# Added value of mandible movement assessment in the management of adult sleep disordered breathing

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# TABLE OF CONTENTS

**THESIS SUMMARY** ..... **1**

**ABBREVIATIONS LIST** ..... **3**

**CHAPTER 1 INTRODUCTION : SLEEP DISORDERED BREATHING DISEASES AND MANDIBLE MOVEMENT STUDY IN THE CONTEXT OF A NEW PORTABLE MONITORING DEVICE** ..... **7**

**INTRODUCTION** ..... **7**

*1. Sleep disordered breathing* ..... *8*

1.1. Epidemiology of SDB ..... 9

1.2. Physiopathology ..... 10

1.3. Mandible movements during sleep in normal subjects and in OSAS ..... 15

*2. Portable monitoring* ..... *21*

2.1. PM classification ..... 22

2.2. Place and limitations of PMs in medical practice ..... 22

2.4. General limitations linked to the gold standard, the PSG. ..... 27

**CONCLUSION** ..... **28**

**REFERENCES** ..... **30**

**CHAPTER 2 – PART 1 ADDED VALUE OF A MANDIBLE MOVEMENT AUTOMATED ANALYSIS IN THE SCREENING OF OBSTRUCTIVE SLEEP APNOEA** ..... **37**

**SUMMARY** ..... **37**

**INTRODUCTION** ..... **39**

**MATERIAL AND METHODS** ..... **40**

*1. Setting* ..... *40*

*2. Participants* ..... *40*

*3. Recordings* ..... *40*

*4. Analysis* ..... *41*

*5. Statistical analysis* ..... *45*

**RESULTS ..... 46**

**DISCUSSION..... 52**

**CONCLUSION ..... 56**

**CHAPTER 2 - PART 2 ADDED VALUE OF A MANDIBLE MOVEMENT AUTOMATED ANALYSIS IN THE SCREENING OF OBSTRUCTIVE SLEEP APNOEA : IS THERE A GENDER INFLUENCE ? ..... 57**

**SUMMARY..... 57**

**INTRODUCTION ..... 59**

**MATERIAL AND METHODS..... 60**

1. *Setting ..... 60*
2. *Participants..... 60*
3. *Recordings ..... 60*
4. *Analysis..... 61*
5. *Statistical analysis ..... 61*

**RESULTS ..... 62**

1. *Whole population ..... 62*
2. *Added value of the MMAA in each gender ..... 64*
3. *Gender specificities and comparison between men and women..... 69*

**DISCUSSION..... 72**

**CONCLUSION ..... 75**

**REFERENCES ..... 76**

**CHAPTER 3 THE SLEEP/WAKE STATE SCORING FROM MANDIBLE MOVEMENT SIGNAL ..... 81**

**SUMMARY..... 81**

**INTRODUCTION ..... 83**

**MATERIAL AND METHODS..... 85**

1. *Subjects and recordings..... 85*

*2. Jaw movements and the portable monitoring device ..... 85*

2.1. Manual scoring rules ..... 86

2.2. Jaw movement processing ..... 86

*3. Statistical data analysis ..... 88*

**RESULTS ..... 89**

**DISCUSSION ..... 94**

**CONCLUSION ..... 98**

**ACKNOWLEDGEMENT ..... 98**

**REFERENCES ..... 99**

**CHAPTER 4 – PART I MANDIBLE BEHAVIOUR IN SEVERE OBSTRUCTIVE SLEEP APNOEA PATIENTS UNDER CPAP TREATMENT ..... 103**

**SUMMARY ..... 103**

**INTRODUCTION ..... 105**

**MATERIAL AND METHODS ..... 105**

*1. Subjects and recordings ..... 105*

*2. Mandible movement recording ..... 106*

*3. Manual scoring ..... 107*

*4. Mandible movement processing ..... 107*

*5. Statistical analysis ..... 109*

**RESULTS ..... 109**

**DISCUSSION ..... 113**

**CONCLUSION ..... 116**

**CHAPTER 4 – PART 2 EVALUATION OF A NEW AUTOMATED PILOT FOR CPAP TREATMENT BASED ON MANDIBLE BEHAVIOUR IN THE OBSTRUCTIVE SLEEP APNOEA SYNDROME ..... 117**

**SUMMARY ..... 117**

**INTRODUCTION ..... 118**

**MATERIAL AND METHODS** ..... **118**

**RESULTS** ..... **120**

**DISCUSSION** ..... **121**

**CONCLUSION** ..... **122**

**REFERENCES** ..... **123**

**CHAPTER 5 MANDIBLE BEHAVIOUR INTERPRETATION DURING WAKEFULNESS, SLEEP AND SLEEP-DISORDERED BREATHING** ..... **125**

**SUMMARY** ..... **125**

**INTRODUCTION** ..... **127**

**MATERIAL AND METHODS** ..... **128**

*1. Recordings* ..... *128*

*2. Definitions* ..... *128*

*3. PSG patterns database* ..... *129*

*4. Scoring sessions* ..... *131*

*5. Statistics* ..... *132*

**RESULTS** ..... **133**

*1. Patient's characteristics* ..... *133*

*2. Global analysis* ..... *134*

2.1. Diagnostic accuracy ..... 134

2.2. Legibility of diagnostic classes ..... 136

2.3. Within- and between-scorer agreement ..... 137

*3. Qualitative discrimination* ..... *137*

**DISCUSSION** ..... **138**

**CONCLUSION** ..... **141**

**REFERENCES** ..... **142**

**CHAPTER 6 CORRELATION BETWEEN OESOPHAGEAL PRESSURE AND MANDIBLE DOWNWARD EXCURSION IN OBSTRUCTIVE RESPIRATORY EVENTS DURING SLEEP. PARTIAL RESULTS OF A PROSPECTIVE STUDY** ..... **145**

**SUMMARY** ..... **145**

**INTRODUCTION** ..... **147**

**MATERIAL AND METHODS** ..... **148**

*1. Subjects and recordings* ..... *148*

*2. Statistics* ..... *152*

**RESULTS** ..... **153**

**DISCUSSION** ..... **157**

**CONCLUSION** ..... **162**

**REFERENCES** ..... **164**

**CHAPTER 7 ADVANTAGES AND DISADVANTAGES OF PORTABLE MONITORING DEVICES : COMPARISON OF THE SOMNOLTER® WITH THE PULSE TRANSIT TIME AND THE WATCH-PAT 100®** ..... **167**

**INTRODUCTION** ..... **167**

*1. General considerations in the validation process of a portable monitoring device* ..... *167*

*2. The pulse transit time and the Watch-PAT 100®* ..... *169*

2.1.The pulse transit time ..... 170

2.2. The Watch-PAT 100® (Itamar Medical Ltd, Caesarea, Israel) ..... 175

**SUMMARY OF THE CHARACTERISTICS OF THE 3 METHODS** ..... **180**

**DISCUSSION** ..... **181**

*1. Comparison of the Watch-PAT 100®, the pulse transit time included in a PM and the Somnolter®* ..... *181*

1.1 Breathing effort and respiratory events ..... 181

1.2. Sleep-wake state assessment and arousal detection ..... 184

*2. Limitations and exclusion criteria in clinical practice* ..... *187*

**CONCLUSION** ..... **190**

**REFERENCES** ..... **191**

**CHAPTER 8 PERSPECTIVES FOR THE FUTURE** ..... **197**

**ANNEX 1 ..... 201**

**REFERENCES ..... 203**

**LIST OF PUBLICATIONS, ABSTRACTS AND ORAL PRESENTATION RELATED TO THE THESIS WORK. ..... 205**

# THESIS SUMMARY

Obstructive sleep apnoea syndrome (OSAS) is a frequently occurring disease with multiple co-morbidities. Left untreated, OSAS has important health and socioeconomic consequences but effective therapies are available. Consequently, its diagnosis is important. The usual pathway for a reliable diagnosis includes detailed sleep history, clinical examination followed by attended full polysomnography (PSG) which is the reference standard for the diagnosis of respiratory sleep disorders. This approach is a time and resource consuming process given its increasing demand. Therefore, several less elaborate sleep portable monitoring (PM) devices have been developed for the diagnosis of OSAS. Up to now however, no single device has been widely accepted as an alternative to PSG because of important limitations such as the lack of sleep/wake status assessment, the lack of detection of arousals during sleep (an important contribution in the calculation of the respiratory arousal index, an index of disease severity, and a criteria used for respiratory events - hypopnoea- scoring).

This thesis focuses on the added value of mandible movement (MM) assessment in a new type of PM system, the Somnolter®, for the detection and diagnosis of sleep disordered breathing (SDB) in adults. Mouth opening is a common observation during sleep in patients suffering from sleep-disordered breathing and is different from mandible posture during sleep in healthy adults.

We demonstrated that this approach allows for a better accuracy in the detection of SDB in an automated analysis, both in men and women. The first finding was a better detection of hypopnoea when compared to a PM without MM analysis, thanks to the associated salient mandible movement (SMM). SMM has been used as a surrogate for respiratory arousal. We also found that this method improved the accuracy of the

apnoea hypopnoea index calculation (AHI), the most important index in SDB severity assessment. The calculation of this AHI depends on the total sleep time (TST) which is the denominator. Thus, the second important finding of this work was the sleep/wake state assessment which provided the TST. Thirdly, we were able to demonstrate that mandible behaviour under CPAP treatment was similar to the one found in healthy subjects. Typically, this translates into a mouth in a more closed position without repeated downward excursions. Indeed, mandible downward excursions and breathing effort are highly correlated. The fourth finding was that the MM analysis might be an interesting non-invasive marker of breathing effort during sleep and is less sleep disruptive than the invasive conventional method (oesophageal pressure).

A fifth finding was the feasibility of successfully training scorers for the visual recognition of these patterns. Specific mandible patterns have been isolated, described and correctly identified in active wakefulness, in quiet sleep, in quiet wakefulness, during obstructive and central apnoea and hypopnoea, during mixed apnoea, during snoring and respiratory related arousals.

The addition of MM assessment to a PM device allows for the identification of sleep/wake state, sleep micro-fragmentation and the detection of excessive breathing effort in obstructive respiratory events. For these reasons, we conclude that the Somnolter® is potentially an interesting alternative to PSG in the management of SDB in adults.

# ABBREVIATIONS LIST

AHI : apnoea hypopnoea index
$AHI_{SMN}$ : number of PSG events in Somnolter® sleep periods / $TST_{SMN}$
aLOW : average of the mandible lowering during sleep
aAMPL : average amplitude of the oscillations of the mandible movement signal
ArI : arousal index
ASDA : American Sleep Disorders Association
AW : active wakefulness
B&A : Bland and Altman
BMI : body mass index
BP : blood pressure
BzD : benzodiazepines
CAH : central apnoea hypopnoea
CI : confidence interval
COPD : chronic obstructive pulmonary disease
CPAP : continuous positive airway pressure
CPSG : PSG recording under CPAP treatment
DPSG : diagnostic PSG recording
ECG : electrocardiogram
EEG : electroencephalogram
EMG : electromyogram
EOG : electrooculogram
GEE : a generalised estimating equation model
HI : hypopnoea index
HR : heart rate
HTA : systemic arterial hypertension
LR - : negative likelihood ratio
LR + : positive likelihood ratio
MA : mixed apnoea
MExc : mandible inspiratory downward excursion
$MExc_a$ : mandible inspiratory downward excursion expressed in absolute value
$MExc_r$ : mandible inspiratory downward excursion in percentage of the maximum mouth opening measured during the calibration
MMAA : mandible movement automated analysis ((MposTe - MposTi)
MM : mandible movement
MMO : maximal mouth opening

Mpos Te : mandible position (Mpos) at end-expiratory time
Mpos Ti : mandible position (Mpos) at end-inspiratory time
MS : multiple sclerosis
NAF : nasal airflow
NP : nasal pressure
NREM-sleep : non-rapid eye movement sleep
OAH : obstructive apnoea hypopnoea
OSA : obstructive sleep apnoea disease (the presence of sleep apnoea and hypopnoea, without symptoms)
OSAS : obstructive sleep apnoea syndrome
PAT : peripheral arterial tone
Pes : oesophageal pressure
PesTe : oesophageal pressure at end-expiratory time
PesTi : oesophageal pressure at end-inspiratory time
POS : body position
PM : portable monitoring
PSG : polysomnography
PTT : pulse transit time
QW/S : quiet wakefulness and quiet sleep
RA : rheumatoid arthritis
RDI : respiratory disturbance index
REM-sleep : rapid eye movement sleep
RERA : respiratory related arousal
SDB : sleep disorders breathing
Se : sensitivity
SMM : salient mandible movement
SMN : Somnolter®
SMM-RDI : respiratory disorder index with MMAA
Sp : specificity
$SpO_2$ : pulse oximetry for the oxygen saturation
$SL\_15_{PSG}$ : sleep latency provided by the PSG: time in minutes between the START time and the first sleep period (including sleep stage 1) lasting 15 consecutive minutes of sleep
SL_PSG : sleep latency provided by the PSG: time in minutes between the START time and the first sleep period (including sleep stage 1) lasting one sleep 30-second epoch
$SL\_15_{SMN}$ : sleep latency provided by the SMN: time in minutes between the START time and the first sleep period (including sleep stage 1) lasting 15 consecutive minutes of sleep

SL_SMN : sleep latency provided by the SMN: time in minutes between the START time and the first sleep period (including sleep stage 1) lasting one sleep 30-second epoch
SS : sleep snoring
SWS : slow-wave-sleep (or stage NREM N3)
TDT : total dark time
TMO : total mouth opening
TST : total sleep time
$TST_{PSG}$ : total sleep time provided by the PSG
$TST_{SMN}$ : total sleep time provided by the Somnolter®
UA : upper airway
UAR : upper airway resistance
UARS : upper airway resistance syndrome
W : wakefulness
WAc : wrist actigraphy

# Chapter 1
# Introduction : Sleep disordered breathing diseases and mandible movement study in the context of a new portable monitoring device

## INTRODUCTION

This thesis is devoted to the assessment of the utility of a new type of portable monitoring system (Somnolter®) for the detection and diagnosis of sleep disordered breathing (SDB) in adults. The unique feature of this system is the provision of mandible movement assessment. The underlying hypothesis is that mandible movements are both passive and active in SDB, guided by underlying, and until now incompletely explored, neurological pathways which could provide important information on pathophysiological and therapeutic aspects of the sleep apnoea syndrome.

SDB and particularly the obstructive sleep apnoea syndrome (OSAS) are highly prevalent and are associated with a high level of morbidity related to sleepiness as well as an increased risk of cardiovascular diseases. The diagnosis is therefore important. The usual pathway for a reliable diagnosis includes detailed sleep history, clinical examination, followed by attended full polysomnography (PSG), which is currently the reference standard for the diagnosis of respiratory sleep disorders. The recording is scored by a trained technician and validated by a sleep physician. This approach is a time and resource consuming process given its increasing demand. Therefore, strategies are explored to define who should undergo a PSG and who could be assessed using alternative diagnostic methods. In this context, portable monitoring (PM) devices have been developed for the assessment of SDB. Up to now however, no single device has been widely accepted as an alternative to PSG.

By demonstrating the specificities of the mandible movement signal during sleep, this thesis focuses on the added value of this new approach in the development of PM devices. Important avenues in the assessment of patients with suspected SDB will be explored :

- screening with the validation of the automated detection of the respiratory events by the Somnolter®,
- the recognition of the salient mandible movement (SMM) associated with respiratory arousals,
- sleep-wake status assessment,
- the mandible movement under continuous positive airway pressure (CPAP) treatment and the rationale for developing an auto-CPAP device guided by the mandible movement,
- the association between MM and breathing effort assessed by oesophageal pressure swings during obstructive respiratory events.

## 1. Sleep disordered breathing

SDB encompasses a variety of disorders. These are defined according to the type of respiratory events found during a polysomnographic recording. The various respiratory events definitions and methods used to identify them are detailed in Annex 1.[1]

The pattern of SDB is typically a cyclical repetition of breathing events (apnoea or hypopnoea) and hyperventilation. The repetition of obstructive apnoea and hypopnoea results in oscillations of arterial blood gas levels and sleep fragmentation. Obstructive events are secondary to partial or complete collapse of one or several parts of the upper airway (UA), resulting in continued breathing effort but inadequate ventilation. The termination of these obstructive events is usually associated with a cortical arousal, favouring reopening of the UA. Resuming of breathing is associated with loud snoring, normalizing oxygen blood

saturation and often overshooting ventilation. On the other hand, central events are characterized by diminished or absent breathing effort, in an intermittent or cyclical fashion, often due to central nervous system or cardiac dysfunction. Resuming of breathing is also characterized by overshooting ventilation. The presence of snoring is often observed and expresses the fact that at least, at the end of the central apnoea, a relative obstruction has taken place.

### *1.1. Epidemiology of SDB*

There is a large body of research and literature available in the field of SDB epidemiology. SDB includes two main syndromes – central and obstructive sleep apnoea syndrome. OSAS is much more frequent.[2] It is associated with multiple co-morbidities. In western countries, obstructive sleep apnoea defined by an apnoea-hypopnoea index (AHI) > 5/hour without reference to any symptoms (OSAS usually refers to an abnormal AHI with associated symptoms such as sleepiness) has a prevalence of 24 % in men and 9 % in women in the adult poupulation.[3] The prevalence of moderate to severe OSAS (apnoea hypopnoea index > 15/h) is 9 % and 4 % in adult men and women respectively. This high prevalence is variable and linked to ethnic or co-morbid factors, particularly obesity which is the main predisposing factor. The consequences of OSAS are important in terms of health (cardiovascular effects[4] such as hypertension, stroke[5,6], daytime sleepiness linked to higher occupational and traffic accidents occurrence[7]) and socio-economic aspects. Treating OSAS allows a significant reduction in cardiovascular complications[8] as well as reduced accidents linked to excessive daytime sleepiness, particularly among car drivers.[9]

*1.2. Physiopathology*

The physiopathology of obstructive respiratory events during sleep is complex and some of its aspects are beyond the scope of this thesis.[10] However, as discussed above, these events are invariably associated with a closure or reduced calibre of the UA.[10,11] At the level of the oropharynx, there is susceptibility of the UA to closure due to the absence of rigid airway support. In normal non-obese subjects however, in passive conditions (no muscle activity), the UA is normally patent and requires about -5 $cmH_2O$ intraluminal pressure (the so-called critical pressure) to collapse.[12] At or below the critical pressure, inspiratory airflow ceases due to closure of the pharyngeal segment of the UA. Accordingly, it is important to analyse the anatomical and physiological factors that influence the UA lumen cross sectional area and the critical pressure during the respiratory cycle. These are:

- the UA lumen cross sectional area in passive conditions (i.e. in static conditions, without any muscle activity);
- the upper airway collapsibility in passive conditions;
- the negative intraluminal pressure during the inspiratory phase of the respiratory cycle (that is in dynamic conditions);
- the activity of the UA dilator muscles.

At any time, the patency of the UA is the result of the balance between the UA dilator muscle activity and the 3 factors which are susceptible to reduce the UA cross sectional area. We first discuss these 3 factors.

In passive conditions (no muscle activity), the UA lumen cross sectional area is influenced by anatomical factors, either constitutional or acquired. Obesity is the main acquired predisposing factor for OSAS.[13] It is associated with an increased amount of adipose tissue surrounding the pharyngeal airway within the limited maxillo-mandible space, leading to its narrowing. Other anatomical characteristics such as hypomaxillia,[14] retrognathia,[15] micrognathia,[16] macroglossia, hypertrophied tonsils or adenoids are also associated with a reduced UA cross sectional area. The

angle between the neck and the head[17] as well as the body position are other factors influencing the passive UA dimensions. During sleep, the weight of the mandible could contribute to its posterior displacement as well as that of the tongue, particularly when lying in the supine position. Finally, lung volume and pharyngeal lumen area are directly related such that reduced lung volumes lead to reduced UA cross sectional area.[18] Since abdominal obesity is associated with reduced functional residual capacity, this also contributes to reduce the UA cross sectional area in obese patients.

By eliminating the neural control mechanisms during anaesthesia and total paralysis, Isono et al. could demonstrate that OSAS patients not only had structurally narrower but also more collapsible UA than age-matched and BMI-matched non-OSAS patients.[19] As discussed above, reduced lung volumes are associated with reduced UA cross sectional area.[18] But reduced lung volumes due to obesity or other factors also compromise UA patency because of its association with increased UA collapsibility.[13]

The negative intraluminal pressure within the UA is dependent on the inspiratory flow but also on the resistance of the airway above the pharynx. Accordingly, nasal obstruction may negatively influence the pharyngeal airway patency.

In case of increased susceptibility for UA collapse, the latter can only be avoided by an increased activity of the UA dilator muscles or alternatively by applying a positive UA intraluminal pressure which is the rationale for continuous positive airway pressure (CPAP), the gold standard therapy for OSAS. Most OSAS patients have an anatomically narrow UA with compensatory increased pharyngeal dilator muscle activity that succeeds to maintain airway patency during wakefulness,[20] but fails to do so during sleep.[21] Individual variability in the ability of UA dilator muscles to maintain UA patency exists and is the basis for different phenotypical characteristics of sleep-disordered breathing events. Accordingly, respiratory events associated with reduced UA patency during sleep vary from simple snoring, upper airway resistance syndrome (UARS), obstructive hypopnoea to obstructive

sleep apnoea. Moreover, episodes of partial or full airway closure can occur in the same patient across the night. Although reduced UA patency is critical in the pathogenesis of OSAS, respiratory control instability during sleep which is out of the scope of this thesis also plays an important role leading either to central or obstructive events, depending on the UA characteristics discussed above.[10,11]

The UA partakes in vital functions such as swallowing and breathing. The coordination of the activity of the various UA muscles for achieving these functions is complex. The act of breathing is orchestrated by the respiratory centres which in turn are influenced by feed-back information received from various receptors. Both central and obstructive events usually occur as part of a periodic breathing pattern under the control of a permanently oscillating system comprising many players such as peripheral as well as central chemoreceptors sensing arterial blood gases ($PaO_2$ and $PaCO_2$), the cardiovascular system, and the respiratory centres.[10,11]

In normal conditions, UA dilator muscles and inspiratory muscles act in a coordinated manner. The respiratory centres receive afferent information from various receptors and command the phasic inspiratory contraction of the UA dilator muscles such that it arises 50-100 msec before that of the diaphragm and the other inspiratory muscles acting on the thoracic cage. The most important and most studied UA dilator muscle is the genioglossus (GG). The activities of the GG and its motor nerve (originating from the XII$^{th}$ cranial nerve pair, the hypoglossal nerve) are phasic (inspiratory bursts) on a tonic permanent state.[22,23] All stimuli that increase ventilation also tend to increase UA patency due to an increase in the phasic contraction of the UA dilator muscles. Accordingly, hypoxia and hypercapnia which are the main stimuli for ventilation also increase the GG phasic contraction.[24, 25] This counteracts the increasingly negative pressure induced by the contraction of the inspiratory muscles[26] in these conditions and prevents UA closure in normal subjects in both the awake and sleep states.

The UA dilator muscles activity is also influenced by mechanoreceptors located in the UA wall. Afferences go up to the brainstem through the glossopharyngeal IX$^{th}$ cranial nerve.

Efferences to the GG go through the hypoglossal motor nucleus. These mechanoreceptors are stimulated by lower (more negative) intraluminal pressures and allow the UA dilator muscles to counteract this negative pressure for maintaining UA patency[10] (see figure 1).

In subjects with OSAS, UA dilator muscles become unable to maintain UA patency during sleep. The GG activity (both tonic and phasic activities) decreases prior to the respiratory obstructive event.[27] This decreased activity may trigger the obstructive respiratory event by decreasing the UA patency. However, during the obstructive event, the GG phasic activity progressively increases, as demonstrated by EMG studies, reaching the highest amplitude before the termination of the obstructive event.[22] UA mechanoreceptors are likely responsible for the gradual increase in GG phasic activity during an obstructive apnoeic event. Moreover, it has been demonstrated that this increased phasic activity is directly related to oesophageal pressure swings during non-REM sleep obstructive apnoeic events,[28] and mirrors the phasic activity of the diaphragm[29] or inspiratory intercostals[30] during these events. This intra-event gradual increase in phasic activity of the GG drastically fall when obstructive apnoeas are treated either by CPAP[31,32] or a mandibular advancement device,[33] suggesting that it is a direct consequence of obstructive events.

Along with the UA mechanoreceptors, nose receptors also detect negative intraluminal airway pressure (in case of increased nasal resistance or airflow) and send afferences through the trigeminal nerve (maxillary branch), inducing compensatory pharyngeal dilator muscle activation in the more collapsible regions.[34]

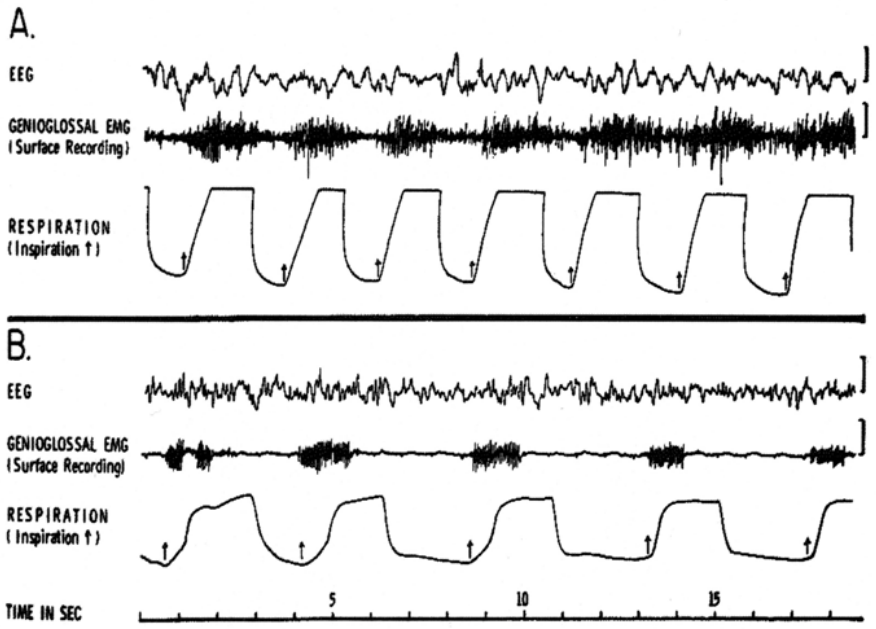


Figure 1: Non-invasive genioglossal EMG recording during NREM-sleep. Extracted from Sauerland E.K. and colleagues. [35]
A. Obese 42 year old patient with SAOS and hypoventilation syndrome during unobstructed breathing. Vigorous inspiratory genioglossal EMG bursts are present.
B. Obese 60 year old patient with history of upper airway obstruction. Recording segment shows well defined inspiratory genioglossal EMG discharges during unobstructed respiration (respiration is monitored by oesophageal transducer). GG inspiratory bursts are pointed by an arrow, starting when inspiration begins. Calibrations: EEG: 100 μV; EMG: 200 μV; time in seconds.

In awake healthy subjects, the tonic activity of the GG is markedly increased in the supine position,[35-37] to counteract the posterior movement of the tongue due to its own gravity.

Importantly, UA dilator activity and its reflex regulation are both influenced by the sleep/wake status. Indeed, the activity of the GG are reduced at sleep onset compared to wakefulness [38] and further so in REM sleep.[22,38] Moreover, the reflex increase in phasic activity of the GG induced by more negative intraluminal pressure is attenuated during NREM sleep as compared to wake[21] and even further during REM sleep. [22,39]

In summary, anatomical features of the UA as well as the control of pharyngeal muscle tone across states of wakefulness and sleep are important to its patency and collapsibility. Sleep is associated with an increased susceptibility of the UA to collapse because of a fall in UA dilator muscle activity (mainly the tonic activity) secondary to loss of the "wakeful" neuronal input and insufficient compensatory response towards negative intraluminal pressure (the phasic activity which is coupled with respiration). The imbalance between UA dilator muscle activity and the other factors reducing UA cross sectional area during sleep is critically implicated in snoring, inspiratory flow limitation, airway closure and OSAS whereas there is a progressive increase in inspiratory muscle activity during these events. During a sleep related obstructive respiratory event, the phasic activity of the UA dilator muscles increases gradually in parallel with the inspiratory muscle activity, up to the event termination.

### *1.3. Mandible movements during sleep in normal subjects and in OSAS*

The mandible is the anchor for many muscles inserted on the anterior wall of the pharynx, the hyoid bone or the maxilla. Among these muscles, some are UA dilators.

The location and articulated integration of the mandible in the UA explain how it could move passively or secondary to the contraction of various muscles, leading to specific movement patterns during sleep in normal or disordered breathing.

Some UA dilator muscles have insertions on the mandible, such as the GG and the geniohyoid muscles. The anatomy of the muscles from the cervico-mandibular region is illustrated in figure 2. Upper airway muscles exhibiting an inspiratory burst pattern are the GG, the laryngeal abductor (posterior cricoarytenoid), the geniohyoid, the tensor palatini, the stylopharyngeus, the styloglossus and the medial pterygoid muscles.

By contracting, the GG generates tongue protrusion, an activity which promotes upper airway patency, which will induce a downward movement of the mandible.[27]

Other muscles like the anterior belly of the digastric could also play a role in maintaining UA patency as well as moving the mandible downward.

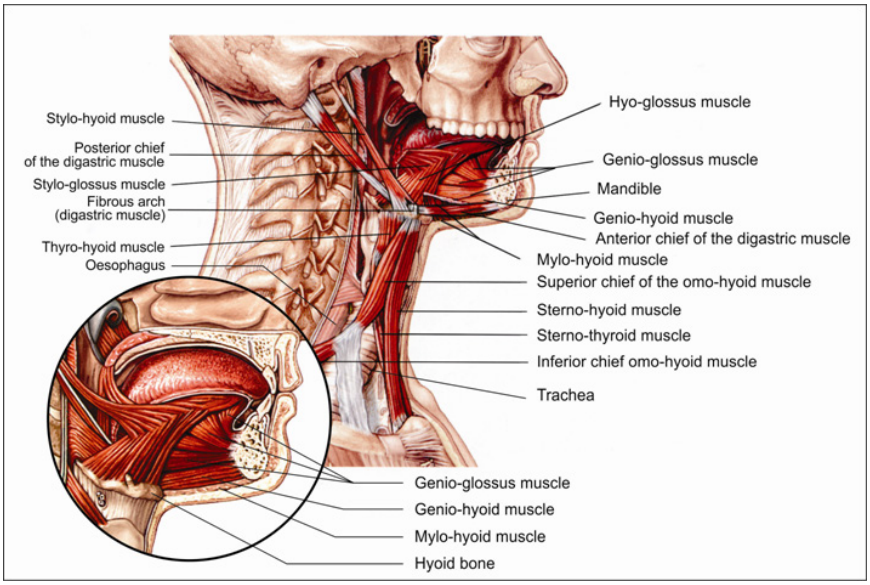


Figure 2 : Muscles of the cervico-mandibular region. Pharyngeal dilator muscles inserted on the mandible are: the genioglossus (which is the ventral wall of the hypopharynx, inserting on the internal surface of the mandible) and the geniohyoid muscles. The hyoid bone lies ventral to the GG muscle and serves as a point of attachment for several muscles: the geniohyoid, the digastric, the thyrohyoid muscles. Submental electromyographical surface electrodes detect activity of: the GG, the geniohyoid, the anterior chief of the digastric, the mylohyoid, the plathysma muscles. As the GG muscle contraction, the mylohyoid, the geniohyoid and the digastric muscles act for mouth opening. Inspired from "Atlas d'anatomie humaine A.D.A.M. ®" Todd R. Olson. 2002.Translated by C. Fontaine. Ed. Pradel, 2012.

In healthy subjects, the movements of the mandible are influenced by wakefulness and sleep. Miyamoto has depicted the influence of sleep, sleep stage and body position on mandible posture in healthy adults. He demonstrated that the proportion of time during which the mandible was in a near-closed position significantly and progressively decreased during sleep. Significantly more time was spent at wider mandible opening as non-rapid-eye-movement (NREM) sleep deepened, but body position had no significant influence on mandibular posture in these healthy subjects.[40]

Miyamoto also showed that the mandibular posture is more opened during sleep in patients with OSAS than in healthy adults, especially during NREM-sleep and in the supine position, and that mouth opening increases progressively during apnoeic episodes and decreases at the termination of those episodes.[41] Hollowell and Suratt found that the mouths of patients with OSAS were open significantly more at end inspiration than at end expiration during the apnoea in both NREM and REM-sleep. A mandible lowering occurred at the end of the apnoea (progressively increasing with every inspiration) in stage 2 and REM-sleep, both mouth opening in these stages were statistically different from equivalent mouth opening of normal subjects.[27]

Mandibular opening at the end of expiration could narrow the upper airway (secondary to an inferior-posterior movement of the mandible), whereas opening at the end of inspiration could reflect efforts which is called the thoracic tug. As the UA is occluded or suboccluded, the contraction of the thoracic inspiratory muscles induces greater negative pressures into the thoracic cavity which in turn are associated with a longitudinal traction on the trachea and on ventro-lateral cervical soft tissues.[42] The tracheal tug is thought to passively contribute to the downward movement of the mandible during the inspiratory phase of obstructed respiratory cycles. During these events, due to the closure of the UA, the dilator muscles see their posterior insertions locked on the anterior wall of the UA. Their shortening (particularly that of the GG) thus may result in a downward movement of the mandible. As the inspiratory phasic activity of the UA dilator muscles increases (simultaneously with increasing breathing effort) during the obstructive apnoeic events, so does the downward movement of the mandible during these events.

The masseter is a jaw-closing muscle (figure 3). During sleep in healthy subjects, it has a reduced tonic activity and no inspiratory activity. A small phasic inspiratory activity has been described in the masseter of OSAS patients.[27] In OSAS patients, at the termination of obstructive apnoeic events, the masseter and submental muscles contract (figure 4). [27,35,37,43] The contraction of the GG is necessary to

restore the UA permeability. The contraction of masticatory muscles - including the masseter - after the apnoea has been assumed to stabilize the mandible (an upward of the mandible without fully mouth closure).[27, 43] Without this stabilisation, the GG contraction could generate a posterior movement of the mandible. The sequence of muscle recruitment at the end of the respiratory event therefore promotes UA patency (figure 4). We have called this closing movement of the mandible at the end of the apnoea the salient mandible movement (SMM).[27, 40, 41]

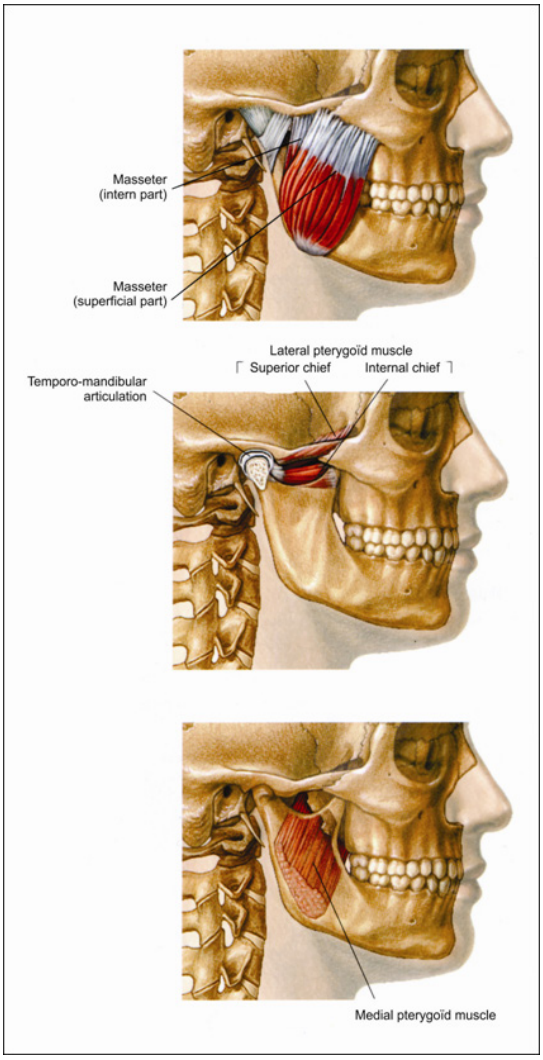


Figure 3 : Illustration of the masticator muscles: masseter and medial pterygoid muscles, both innervated by the third branch of the V$^{th}$ cranial nerve. Temporalis muscle is not showed. Inspired from "Atlas d'anatomie humaine A.D.A.M. ®"

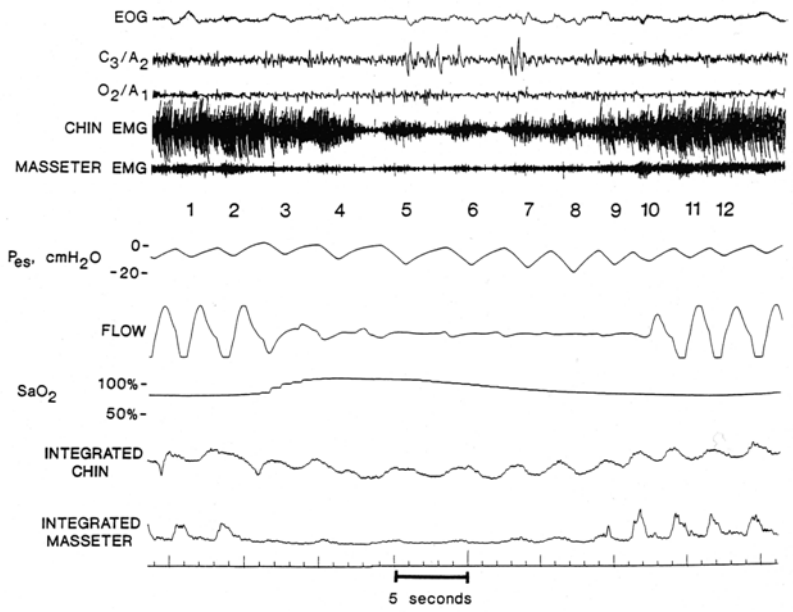


Figure 4: An obstructive respiratory event where chin and masseter electromyograms (EMG) illustrate the drop in tonic activity at the beginning of apnoea, with progressive increase in phasic (inspiratory) activity during the event. The contraction of the chin muscles (mainly the GG) and masseter is necessary to restore the UA patency. EOG: electro-oculogram with two EEG derivations ($C_3/A_2$ and $O_2/A_1$); Flow: nasal airflow; Pes:oesophageal pressure. Extracted from Hollowell and Suratt. [27]

To summarise, during obstructive sleep respiratory event, a passive gradual lowering of the mandible occurs, characterized by an oscillating pattern (cyclical downward excursions of the mandible) linked to inspiratory effort that increases in amplitude during obstructive respiratory events, ending with a closing active movement of the mandible (figure 5). This oscillating pattern is absent during central respiratory events. These mandible movement patterns thus potentially provide meaningful information to recognize and classify SDB as will be discussed in this thesis.

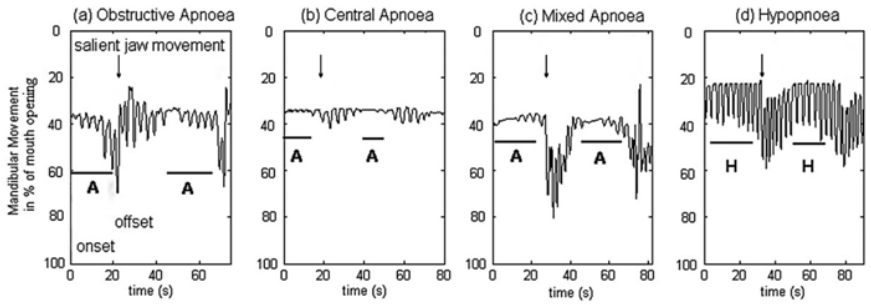


Figure 5: Typical mandible movement patterns occurring during sleep-related respiratory events: obstructive apnoea (a), central apnoea (b), mixed apnoea (c) and hypopnoea (d). The salient mandible movement (pointed by an arrow) appears at the end of the respiratory event, after oscillations of the mandible which are part of its definition.

## 2. Portable monitoring

Portable sleep apnoea monitoring devices, becoming less intrusive and self-applicable, have been developed. As the access to the gold standard diagnostic test (full PSG) is limited, PM devices have been developed for the primary assessment of SDB. The validity of these alternatives to PSG remains disputed because of methodological concerns regarding their evaluation (comparison with the gold standard, studied populations, visual or automated analysis…). In the validation process of a PM, many factors must be considered, including its distinctive

features.

*2.1. PM classification*

The methods used for investigations of sleep-disordered breathing have been classified in 4 types by the American Sleep Disorders Association (ASDA)[44] :

- The type I is the standard PSG which includes : in-lab registration of minimum 2 electroencephalography (EEG) derivations, submental electromyogram (EMG), electroculography (EOG), airflow, thoraco-abdominal movements, pulse oximetry for the oxygen saturation ($SpO_2$) and electrocardiogram (ECG) under the supervision of a trained sleep medicine personnel. This procedure is called attended PSG.
- The type II is similar to type I but without monitoring of the acquired signals by a technician. This procedure is usually called unattended or home PSG.
- The Type III registers at least four parameters, including 2 ventilatory signals (airflow, respiratory movements), $SpO_2$ and ECG or cardiac frequency.
- Type IV registers one or two variables, generally $SpO_2$ and/or nasal airflow.

Accordingly, PM belongs to the category III or IV.

*2.2. Place and limitations of PMs in medical practice*

The literature on PMs is extensive and complex to analyse, due to the existence of different PM types and to the variability of the recording conditions (attended or not, at home or in the hospital setting). Results depend on the population studied and particularly the pre-test probability of having OSAS. Until the beginning of the 2000s, the lack of standardisation of these methods (particularly types III and IV), the variability in measurement techniques and in their interpretation were identified as problematic. Furthermore, the lack of rigorous validation and cost/benefit

assessment were pointed in many reviews.[44-48] In the recent years, many papers on the subject have been published. A Pubmed search on April, 2014 for the term « portable sleep monitoring » retrieved 472 references including 65 for the year 2013. The role of PM in the assessment of OSAS has been studied in both the screening and diagnostic processes.

Reviews on the place of PM research have led to the conclusion that a diagnosis of OSAS can be performed using this type of device providing certain conditions are met. These devices are reliable if they are used under the supervision of trained personnel for sleep medicine and if the subjects investigated have a high pre-test probability of suffering from sleep-disordered breathing, without any other sleep disorders or comorbidities.[49,50] The high pre-test probability is estimated by the sleep medicine specialist and dependent on questionnaires or subjective appreciation. Many sleep disorders exist and the relative impact of mixed disorders in the general population is likely not negligible. Nevertheless, their respective impact on PM results are probably variable (e.a. the arousal linked to periodic limb movement, sleep speaking for our device...). The question of the place of these PMs in the screening of OSAS in older patients or patients with multiple co-morbidities (e.a. cardiovascular disease in case of a PM using autonomic nervous activity study) and medications is also still open.

However, used in the right setting, automated analysis applied to signals from PM might offer a significant gain in time with good diagnostic performance.

As compared to PSG, most of type III PM have 2 major limitations.

1. First, with PSG, the sleep-wake assessment provided by the EEG allows the calculation of an AHI using the total sleep time (TST) as denominator. The lack of sleep/wake assessment with most of type III or IV PM imposes the use of the time in bed (TIB) as denominator for the calculation of a respiratory disturbance index (RDI). This leads the RDI to be an underestimate of the AHI, the weight of the underestimation depending on the time spent awake during the night which

remains unknown with most PM. Accordingly, PM allowing to distinguish sleep and wake states would have a clear advantage.

2. Second, most PMs are not able to detect arousals during sleep, hereafter designed as arousals. Indeed, arousals are defined on the basis of an EEG that is included only in type I or II methods. However, there is a potential for some PMs to detect surrogates for arousals. Detection of arousals is of importance for two reasons.

- Arousals partake in the definition of hypopnoeas which includes the association of an airflow reduction as well as a desaturation and/or an arousal. Detection of hypopnoeas is essential in the staging of the disease since it influences the AHI index.
- In the management of OSAS patients, the AHI is not the only polysomnographic outcome measure to predict health problems associated with OSAS. Excessive daytime sleepiness is related to the number of arousals. Here again, PMs able to detect respiratory arousals or surrogates and to calculate an arousal index (number of arousals per hour of sleep) would have an advantage.

There are methodological limitations in the validation procedure of PMs. An event-by-event analysis is preferable to correlate the respiratory events identification by each studied method. But generally, a separate analysis (PSG scorers are blinded to the PM signals) of the PSG and the PM recordings is recommended. In practice, this will lead to cumbersome steps in the procedure with many scorers and interventions.

## 2.3. Description of the method

The originality of the Somnolter®, the type III PM studied in this thesis is the mandible movement analysis, a signal provided by the Jawsens® (Nomics, Belgium). The sensors are shown in figures 6 & 7.

The mandible movement signal processing has been described by Senny et al.[51,52] This device includes two sensors (magnetically coupled resonant circuits, one transmitter and one receiver). The signal gives a specific pattern over time called the jaw activity (Jawac). Physical calibration is done by asking the patient to first close the mouth and then to fully open it. The Jawsens® (figure 6) is integrated into the multisignal analysis software provided by the Somnolter® (figure 7).

The Somnolter® is a respiratory polygraphy including signals for :

- nasal airflow (Protech nasal canula),
- $SpO_2$ (finger oximetry probe),
- thoracic movements (respiratory impedance plethysmography belt),
- body position
- mid-sagittal mandible movement (MM) (Jawsens®).

In adults, the mid-sagittal jaw movement analysis has been shown to be efficient for respiratory events detection[51] and sleep/wake discrimination.[52]

The future is the multi-physiological signal approach of respiratory disorders and sleep/wake assessment, combined for a better accuracy in the diagnostic approach. The scoring of the recordings could be totally automated or manual with the assistance of computer software.

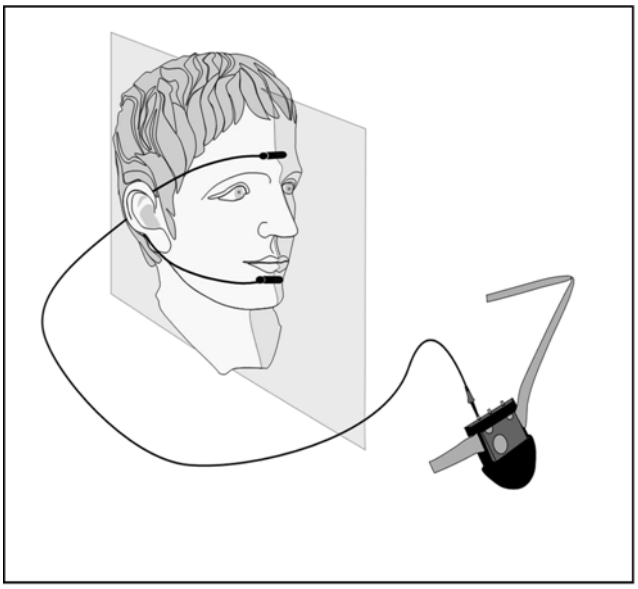

Figure 6 : The Jawsens® : mandible sensors, each embedded in a small cylinder (7 mm diameter; 25 mm main axis), are placed perpendicularly to the medium line of the face, parallel to each other, one on the chin and the other on the forehead. The output voltage is a cubic function of the distance between them. The electronic circuit converts distance into voltage. The voltage is sampled at 10 Hz, digitally linearized and stored on a computer. The signal can be expressed either in absolute value (millimetre) or in normalized value (percentage of maximal mouth opening).

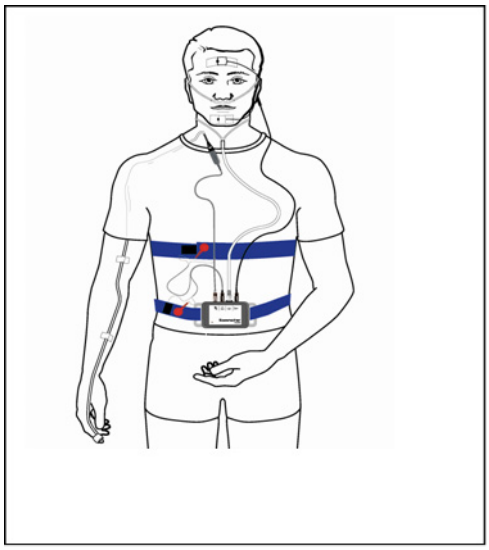

Figure 7 : The Somnolter®

*2.4. General limitations linked to the gold standard, the PSG.*

In the validation procedure of PM, some important aspects of the PSG must be kept in mind.

The PSG is a physiological recording. But, almost all the recorded signals are uncalibrated and the visual scoring is based on pattern identification of qualitative signals. The sensors and recording equipment provided by manufacturers are not standardised.

The current criteria used for stage sleep were defined fifty years ago to characterize sleep in normal individuals. The epochs duration is 30 seconds and the predominant state is used to define wakefulness or sleep and sleep stage. The scoring of abnormal respiratory events, in particular hypopnoea, relies on different definitions which could lead to different interpretations based on the definition used. It is therefore important to detail the criteria and definitions used in both the PSG and the PM.

Despite the improvement of the technology and analysis used in PMs, the correlation between PSG and the PM (registered simultaneously) suffers from these limitations.

# CONCLUSION

The aim of the present thesis is to assess the diagnostic and screening validity of a PM device in OSAS. This equipment (respiratory polygraphy; Somnolter®) does include a sensor evaluating the mouth opening (Jawsens®) and its specific behaviour over time. The apparatus will be validated against the diagnostic standard (PSG) in an attended and automated way.

The salient mandible movement, as a surrogate for arousal, contributes to hypopnoea detection in an automated analysis combined with $SpO_2$ and nasal airflow. The added value of the mandible movement automated analysis in the screening of OSAS is described in chapter 2. The validity of the device in men and women is detailed. Chapter 3 is dedicated to the sleep/wake state assessment by the automated scoring of the mandible movement. The mandible behaviour under CPAP treatment and its interest to therapeutic approach are depicted in chapter 4.

After these first chapters using the automated analysis provided by the Somnolter®, a visual approach was chosen to explore the characteristics of mandible behaviour on the recordings. In chapter 5, we postulated that all the typical mandible patterns could be visually recognised on isolated Jawsens® recordings to identify active wakefulness, quiet wakefulness and quiet sleep, snoring, respiratory events and the presence of an associated effort (obstructive and mixed events).

In chapter 6, we tested the hypothesis that the amplitude of the mandible movement during obstructive respiratory events is related to the magnitude of the inspiratory effort, as assessed by oesophageal pressure deflection.

Finally, the respective advantages of the Somnolter® and 2 other methods included in PM devices that share interesting characteristics in the approach of SDB (the

peripheral arterial tone in the Watch-PAT and the pulse transit time) are discussed in chapter 7.

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