obtained for the features, where no statistical significance is observed.
### Table 31

Mean value of features for the 2018 respiratory arousals (RESP AR) and 2001 spontaneous arousals (SPONT AR). m=mean; s=standard deviation; p=statistical significance with Mann-Whitney U test. t2 is in µV. s2, s3, s4, s5, and s9 are the normalized frequency band powers as a fraction of the total power multiplied by 100. s7 is the ratio between band powers s2 and s3 over band s5. Derivations a) C3A2, b) C4A1 and c) O1A2.

<table>
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<tr>
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<td>16.40</td>
<td>6.24</td>
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<td>27.13</td>
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<td>16.49</td>
<td>6.57</td>
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<tr>
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<td>0.955</td>
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|     |     |     |     |     |     |     |     |
| b)  |     |     |     |     |     |     |     |
| RESP AR | m 10.60 | 29.84 | 26.37 | 13.20 | 16.07 | 6.23 | 39.53 |
| SPONT AR | m 10.34 | 29.96 | 25.97 | 13.21 | 16.08 | 6.45 | 39.92 |
|      | s 2.63 | 7.42 | 6.77 | 3.68 | 6.04 | 3.35 | 7.40 |
|      | s 2.50 | 6.85 | 6.25 | 3.78 | 5.04 | 3.18 | 5.98 |
|      | p 0.646 | 0.859 | 0.936 | 0.853 | 0.815 | 0.646 | 0.675 |

|     |     |     |     |     |     |     |     |
| c)  |     |     |     |     |     |     |     |
| RESP AR | m 7.42 | 32.23 | 26.80 | 11.44 | 14.63 | 7.19 | 42.39 |
| SPONT AR | m 7.38 | 32.48 | 26.13 | 11.58 | 14.71 | 7.30 | 42.16 |
|      | s 2.14 | 6.99 | 7.87 | 3.35 | 5.46 | 4.28 | 7.46 |
|      | s 1.88 | 6.40 | 6.25 | 3.51 | 4.27 | 3.52 | 6.22 |
|      | p 0.910 | 0.704 | 0.923 | 0.987 | 0.796 | 0.519 | 0.859 |
In Table 32 mean values for the two groups of subjects (under and above the cut-point of severity 30h⁻¹) for the previously described subset of features are shown. This table gives evidence of the alikeness of the mean value of the features for opposite groups of severity. This is evident for both respiratory and spontaneous arousals where again no statistical significance was obtained for any feature except for feature s3 which shows a slight decreasing tendency of the alpha band power on spontaneous arousals with increasing AHI severity (Figure 47). However, this is not confirmed for derivations C4A1 and O1A2, as it can be seen in Table 32 b) and c).

As an example, in Figure 48 and Figure 49, we can observe that for features s5 and s7, there is no clear relationship/correlation with the AHI (p>0.05). This is seen whether for respiratory or spontaneous arousals (left and right panels of Figure 48 and Figure 49, respectively) and confirmed for the 3 EEG tracing arousals. The later observations led us to question whether, after all, there were any differences between the features for the two kinds of arousals for all subjects.
Table 32 Mean value of features for two groups of subjects: SAHS $<30\text{h}^{-1}$ and SAHS $\geq 30\text{h}^{-1}$, for respiratory arousals (RESP AR) and spontaneous arousals (SPONT AR). $m=$mean; $s=$standard deviation; $p=$statistical significance with Mann-Whitney $U$ test. Description of features is given in Table 31. Derivations a) C3A2, b) C4A1 and c) O1A2.

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<td>16.61</td>
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<td>39.75</td>
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Figure 48  Mean value for feature s5 for respiratory (left panel) and spontaneous arousals (right panel) of all 45 subjects, for the 3 EEG tracings a) C3A2, b) C4A1 and c) O1A2. Linear regression fit is shown. \( r \) is the correlation coefficient and \( p \) is the statistical significance with Mann-Whitney U test. Each point corresponds to a subject, represented their AHI.
Figure 49 Mean value for feature s7 for respiratory (left panel) and spontaneous arousals (right panel) of all 45 subjects, for the 3 EEG tracings a) C3A2, b) C4A1 and c) O1A2. Linear regression fit is shown. $r$ is the correlation coefficient and $p$ is the statistical significance with Mann-Whitney $U$ test. Each point corresponds to a subject, represented their AHI.
Guided by the preceding results, we decided to focus our study on each feature individually and on examining the correlation between the value of each feature for respiratory and spontaneous arousals. For that, we studied the correlation (correlation coefficient) between the mean value of each feature for the respiratory arousals and spontaneous arousals of each of the 45 subjects. The linear regression fit of the data was performed as well as the Bland-Altman analysis. The Bland and Altman plot is based on the relation between the mean of two individual values and the difference between these values. By calculating the mean and the standard deviation of these differences, it is possible to calculate the confidence limits for these differences (22),(23). In Figure 50, Figure 51 and Figure 52 the correlation, line of equality and Bland-Altman plots between the mean value for features t2, s3 and s9 of respiratory and spontaneous arousals (for the 3 EEG tracings) are shown.

With respect to derivation C3A2 we obtained very good correlation ($r \geq 0.8$, $p < 0.01$) between the mean value of respiratory and spontaneous arousals for 11 features out of whole set of 18 features (Figure 53 a)). The Bland-Altman analysis data for those same 11 features is also shown in Table 33 a).

In the case of features t4, t6 and s1, where the linear regression presented slope values between 0.4-0.66, we still observed a rather good correlation between the two kinds of arousals (Figure 53 a)). This means that, when considering these three features, we can affirm that there is a strong relationship between the two types of arousals but not a good concordance between them. Nonetheless, for the remaining features in Figure 53 a), we could observe a fine agreement between the two kinds of arousals in addition to the evident strong correlation. As shown in Figure 50 (left panel figures), the 45 points, each representing a subject, lie along lines very close to the line of equality (with slopes ranging from 0.78 up to 0.85). The Bland-Altman plots (Figure 50, right panel) show that for feature t2, all points fall within the small limits of agreement with 95% confidence interval: -2.166 (LLA) and +2.572 (ULA). Furthermore, the limits of agreement values are less than half of the minimum average value (MinVal) of both respiratory and spontaneous arousals (see Table 33 a)). For features s3 and s9 (Figure 50 B and C, respectively) the obtained bias was slightly negative but very close to zero (-0.214 and -0.028, respectively) as were all points that lie between the limits of agreement. Once again, for these two features the LLA and ULA were half then the minimum value of the average between these two kinds of arousals.

In the case of derivation C4A1, we obtained very good correlation ($r \geq 0.8$, $p < 0.01$) between the mean value of respiratory and spontaneous arousals for 9 features out of whole set of 18 features (Figure 53 b)). The Bland-Altman analysis data for those 9 features is also shown in Table 33 b). In Figure 51 (left panel figures), the 45 points, each representing a subject, lie along lines very
close to the line of equality (slopes ranging from 0.71 up to 0.85). The Bland-Altman plots (Figure 51, right panel) show that for features t2, s3 and s9, the majority of points fall within the small limits of agreement with 95% confidence interval. For features t2, s2, s3, s8, s9 and s12 (Table 33 b)) the obtained bias was very close to zero and all points that lied between the limits of agreement. Once again, for these features the LLA and ULA are half then the minimum value of the average between these two kinds of arousals.

With regard to derivation O1A2, we obtained very good correlation ($r \geq 0.8$, $p<0.01$) between the mean value of respiratory and spontaneous arousals for 7 features out of whole set of 18 features (Figure 53 c)). The Bland-Altman analysis data for those 7 features is also shown in Table 33 c). In Figure 52 (left panel figures), the 45 points, each representing a subject, lie along lines very close to the line of equality. The Bland-Altman plots (Figure 52, right panel) show that for features t2, s3 and s9, the majority of points fall within the small limits of agreement with 95% confidence interval. For features t2, s3 and s9 (Table 33 c)) the obtained bias was very close to zero and all points that lied between the limits of agreement. For these features the LLA and ULA are half then the minimum value of the average between these two kinds of arousals.
Figure 50 Features for derivation C3A2. A) t2, B) s3 and C) s9. Left panel: Line of equality between the mean value of each feature for respiratory (axis x) and spontaneous (axis y) arousals. Right panel: Bland-Altman’s plots for the agreement between respiratory arousals and spontaneous arousals. Mean±2SD = Lower and upper limits of agreement (LLA and ULA). Each dot on the plots represents a subject. All 45 subjects are represented.
Figure 51 Features for derivation C4A1. A) t2, B) s3 and C) s9. Left panel: Line of equality between the mean value of each feature for respiratory (axis x) and spontaneous (axis y) arousals. Right panel: Bland-Altman’s plots for the agreement between respiratory arousals and spontaneous arousals. Mean±2SD = Lower and upper limits of agreement (LLA and ULA). Each dot on the plots represents a subject. All 45 subjects are represented.
Figure 52 Features for derivation O1A2. A) t2: std deviation

\[ y = 0.742x + 1.871 \]
\[ r = 0.841 \]
\[ p = 4.58\times10^{-13} \]

B) s3: alpha band

\[ y = 0.737x + 6.380 \]
\[ r = 0.928 \]
\[ p = 4.44\times10^{-20} \]

C) s9: FMaxPeak band

\[ y = 0.672x + 13.654 \]
\[ r = 0.807 \]
\[ p = 2.09\times10^{-11} \]

All 45 subjects are represented.

Chapter V - Arousals  J.M.G. Mesquita
Figure 53 Bar plots of line of equality slope and correlation coefficient values. Results are shown for features with good correlation between respiratory and spontaneous arousals and high statistical significance ($p<0.01$). Results for derivations: a) C3A2, b) C4A1 and c) O1A2.
### a) Derivation C3A2

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Table 33 M= mean of the differences or bias; SD = standard deviation of the differences; MinVal and MaxVal= minimum and maximum, respectively, value of the average between RESP and SPONT; LLA and ULA = Lower (M-2SD) and Upper (M+2SD) limits of agreement with 95% confidence interval. Results for derivations: a) C3A2, b) C4A1 and c) O1A2.
V.8.4 - Conclusions

The work shown on this section was motivated by the sparked controversy around the role of arousals during sleep (101),(118),(234),(235). Many studies have revolved around this topic but very few focused on the study of actual content of the two main types of arousals. Tauman et al. (207) studied the indices of respiratory and spontaneous arousals and their correlation with the AHI, the SPS and the ESS whereas Dingli et al. (47) tried to correlate them with sleep staging. In our perspective, the lack of research in this specific issue may be causing the underestimation of the importance of spontaneous arousals and their contribution to sleep fragmentation in patients suffering from SAHS. Motivated by the former argumentations and also by the preliminary results (139) we propose to study in depth the time and frequency features of the two kinds of arousals on three EEG tracings (C3A2, C4A1 and O1A2) on subjects with SAHS. With respect to the previously obtained results (V.7-Spectral analysis of EEG arousals section) we altered the high pass filter specifications, in order to make it more accurate. Ultimately, for that reason the total number of arousals increased to a total of 4019.

Firstly, we investigated the differences between the 2018 respiratory and 2001 spontaneous arousals and observed no statistically significant differences between them.

Secondly, we attempted to correlate our set of features for both respiratory and spontaneous arousals with the AHI of the subjects. We observed great dispersion of the values and no correlation whatsoever for all the features. Furthermore, we also engaged on the task of grouping our subjects according to the AHI cut-point of 30h⁻¹ and tried to uncover the differences between the two groups of subjects but, once again, we also obtained similar values for both respiratory and spontaneous arousals.

This led us to compute the mean value of each feature for each of the 45 subjects and draw the line of equality between the respiratory and spontaneous values. For almost the whole set of features we obtained good correlation between the two kinds of events (r≥0.8, p<0.01). Nonetheless, it should be emphasized that the correlation coefficient can be subjected to criticism. Bland and Altman (22),(23) point out that the limitation of this correlation is the fact that it detects the relationship power between the variables, not the individual concordance between them. Therefore, it is possible to obtain a high correlation and a poor clinical concordance.

With respect to derivation C3A2, for the 11 features for which a good correlation (r≥0.8, p<0.01) was obtained, we performed the Bland-Altman analysis. When this analysis was employed we observed that for features t4, t6 and s1, a noticeable scattering was observed on the respiratory and spontaneous differences, allowing us to conclude that there is little agreement for these features between the two kinds of arousals, despite their good correlation (Figure 53 a)). On the
other hand, for features t2, s2, s3 and s9, besides obtaining a strong correlation we also observed a fine agreement between the two kinds of arousals. The very small bias (close to zero) of the mean differences between the two episodes jointly with the fact all points lie within the upper and lower limits of agreement with a 95% confidence interval gives evidence of that degree of agreement. In what concerns the other two derivations, C4A1 and O1A2, 9 and 7 features, respectively, obtained very good correlation results ($r \geq 0.8$, $p < 0.01$). Overall, the features that best performed in the Bland-Altman analysis for these two derivations were t2, s3 and s9 (Figure 53 b and c)).

More specifically, if we take a closer look at the features and their actual meaning, we can affirm that based on our results (Figure 50 B, Figure 51 B, and Figure 52 B): a subject having a given percentage of alpha band content (feature s3) on his respiratory arousals will have approximately the same alpha band content on his spontaneous arousals (weighted by the slope). Analogous conclusions can be extended to frequency band theta (s2), to the standard deviation of the arousals (t2) and the frequency peak band percentage over the total spectrum (s9).

Our results showed that the content of respiratory arousals on a mild SAHS subject is similar to that of a severe one. Moreover, with regard to spontaneous arousals, similar results were obtained. Our findings also revealed that no differences are observed between the features of these two kinds of arousals on a same subject. Thus, each subject has almost like a fingerprint or signature for his arousals’ content and is similar for both types of arousals. In addition, this signature has no correlation with SAHS severity (135).

In summary, the study indicates that there is great similarity between the content of respiratory and spontaneous arousals and that there is no correlation with the degree of SAHS severity and this is observed in the three EEG tracings (C3A2, C4A1 and O1A2). The trigger mechanisms of the two arousals are different. However, our results showed that the brain response is fairly the same for both of them. These findings raise doubt towards current beliefs on respiratory arousals being the main cause for sleep fragmentation and the importance sleep clinicians assign to respiratory arousals when providing a final diagnosis. Our findings suggest that the impact of spontaneous arousals in SAHS should not be underestimated.
V.9 - Conclusions and future prospects

The emergence of sleep disorders medicine brought renewed attention to the significance of the brief arousal as a consequence of primary sleep disorders and a determinant of the associated daytime sleepiness. To encourage further research and allow consistency of definitions for arousals, in 1992 the American Sleep Disorders published an arousal scoring manual for EEG arousals (11) which, in brief, defines arousals as an abrupt shift in EEG frequency of 3s or more in duration, which may include theta, alpha and/or frequencies greater than 16 Hz but not spindles.

The mechanisms that govern the sleep-waking cycle and arousability influence the features of breathing during sleep. Frequent shifts between sleep and wakefulness occur in patients with sleep apneas, whether central or obstructive, with the arousals often appearing during the periods of increased breathing that separate the apneas. According to many, these arousals are essential for the termination of obstructive apneas and perhaps central apneas as well (17),(28),(178),(187). However, other studies in patients with obstructive apneas suggest that breathing can reappear without any changes in sleep state and that in fact arousals may sometimes favour the recurrence of apneas (42),(85),(101),(118),(218),(234). It has been argued whether arousals are harmful, in that they promote instability of breathing and sleep, or are lifesaving (78),(178),(234). Fairly recently, authors have shown that decreasing arousability tends to stabilize breathing, supporting the idea that arousal can be destabilizing have an adverse effect and tend to perpetuate instability of breathing and apneas (101),(118),(234).

The ASDA bluntly points out on its arousal scoring manual that “the important fact is that the arousals result in fragmented sleep rather than shortened sleep. Just as with shortened sleep, it now is clear that sleep fragmentation leads to increased daytime sleepiness” (11). Furthermore, several previously mentioned publications have demonstrated that the arousal phenomenon is a key mediator of sleep fragmentation in SAHS subjects and the main responsible for daytime impairment (in areas such as alertness/wakefulness and psychomotor functioning) on subjects suffering from this disease. Alongside with the rising controversial debate on the topic of arousal scoring and its actual role on the sleep process, there has been a rising discussing concerning the role of two types of arousals, respiratory and spontaneous arousals, in the sleep of SAHS subjects.

Respiratory arousals are immediately correlated with the severity of SAHS since they occur following or overlapping an apnea/hypopnea (21). Being a mechanism of recovery from respiratory events during sleep, arousals are nonetheless considered to be important markers of the morbidity of this disease (169),(181),(193). Nevertheless, spontaneous arousals have also demonstrated to
lead to excessive daytime sleepiness and reduced psychomotor functioning (30),(154),(172),(241). Spontaneous arousals can result as an activation of an organic trigger such as intestinal passage, excessive bladder loading, organ dysfunction, harsh episodes of bruxism and other unknown causes.

Given its patent correlation with SAHS, respiratory arousals continue to deserve top place on the arousal research topic (42),(58),(101),(169),(204) but very few literature can be found reporting the function, effect and consequences of spontaneous arousals in SAHS disease. To the best of our knowledge, prior to our work, no authors had performed an actual comparison between the content of respiratory and spontaneous arousals in a wide range of SAHS subjects.

With the purpose of characterizing and assessing the differences between the two types of arousals we firstly engaged on their characterization by building a set of features and using it to classify a total of 7032 arousals (from 47 subjects) in those two types. However, the classification performance results were poor and did not upgrade after improving our arousal definition in order to attest for the fact that we were actually classifying events that were truly respiratory and truly spontaneous. Our attempts to observe differences for opposite levels of severity, led us to question even more the inability to discriminate these two events given that their trigger mechanisms are thought to be different.

Hereafter, we performed the EEG spectral analysis on a total of 3980 arousals (from 45 subjects) composed of both respiratory and spontaneous arousals. After listing all possible situations while scoring these two types of arousals we made sure to performed our analysis only to respiratory arousals that occurred within 3 seconds (or less) following or overlapping respiratory events (apnea or hypopnea) and to spontaneous arousals that did not overlap with any respiratory events. Our goal was to determine if any differences could be found between these two kinds of arousals through the analysis of their spectral content and for each subject individually. The visual inspection of the shapes of the mean PSD curves for respiratory and spontaneous arousals allowed us to attain the similarity for all levels of SAHS severity and on all 3 derivations. Furthermore, the computed band power values showed no difference between respiratory and spontaneous arousals (139).

Finally, motivated by our previous findings which introduced the notion of the similarity between the spectral content of those two kinds of arousals, we decided to further investigate on this line by adding new features to the analysis, correlating those features with the SAHS severity of the subjects and studying the correlation and agreement between the features of respiratory and spontaneous arousals. Our methods were performed on a database of 45 subjects with a total of 4019 arousals: 2018 respiratory and 2001 spontaneous. Results showed that the content of respiratory arousals on a mild SAHS subject may be similar to that of a severe one. In what concerns
spontaneous arousals, similar results were obtained. Our findings also revealed that no differences are observed between the features of these two kinds of arousals on a same subject. We can affirm that based on our results: a subject having a given percentage of alpha band content on his respiratory arousals will have approximately the same alpha band content on his spontaneous arousals (weighted by the slope). Analogous conclusions can be extended to other features computed during the process. As a result, each subject has almost like a fingerprint or signature for his arousals’ content and is similar for both types of arousals. In addition, this signature has no correlation with SAHS severity (135).

In conclusion, the aforestated findings indicate that there is great similarity between the content of respiratory and spontaneous arousals and that there is no correlation with the degree of SAHS severity and this was confirmed for the three EEG tracings (C3A2, C4A1 and O1A2). Even though the trigger mechanisms of the two arousals are different, our results showed that the brain response is fairly the same for both of them. These findings raise doubt towards current beliefs on respiratory arousals being the main cause for sleep fragmentation and the importance sleep clinicians assign to respiratory arousals when providing a final diagnosis. The fact that the respiratory arousals continue to deserve preferred attention on the arousal research topic may contribute to overrating the importance of the former in detriment of spontaneous arousals. The impact that respiratory arousals have in the sleep of SAHS patients is rather unquestionable but our findings suggest that the impact of spontaneous arousals in SAHS should not be underestimated.

**V.9.1 - Future Prospects**

In what concerns the arousal scoring topic we believe that the scoring of the two types of arousal doesn’t get the deserved attention in this research field and a proper and widely approved agreement is needed. Respiratory arousals are generally defined as the ones following, overlapping or adjacent in a small window of time (usually 3 seconds) to apneas/hypopneas (47),(207). However, there is still no widely approved consensus and there are hardly any studies reporting the value of that window of time.

On the other hand, spontaneous arousals may be caused by undetected respiratory events, severe snoring episodes or even upper-airway intermittent obstruction. Thus, these latter spontaneous arousals would have to be included in an exceptionable group of respiratory-driven arousals since they should be distinguished from the spontaneous arousals that result as an activation of an organic trigger such as intestinal passage, excessive bladder loading or organ
dysfunction and other unknown causes. Another future development may be the investigation of the possible relationship between harsh snoring events and the subsequent production of arousals. We suspect that snoring episodes may sometimes be the cause, besides apnea and hypopnea events, of arousal event production. This would eventually explain the occurrence of many of the spontaneous arousals and would compel the enlargement of the definition of respiratory arousals as we currently know it, since snoring events would fulfil the criteria to be considered respiratory disruptive events that trigger an arousal. This specific research may turn out to be possible with our database of signals provided that it consists of snoring sound signals that were acquired simultaneously during full-night PSG study.

Even though to our knowledge, no works have been published on this matter neither using this set of features nor any other, we are aware that more efforts can be put on the task of uncovering the differences between the two types of arousals. Increasing the set of may offer improvements on that purpose.

The scoring of arousals and the controversial discussions around its role in sleep may have added much to our understanding of the sleep process but significant work on the neurophysiology of arousal and its mechanisms of occurrence in SAHS still needs to be done. We are convinced that our findings on respiratory and spontaneous arousals provide an improved awareness on the effect trigger mechanisms have in the brain response of these two different types of arousals. Both events are equally impairing and represent detrimental and harmful features for sleep. Further research on this matter is, therefore, highly recommendable while it will surely continue to offer new insights on SAHS disease.
Sleep is a required activity, not an option. Even though the precise functions of sleep remain a mystery, sleep is important for normal motor and cognitive function. After sleeping, we recognize that changes have occurred, as we feel more rested and more alert. Sleep is an active/dynamic process involving specific cues for its regulation. Although there are some modest decreases in metabolic rate, the regulatory system in the body does not shut down during sleep. Also, the endocrine system increases secretion of certain hormones during sleep, such as growth hormone and prolactin, whose functions are associated with the regulation of the immune system. Untreated and undiagnosed sleep disorders can cause problem sleepiness and may be associated with difficulty in concentrating, memory lapses, loss of energy, lethargy and emotional instability.

SAHS is recognized to be the more prevalent and more amenable to treatment of all SDB syndromes (228). SAHS consists on the recurrent occurrence of airflow cessation/reduction during sleep leading to decreases on the oxyhemoglobin saturation and arousals that cause unrefreshing sleep, excessive daytime sleepiness (EDS) and neuropsychiatric, respiratory, cardiac, metabolic and/or inflammatory disorders. The main clinical triad for SAHS is made up of 3 signs/symptoms (33): chronic snoring, apneas and hypopneas and excessive daytime sleepiness (EDS). EDS is caused by increased arousals from sleep and it is usually the first complaint that brings a person to see the doctor closely followed by the complaint of loud snoring (often reported by the person’s partner). EDS resulting from SAHS can follow-on morning headaches, cognitive impairment and other previously mentioned problems. On the other hand, SAHS may also cause a number of serious and life-threatening repercussions such as hypertension, cardiovascular and cerebrovascular diseases, metabolic syndrome, vehicular or other accident due to sleepiness and increase risk of death.
Despite its prevalence and being considered a first-rate health problem, SAHS is underrecognized by most primary care physicians. Studies have demonstrated that undiagnosed patients double the expenditure of health care resources compared with diagnosed and treated patients (10),(51). The gold standard for diagnosing SAHS is an overnight polysomnographic study performed at the hospital, a laborious, expensive and time-consuming procedure in which multiple biosignals are recorded. Furthermore, sleeping in a totally different environment like a sleep centre imposes stress and anxiety to the patients and the extensive wiring that is required during polysomnography can furthermore disrupt or impede their normal sleep. To overcome this issue several collaborations between engineers and sleep specialist have suggested and continue to offer alternative approaches and simplified methods to aid the screening of SAHS based on a reduced number of signals – or even a single one – such as snoring signal (37).

The demand for easier, cheaper and less obtrusive diagnostic approaches urged the technological advances that moved evaluation of SAHS out of an artificial sleep laboratory, and into a home environment, with increased comfort, lower expense, and quicker analysis of results. While in search of alternatives for SAHS diagnosis sleep researchers mainly focus on the analysis of abnormal respiratory events such as snoring, apneas and hypopneas; increases in blood pressure or frequent cyclical variations in heart rate and arousals from sleep. All of the former are known to be either chief signs/symptoms or clinical manifestations of SAHS.

Ultimately, with this thesis we believe we were able to offer improvements to the current approaches to diagnosis and assessment of patients with SAHS. Alongside, we consider to have added new insights and further understanding on the pathophysiology and mechanisms that underlie SAHS. Our work focused on the study of snoring and arousals. Our achievements have proven that, whilst being recognized key markers of SAHS, they should be fully appreciated as essential tools for SAHS diagnosis. All results and achievements derived from this thesis were submitted and published in international journals and national and international scientific conferences (VII-Publications section). Likewise to the layout of the I.1-Objectives section, the final conclusion remarks are also divided in two parts: Snoring and Arousals. For further information the reader should refer to the conclusions sections of each theme results’ section: Snoring/ IV.7-Conclusions and future prospects and Arousals/ V.9-Conclusions and future prospects.
VI.1 - Snoring

Snoring is known to be an important clinical hallmark of SAHS. As such, it is a useful and an easily accessible signal to screen this disease. Concealed acoustic information in snoring events that points to the presence of SAHS is an ongoing line of research and was pioneering in the SAHS research field. But sometimes the question, however, is not the presence or absence, but the degree of SAHS. The robustness of methods based on the acoustic analysis of snoring episodes has proven to be effective and reliable in screening of SAHS. However, we felt that research on the study of all night snore episodes as a temporal sequence was lacking and could provide new information on SAHS disease.

Our methods were applied to a 34 subjects’ database (on a total of 74439 snores). We have used less complex approaches mostly based on time domain parameters, as an alternative to the aforementioned acoustic analysis of snores and concluded that key information on SAHS severity can be extracted from the analysis of the features derived from the time interval between regular snores. For that, we built a new methodology which consists on applying an adaptive threshold to the whole night sequence of time intervals between successive snores. This threshold enables to identify regular and non-regular snores and the two snoring patterns that comprise regular snores (single snoring pattern: when the subject snores once per breathing cycle and double snoring pattern: the subject snores both in inhalation and exhalation). Moreover, we demonstrated the correlation between features of regular and non-regular snores and the severity of SAHS.

Normal non-regular snores were presented as an alternative to the study of post-apneic snores since in the latter case there are very few or sometimes even inexistent accountable episodes on simple snorers and mild SAHS subjects carry on any feasible analysis.

Finally, we were able to correlate the variability of time interval between successive snores in short 15 minute segments and throughout the whole night with the subject’s SAHS severity. Severe SAHS subjects show a shorter time interval between regular snores ($p=0.0036$, AHI cp: 30h⁻¹) and less dispersion on the time interval features during all sleep. Conversely, lower intra-segment variability ($p=0.006$, AHI cp: 30h⁻¹) is seen for less severe SAHS subjects.

Also, we have shown successful in classifying the subjects according to their SAHS severity using the features derived from the time interval between regular snores. We attained classification accuracy values of 88.2% (with 90% sensitivity, 75% specificity) and 94.1% (with 94.4% sensitivity, 93.8% specificity) for AHI cut-points of severity of 5 and 30h⁻¹, respectively. The features proved, thus, to be reliable predictors of the subjects’ SAHS severity.
In summary, we consider to have succeeded in accomplishing all the initially proposed objectives. From our bulk of achievements we highlight our proposed adaptive threshold (and the identification of regular and non-regular snores) which represents a methodological advance in the field of snoring analysis, paving the way to allow better understanding of SAHS pathophysiology and more objective diagnosis. Additionally, it can be easily integrated in any portable and low-cost bedside monitor that performs automatic analysis of snoring episodes.

The proposed method, when applied to snoring analysis, will not likely replace the conventional SAHS diagnosis procedure through a polysomnographic study and a complete clinical evaluation, but it can significantly improve the management of this pathology by providing the possibility of a primary home diagnosis. This pre-test for diagnosis may be useful for evaluating if polysomnography is really required or if lighter treatment methods should be suggested even without performing polysomnography. Moreover, it can also be helpful for the follow-up of snorers without SAHS before and after application of medical and surgical therapies.

VI.2 - Arousals

Arousals are defined as temporary intrusions of wakefulness into sleep. Arousals lead to poor sleep quality and daytime sleepiness which may lead EDS (constituent of the main clinical triad of SAHS). Because of its profound effects on daily life and, more critically, its association with increased risk of road traffic accidents, EDS is the usual reason for medical consultation and posterior treatment of SAHS. Since daytime hypersomnolence and EDS are the direct result of recurrent arousals during sleep, understanding their adverse impact on the brain response and estimating the degree of sleep fragmentation caused by them is an important part of a respiratory sleep study.

Given its patent correlation with SAHS, respiratory arousals have always deserved top place on the arousal research topic and very few literature can be found reporting the function, effect and consequences of spontaneous arousals in SAHS disease. To the best of our knowledge, prior to our work, no authors have performed an actual comparison between the content of respiratory and spontaneous arousals in a wide population of SAHS subjects.

Provided that the two types of arousals are triggered by different mechanisms we initially hypothesized that there might exist differences between their EEG content. After characterizing our arousal database (composed of both respiratory and spontaneous arousals) using a set of temporal,
marginal and spectral features we attempted to assess the differences between the two types of arousals. Hereafter, we observed, through the study of the PSD curves and the frequency band power values, no differences between the content of respiratory and spontaneous arousals. This was confirmed for opposite levels of SAHS and for the 3 EEG arousal tracings (C3A2, C4A1 and O1A2).

The similarity between both types of arousals was further investigated by adding more features to the analysis, performing the correlation and studying the agreement between the features of both types of arousals for each subject individually. This way, we could carry out an intra-subject study rather than using all arousals from all subjects at once. The methods were performed on a database of 45 subjects with a total of 4019 arousals: 2018 respiratory and 2001 spontaneous. Our results showed that the content of respiratory arousals on a mild SAHS subject may be similar to that of a severe one. With regard to spontaneous arousals, similar results were obtained. Furthermore, we also attained that a subject having a given percentage of alpha band content on his respiratory arousals will have approximately the same alpha band content on his spontaneous arousals (weighted by the slope). Analogous conclusions can be extended to other features computed during the process. Thus, our findings revealed that no differences are observed between the features of these two kinds of arousals on a same subject ($r \geq 0.8$, $p < 0.01$ and all points lying within the upper and lower limits of agreement of Bland-Altman analysis with $p < 0.05$). Instead, each subject has almost like a fingerprint or signature for his arousals’ content and is similar for both types of arousals. In addition, this signature has no correlation with SAHS severity.

Also in this line of work, we believe that the objectives we set ourselves have been achieved. Overall, our findings indicate that there is great similarity between the content of respiratory and spontaneous arousals and that there is no correlation with the degree of SAHS severity and this was confirmed for the three EEG tracings (C3A2, C4A1 and O1A2). Although the trigger mechanisms of the two arousals are known to be different, our results showed that the brain response is fairly the same for both of them.

We conclude that spontaneous arousals should be regarded as serious markers of SAHS morbidity. Likewise to respiratory arousals, the former events lead to excessive daytime sleepiness and reduced psychomotor functioning. Both events are equally impairing, promote instability of breathing and represent detrimental and harmful features for sleep. In addition to this, the causes and underlying mechanisms which produce spontaneous arousals have not yet been explained in its entirety. Our remarks question the importance sleep clinicians currently assign to respiratory arousals when providing a final diagnosis on SAHS. The fact that the respiratory arousals continue to
deserve preferred attention on the arousal research topic may be contributing to this. The impact that respiratory arousals have in the sleep of SAHS patients is unquestionable but research on spontaneous arousals should be continuously encouraged so that the impact of spontaneous arousals in SAHS stops being underestimated.
During the elaboration of this thesis the outcomes and conclusions were published in the form of the following journal papers, conference papers and seminars:

**Journal papers:**

- J. Mesquita, J. Solà-Soler, J.A. Fiz, J. Morera, R. Jané. All night analysis of time interval between snores in subjects with Sleep Apnea Hypopnea Syndrome, Medical and Biological Engineering and Computing, vol 50(4), 373-381, March 2012 DOI: 10.1007/s11517-012-0885-9


**EMBC conferences (Engineering in Medicine and Biology Society (EMBS) annual international conference of the IEEE):**


Chapter VII - Publications

J.M.G. Mesquita

Database, Engineering in Medicine and Biology Society (EMBS), 2011 Annual International Conference of the IEEE, 30 Aug-3 Sept 2011, 8331 – 8333


CASEIB (Congreso anual de la Sociedad Española de Ingeniería Biomédica) and IBEC symposiums:


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