# DRUG-INDUCED SLEEP ENDOSCOPY IN PATIENTS WITH SLEEP-DISORDERED BREATHING

### A PATIENT SELECTION TOOL FOR SURGICAL AND MANDIBULAR ADVANCEMENT THERAPIES

DE ROL VAN SLAAPENDOSCOPIE IN DE EVALUATIE VAN SLAAPGEBONDEN ADEMHALINGSSTOORNISSEN

Selectie voor chirurgische en tandheelkundig ondersteunde behandeling

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# DRUG-INDUCED SLEEP ENDOSCOPY IN PATIENTS WITH SLEEP-DISORDERED BREATHING

De rol van slaapendoscopie in de evaluatie van slaapgebonden ademhalingsstoornissen

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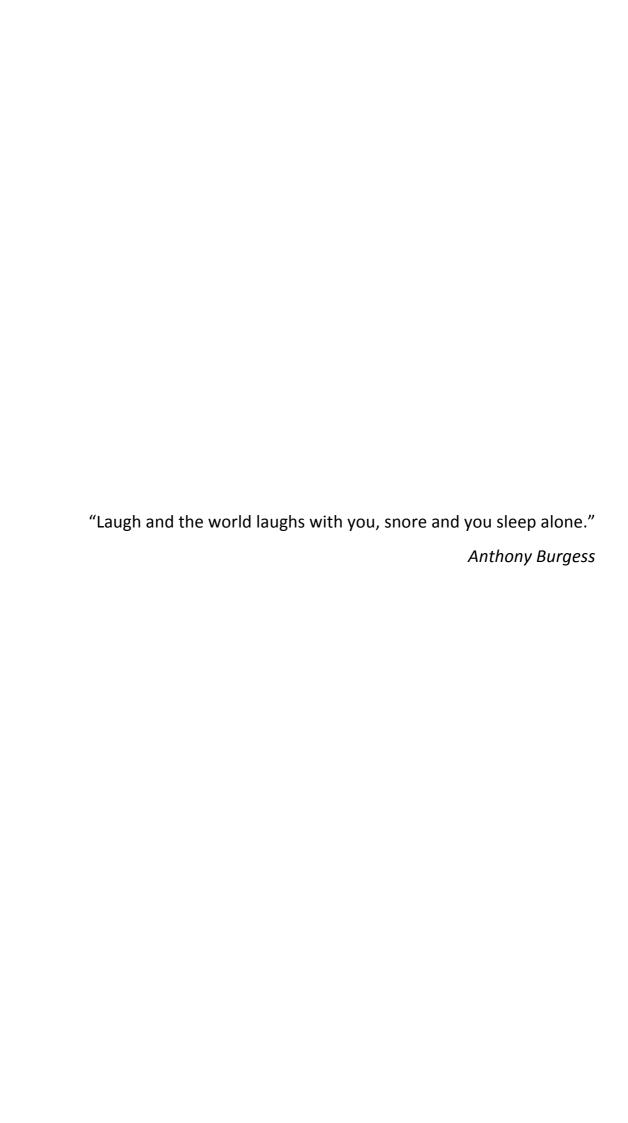
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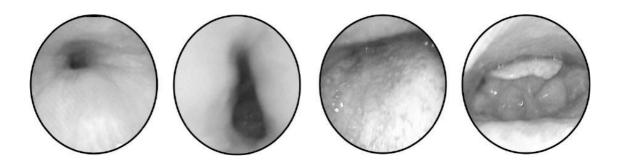
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## **Chapter 1**

General introduction

#### **GENERAL INTRODUCTION**

#### **Historical perspective**

Although research activity on sleep-disordered breathing only started to explode over the last three decades, the existence of this disorder obviously dates from distant times. It has been suggested that its history goes back to 360 BC <sup>1, 2</sup>. Prominent historical figures suspected to have suffered from sleep-disordered breathing included Napoleon Bonaparte (1769-1821) <sup>3</sup>, Queen Victoria (1819-1901) <sup>4</sup>, Johannes Brahms (1833-1897) <sup>5</sup>, and Winston Churchill (1874-1965) <sup>6</sup>. A stereotypical, severe form of sleep apnea was described by Charles Dickens in his Pickwick Papers (1837). Joe, a supporting character, had such excessive daytime sleepiness that he fell asleep standing up, while knocking on a door <sup>7</sup>. Later in the 19<sup>th</sup> century, this "fat boy" Joe was referred to in clinical descriptions of other hypersomnolent, obese, and loudly snoring patients, leading to the use of the term "Pickwickian Syndrome". This term would later become replaced by obstructive sleep apnea (OSA).

London physician W.H. Broadbent provided one of the early scientific descriptions of OSA, characterizing it as a failure of inspiration to overcome the resistance in the pharynx, with audible signs of snoring and periods of perfect silence with ineffectual chest movements <sup>8</sup>. Naming it the "Pickwickian Syndrome", Bickelmann et al. reported on the association of alveolar hypoventilation with obesity <sup>9</sup>. OSA as it is known nowadays was first clinically described by Guilleminault et al. <sup>10</sup>. Initially, the only treatment to be considered effective was a tracheostomy <sup>11-13</sup>. In 1964, Ikematsu was the first to describe the uvulopalatopharyngoplasty (UPPP) to surgically correct anatomic abnormalities in patients with obstructive sleep apnea syndrome, and widespread use of the technique followed after its introduction in the US by Fujita in 1981 <sup>14, 15</sup>. In that same year, a non-surgical breakthrough followed: the introduction of continuous positive airway pressure (CPAP) by Sullivan and co-workers, who in their first experiments generated airflow from a vacuum cleaner motor <sup>16</sup>. This new era in sleep medicine would be marked by increasing research efforts on epidemiological and cardiovascular aspects of OSA as well as treatment options other than CPAP.

#### **Definitions and epidemiology**

Sleep-disordered breathing (SDB) is a continuum ranging from intermittent snoring over full-blown OSA to the obesity-hypoventilation syndrome <sup>17, 18</sup>. OSA is characterized by recurrent episodes of apnea and hypopnea during sleep that are caused by repetitive partial or complete upper airway collapse and often result in decreased oxygen blood levels and arousal from sleep <sup>19</sup>. This results in sleep fragmentation <sup>20</sup> and is accompanied by symptoms such as excessive daytime sleepiness, witnessed snoring or apneas, recurrent awakening from sleep, or choking or gasping during sleep <sup>21</sup>. Based on the apnea-hypopnea index (AHI), OSA may be classified as mild (AHI 5-15), moderate (15-30), or severe (AHI>30). Based on population-based studies, the prevalence of OSA syndrome (OSAS) <sup>19, 21</sup> ranges from 1.2-6% in adult women and 3.1-14% in adult men <sup>22-32</sup>. The Wisconsin sleep cohort study revealed that 93% of women and 82% of men with moderate to severe OSA were not yet clinically diagnosed <sup>33</sup>.

#### Pathogenesis and risk factors

Complex factors contribute to the pathogenesis of OSA, including changes in upper airway behavior, mechanical and tissue characteristics, and neuromuscular function. These factors may contribute and interact in different extents in individual patients, potentially leading to different "phenotypes" of OSA <sup>34</sup>.

The upper airway section from the palate to the hypopharynx consists of muscles and soft tissues, lacking rigid supporting structures and therefore being prone to collapse <sup>35</sup>. As the length of this pharyngeal section is rather long in men, this may partly explain the male predisposition to OSA <sup>36</sup>. Furthermore, functional and anatomic changes of the upper airway soft tissue structures related to supine position may aggravate OSA <sup>37, 38</sup>. Surface adhesive forces between mucosal tissues may also have an influence on the stability of the upper airway, particularly when considering the greater positive pressure needed to open a closed airway when compared to the closing pressure <sup>39, 40</sup>.

Differences in upper airway structures in OSA patients and controls were clinically evaluated using computed tomography and magnetic resonance imaging. In general, smaller minimal upper airway areas, thicker lateral pharyngeal muscular walls, increased tongue and

total soft tissue volumes were found in OSA patients <sup>41, 42</sup>. Studies on craniofacial structures indicated that increased lower face height, backward displacement of the maxilla and mandible, and a longer distance from the hyoid bone to the mandibular plane could be associated with OSA <sup>43-45</sup>.

In imaging studies, the cross-sectional area of the upper airway is seen lowest at the end of expiration 46, 47. These findings were confirmed in studies using forced oscillation technique (FOT) to assess the airway impedance in OSA patients during sleep 48, 49. Measuring the pressure at which the upper airway collapses during sleep (Pcrit) can also provide additional information on upper airway calibers during sleep 50, 51. Applying this technique, Isono et al concluded that a passive pharynx is more narrow and collapsible in OSA patients than in matched controls, under conditions of general anesthesia and muscle paralysis <sup>52</sup>. During wakefulness, the mechanisms inducing upper airway collapse are counteracted by upper airway dilator muscle activity to maintain airway patency. The interaction of a diminished ability of the upper airway dilator activity and pharyngeal anatomy is considered important in the pathogenesis of OSA 35, 53-55.

Airway collapsibility may be adversely affected by obesity through fat deposition in the airway or by means of reduction in lung volumes 34, 56, 57, although the exact causal mechanism remains unclear <sup>54</sup>. Accordingly, BMI and neck circumference correlate with presence and severity of OSA <sup>58</sup>.

OSA is more common in males and both anatomical and functional upper airway differences as well as hormonal influences are considered to attribute to this male predisposition <sup>59</sup>. In addition to the increased pharyngeal length in men, as explained before, the male predisposition may also be explained by an increased pharyngeal fat deposition as compared with women 60. This finding may also relate to obese men being at higher risk of developing OSA than obese women. Based on literature, a possible protective effect of higher levels of progesterone/estrogen or lower levels of testosterone may result in a lower prevalence of OSA in premenopausal women <sup>61</sup>.

Moreover, OSA is also believed to be more prevalent among older individuals <sup>22, 62</sup>, although this association arises up to 65 years and disease severity appears to decrease afterwards <sup>25, 62</sup>.

Alongside obesity and gender, several other risk factors are believed to have particular population health significance, such as alcohol consumption, smoking, and nasal congestion <sup>63</sup>. Although alcohol has a relaxing effect on dilator muscles including those of the upper airway, which may induce or aggravate OSA <sup>64</sup>, epidemiologic reports on long-term alcohol use patterns on the occurrence of OSA are discrepant <sup>30</sup>. Smoking may be considered a risk factor as cigarette smoke could lead to airway inflammation, thereby inducing changes in mechanical and neural properties of the upper airway, as well as an increased collapsibility during sleep <sup>30</sup>. Nighttime nasal obstruction, whether due to mechanical or inflammatory causes has been linked to OSA. The AHI was found to increase in seasonal allergic rhinitis patients and inversely, the AHI decreased in OSA patients with reversible nasal obstruction using nasal corticosteroid spray <sup>65, 66</sup>.

#### **Health effects**

OSA has major consequences on an individual's health status and the significant morbidity and excess mortality induced by this disorder need to be adequately addressed by both patient and physician. The consequences of sleep fragmentation that characterizes OSA include impaired neurocognitive functioning, decreased quality of life, and increased risk of traffic and/or occupational accidents <sup>67-70</sup>. Long-term cardiovascular consequences of OSA may include hypertension, coronary disease, and stroke <sup>71-75</sup>. Moreover, associations between OSA and insulin resistance, type 2 diabetes and metabolic syndrome are reported <sup>76, 77</sup> and these are most likely bidirectional <sup>58</sup>. However, the indications that OSA is indeed associated with the development of diabetes are yet to be confirmed in longitudinal studies <sup>78-80</sup>

#### **Diagnosis**

#### Clinical assessment

Clinical presentation of suspected OSA patients varies, with a broad spectrum of nighttime and daytime symptoms (table 1) <sup>58</sup>. Snoring is the most frequent symptom of OSA and is caused by vibration accompanying upper airway narrowing. A visual analogue scale (VAS) can be used to document the severity of snoring 81.

General medical information, including comorbidities, surgical history, occupation, alcohol and tobacco consumption and use of medication should be collected. Ideally, the bed partner is also interviewed, as he/she can provide additional information on snoring, apneas and other observations on nighttime as well as daytime behavior of the patient. The extent of daytime sleepiness can be assessed by means of the Epworth Sleepiness Scale (ESS), a self-administered questionnaire that provides a measurement of the patient's general level of daytime sleepiness 82 (table 2). An ESS score ≥11/24 implies excessive daytime sleepiness (EDS).

**Table 1.** Symptoms and signs of obstructive sleep apnea

Nighttime symptoms	Daytime symptoms
Witnessed apneas	Excessive daytime sleepiness
Snoring	Fatigue
Nocturnal choking	Morning dryness of the mouth
Disturbed sleep	Morning headache
Thirst during the night	Difficulty concentrating
Nocturnal diuresis, enuresis	Irritability, mood changes
Nocturnal sweating	
Nasal congestion	
Excessive salivation	
Gastro-esophageal reflux	
Impotence	

Table 2. The Epworth Sleepiness Scale (ESS).

Situation	Chance of dozing	
	(0, 1, 2, 3)*	

Sitting and reading

Watching TV

Sitting inactively in a public place (e.g. a theatre or a meeting)

As a passenger in a car for an hour without a break

Lying down to rest in the afternoon when circumstances permit

Sitting and talking to someone

Sitting quietly after a lunch without alcohol

In a car, while stopped for a few minutes in the traffic

Medical history is followed by an ear, nose and throat (ENT) evaluation. The physical examination should include height, weight, and neck circumference. Subsequently, the body mass index (BMI) can be calculated as follows: weight (kg) / height<sup>2</sup> (meter). Specific ENT focuses are the pharyngeal dimensions and possible anatomical upper airway abnormalities. A standardized grading classification can be used to describe tonsil size: grade 0 (previous tonsillectomy), grade I (tonsils in tonsillar fossa, barely seen behind the anterior pillars), grade II (tonsils visible behind the anterior pillars), grade III (tonsils extended three quarters of the way to the midline), grade IV (tonsils completely obstructing the airway, also known as "kissing" tonsils).

Similarly, the oropharyngeal position of the tongue can be classified, using the modified Mallampati grading system: grade I (tonsils, pillars, and soft palate clearly visible), grade II (the uvula, pillars, and upper pole visible), grade III (only part of the soft palate visible; the tonsils, pillars, and base of the uvula cannot be seen), grade IV (only the hard palate visible) <sup>83</sup>. This classification was based on a staging system introduced by Mallampati to predict difficult intubation <sup>84</sup>.

<sup>\* 0:</sup> would never doze; 1: slight chance of dozing; 2: moderate change of dozing; 3: high chance of dozing

#### *Polysomnography*

A full-night polysomnography (PSG) is traditionally considered the most comprehensive and reliable objective monitoring method for the diagnosis of sleep-related breathing disorders. This procedure is usually preceded by a pulmonary function test, to exclude underlying pulmonary disease. A standard full-night PSG provides information on respiration, oxygen saturation and sleep state, as well as on body position, pulse rate and heart rhythm, limb movements and snoring sounds. It therefore comprises recording of respiratory data including nasal airflow using an external thermistor, nasal pressure by means of a nasal pressure cannula and respiratory effort through thoracic and abdominal piezoelectric bands. It also includes electrocardiography (ECG), electroencephalography (EEG), right and left electrooculography (EOG), and electromyography (EMG) of the chin, the genioglossus and tibialis anterior muscle. Oxygen saturation is monitored using a pulse oximeter with a finger probe. Snoring is qualitatively registered by a microphone and body position is recorded using a piezoelectric sensor.

#### Home monitoring

Under certain conditions, ambulatory monitoring may be an alternative to an attended cardiorespiratory PSG. This type of monitoring must include recording of oxygen saturation, airflow, respiratory effort, heart or pulse rate, and body position. It must be noticed that with this method, obstructive and respiratory events cannot be distinguished and sole automatic scoring should be avoided 85.

#### **Treatment**

#### Behavioral strategies

Weight loss should be advised to all overweight or obese OSA patients, as significant decreases in body weight are not only associated with reduced OSA severity but may also be beneficial to other obesity-related health problems <sup>86-88</sup>. However, it is recommended to combine weight loss with positive airway pressure, oral appliance or surgical treatment, as these therapies have an immediate response, contrary to dieting <sup>89</sup>. Body positional therapy may be effective in well-selected patients, especially in younger patients with lower AHI and BMI, but data on long-term compliance and success are needed to affirm its role in OSA treatment <sup>37, 90-92</sup>. General measures that may be discussed with the patient are smoking cessation and avoidance of alcohol and sedative drugs <sup>63, 81</sup>. Based on current literature, there is insufficient evidence to recommend the use of drug therapy in the treatment of OSA <sup>93</sup>. Future research may focus on individual patient assessment of the dominant mechanisms of OSA and subsequently better matching of drugs, as well as combined therapy, e.g. CPAP or oral appliance therapy plus pharmacotherapy <sup>93, 94</sup>.

#### Continuous positive airway pressure therapy

Continuous positive airway pressure (CPAP) was introduced by Sullivan in 1981 and has generally become the first-line therapy for moderate to severe OSA since <sup>16</sup>. CPAP consists of an (oro)nasal mask that is connected to a flow generator by a tube. The flow generator provides a pressure high enough to prevent upper airway collapse and thereby maintain airway patency. There is adequate evidence on the high effectiveness of CPAP <sup>95, 96</sup>. CPAP demonstrates significant improvements in objective and subjective sleepiness, measures of quality of life and cognitive function, and moreover, lower blood pressures <sup>96</sup>. CPAP is a chronic treatment requiring compliance and optimal time of use to indeed counteract OSA. It was suggested that using a mean AHI as outcome for CPAP therapy is more realistic than using arbitrary compliance rates, which, in fact, could hide insufficient reductions in AHI <sup>97</sup>. Despite its high effectiveness, the acceptance, compliance and long-term use of CPAP can be cumbersome in some patients <sup>98-100</sup>. However, 5–50% of patients refuse to start or

discontinue CPAP therapy already in the first week <sup>101, 102</sup>. At 1-year follow-up, 20–50% of patients discontinue CPAP  $^{99,\,103}$ .

Auto-CPAP and bilevel CPAP are variants where air pressure is automatically adjusted or inspiration and expiration pressure are set separately, respectively. These therapies may be offered in cases of compromised CPAP adherence, although data on the influence on adherence are inconclusive <sup>100</sup>.

#### Oral appliance therapy

Oral appliance therapy can be a first-line treatment for patients with mild to moderate OSA or an alternative for patients with mild to severe OSA who are reluctant or non-responding to CPAP, or fail to use CPAP <sup>104</sup>. Oral appliances can be divided into 2 categories: 1) mandibular advancement devices (MADs), that induce a forward repositioning of the mandible and attached structures such as the tongue, and 2) tongue retaining devices, that hold the tongue forward by means of a negative pressure in a soft plastic bulb <sup>105</sup>.

MADs are currently the most common class of oral appliances used to treat OSA and custom-made MADs are to be preferred and recommended over prefabricated devices <sup>106</sup>. MADs are worn intra-orally during the night and mechanically protrude the mandible, commonly with a design to gradually protrude the mandible applying a mechanical advancing mechanism 107, 108. The aim is to increase the cross-sectional upper airway dimensions by advancement of the mandible and tongue, resulting in improved upper airway patency 109-111, although the exact mechanism by which MADs counteract OSA is still a subject of research. As with CPAP, compliance is a key issue for MAD therapy, as this too is a long-term treatment that relies on a regular and consistent wearing. The safety and feasibility of objective measurement of MAD compliance have been illustrated in literature <sup>112</sup>. MAD therapy is significantly effective in reducing AHI, snoring, sleepiness, and blood pressure <sup>113-116</sup>. In literature, self-reported initial adherence rates of 96% were described, but adherence rates tend to decrease with the duration of use, with rates varying from 48% up to 90% for follow-up periods longer than 12 months <sup>105, 117-121</sup>. When compared to CPAP in randomized controlled trials, MAD reduces the AHI to a lesser or similar extent, although MADs are often preferred by patients over CPAP <sup>117, 122-127</sup>. It must be addressed that most of these studies assessed MADs in a fixed position instead of allowing adjustment for optimized treatment effect <sup>128</sup>. No clinically relevant differences were found between MAD and CPAP in treatment of mild for moderate OSA with both treatment modalities objectively titrated <sup>129</sup>. Subjectively, MADs are generally considered less noisy and obtrusive than CPAP and in addition, power supply is unnecessary for MAD therapy. MAD therapy can thus also be an adjuvant therapy if CPAP use is temporarily cumbersome. CPAP may also be combined with MAD, possibly allowing decreased CPAP pressure and therefore increased CPAP adherence <sup>130, 131</sup>

#### Surgical therapy

Surgical procedures for OSA include upper airway surgery as well as bariatric surgery. Upper airway surgery can involve soft tissue and/or skeletal structures, and tracheostomy. Most of these surgical procedures permanently modify upper airway anatomy, aiming at endured improvement of the upper airway patency. An important limitation is the limited number of controlled studies on effectiveness and long-term outcomes of upper airway surgery <sup>132</sup>. An anatomic-based overview of contemporary procedures will be provided hereafter.

#### Nose

Septoplasty, turbinoplasty, and radiofrequency (RF) volume reduction of the turbinates can be performed in patients with nasal obstruction that hinders the use of CPAP, but are not to be considered solitary treatment options for OSA <sup>133-135</sup>.

#### Oropharynx

The most well-known oropharyngeal surgical procedure is the uvulopalatopharyngoplasty (UPPP) <sup>15</sup>. The UPPP procedure consists of trimming and reorienting of the posterior and anterior tonsillar pillars, excision of the uvula and posterior portion of the palate, and tonsillectomy, if not previously performed. Other palatal procedures include the uvulopalatal flap technique, Z-palatoplasty, transpalatal advancement pharygoplasty, palatal implants and lateral pharyngoplasty. Although reported outcomes were slightly better, these techniques are less widespread than UPPP and experience is limited <sup>136-140</sup>. More or less the same applies to RF volume reduction of the palate, a minimal invasive outpatient clinic

procedure that can reduce snoring, but may be less effective as a single stage procedure in mild OSA <sup>141, 142</sup>.

#### Tongue

Tongue surgery aims at increasing the lower pharyngeal upper airway lumen in patients with macroglossia and tongue base collapse during sleep 140. RF tongue base reduction is currently the most applied tongue base procedure in OSA. As with RF volume reduction of the palate, the procedure requires multiple treatment sessions and its feasibility, safety, and efficacy in reducing tongue volume, were demonstrated in several studies <sup>143-145</sup>. Moreover, RF tongue base reduction was shown to positively affect snoring, quality of life, and on AHI, although modest and especially in patients with low BMI and mild to moderate disease <sup>143</sup>, <sup>145</sup>. In patients with distinctive tongue base hypertrophy, transoral robotic tongue base surgery has been proven feasible and well tolerable, and further research is awaited to assess the effect on OSA <sup>146, 147</sup>. Novel techniques involving hypoglossal nerve stimulation are promising, but further research on patient selection, optimizing efficacy and long-term results is necessary to present this technique as a viable alternative to the currently available therapies <sup>148, 149</sup>. More details on this procedure can be found in chapter 7. Adjustable tongue advancement, through placement of a tissue anchor in the tongue base and an adjustment spool at the mandible, was found to be a feasible and relatively safe procedure, but for this technique further research is needed on the efficacy, technical improvements and refinements of the procedure <sup>150</sup>.

#### Maxilla and mandible

Maxillomandibular advancement (MMA) and genioglossus advancement both act on the maxillar and/or mandibular structures. MMA is considered a very effective treatment for OSA and can be of particular interest in cases of additional micrognathia or retrognathia, although this is no prerequisite <sup>151-153</sup>. MMA enlarges the upper airway and decreases upper airway collapsibility, by forward-fixing the maxilla and mandible approximately 10 mm via Le Fort I maxillary and sagittal split mandibular osteotomies <sup>154</sup>. Genioglossal advancement consists of forwarding the geniotubercle, in order to place sufficient tension on the tongue,

preventing it from collapsing. It is therefore understandable that outcomes of this advancement depend on the intrinsic tension of the tongue muscle <sup>155</sup>.

#### **Epiglottis and hyoid**

Epiglottoplasty is mostly performed as part of multilevel surgery, although it may also be performed as a solitary procedure in OSA patients with laryngomalacia <sup>156-159</sup>. Hyoid suspension comprises of advancement of the hyoid bone by fixation to the thyroid cartilage, thereby increasing the retrolingual upper airway space <sup>160</sup>. Reported success rates vary, but generally it is not considered an efficacious stand-alone treatment for hypopharyngeal airway obstruction in most patients with OSA <sup>161</sup>.

#### Other

Multilevel surgery, tracheostomy, and bariatric surgery are special entities within the spectrum of upper airway surgery. Multilevel surgery may consist of various combinations of the above-mentioned procedures and adequate preoperative upper airway assessment is vital to obtain an accurate impression of the multilevel upper airway collapse pattern. Tracheotomy may be physically and socially very invasive, but it is a highly effective treatment for OSA, as it bypasses the collapsible segment of the upper airway and ensures unobstructed breathing. Lastly, bariatric surgery is reserved for morbid obese OSA patients 162, 163.

#### Upper airway assessment and individualized treatment

The aim of upper airway evaluation is not only to gain a better insight into the complex pathophysiology of upper airway collapse but also to improve treatment success rates by selecting the most appropriate therapeutic option for the individual patient <sup>164</sup>. Various techniques of upper airway assessment have been introduced over the years, including X-ray cephalometry, computed tomography (CT) scanning, magnetic resonance imaging (MRI), pressure measurements and sleep endoscopy. Stuck et al provided a useful literature overview on upper airway evaluation in OSA, including the prognostic value of different upper airway assessment techniques for non-PAP therapies <sup>165</sup>.

#### *X-ray cephalometry*

This 2-dimensional technique focuses mainly on craniofacial skeletal morphology and has shown its value in assessing typical OSA features of the upper airway. With regard to MAD treatment outcome, several predictive cephalometric parameters have been described in literature, such as hyoid bone position, oropharyngeal airway dimension, and tongue size 166-<sup>170</sup>. Detailed information on predictors of MAD treatment outcome is provided in chapter 4 of this thesis. The predictive value of X-ray cephalometry for UPPP is less apparent, with only a few studies reporting retro- or micrognathia as a predictor <sup>171-174</sup>. However, lateral X-ray cephalometry does have an important role as a preoperative evaluation for MMA <sup>175</sup>.

CT

CT scanning allows for more detailed soft tissue contrast as well as three-dimensional reconstruction, but also implies considerable radiation. As with X-ray cephalometry, CT scanning is mostly performed during wakefulness. In literature, the effect of MAD on upper airway morphology as assessed during CT scanning has been described by several authors and increased minimal cross-sectional upper airway areas were found with the MAD in situ  $^{166,\ 176}$ . Functional imaging using computational fluid dynamics on CT-images of head and neck could be of predictive value in MAD predicting treatment success, with a decrease in upper airway resistance and in an increase in upper airway volume correlating with both a clinical and an objective improvement <sup>177</sup>. CT assessment of the upper airway after UPPP

indicated increased upper airway dimensions <sup>178</sup>, but further research is needed to prospectively confirm these findings.

#### MRI

In contrast to X-ray cephalometry and CT scanning, MRI does not involve radiation. Furthermore, MRI provides very good soft tissue contrast and also allows for three-dimensional assessment. MRI has added important insights to the understanding of pathophysiology of OSA. As for prediction of MAD treatment outcome, increased upper airway dimensions on MRI were positively associated with MAD treatment outcome <sup>179</sup>. Sanner et al. showed that using MRI combined with the Mueller maneuver, improved upper airway patency with MAD correlates with treatment success <sup>180</sup>. The effects of upper airway surgery have also been assessed by means of MRI, although this mainly focused at radiofrequency therapy and it was indicated that the mechanism of action involves mainly functional changes, rather than upper airway enlargement <sup>165</sup>.

#### Flow and pressure measurements

Flow-volume curves have been described as an assessment tool for OSA <sup>181, 182</sup> and more recently, the predictive value of this technique for MAD treatment outcome was assessed. A derived prediction model, using flow–volume curves performed during wakefulness, was not sufficient to reliably predict MAD treatment outcome <sup>183</sup>. Changes in upper airway pressure can be measured with catheters. This involves placement of the catheter in the upper airway and may lead to irritation or disturbed sleep, depending on the size of the catheter. Furthermore, it does not provide upper airway images and therefore it lacks visualization of both soft and bone upper airway structures, in contrast to other techniques such as CT scanning, MRI or sleep endoscopy. Therefore, anatomic abnormalities will be less likely to be detected and in addition, hypopharyngeal and epiglottis obstructions might be less reliably discriminated. However, pressure measurements can describe collapse patterns for longer periods, as first reported by Hudgel et al. <sup>184</sup>, and may have a role in patient selection for soft palate surgery <sup>165</sup>.

Critical closure pressure (Pcrit) is the nasal mask pressure at which the collapsible segment of the upper airway completely obstructs. In normal controls, this is on average

below -8 mbar, against positive values in patients with obstructive apneas <sup>185</sup>. Measuring Pcrit is a valuable tool for assessment of upper airway collapsibility, including the effects of a particular treatment on this collapsibility <sup>186</sup>. Evaluation of the Pcrit change induced by a particular treatment can be used for optimizing patient selection for a specific treatment or combinations thereof <sup>187</sup>.

#### Sleep endoscopy

Sleep endoscopy can be performed during natural sleep or drug-induced sleep. Performing this procedure during natural sleep was first reported in 1978 <sup>188</sup>. Although it has the advantage of being performed during natural sleep, it is considered cumbersome, mainly due to practical difficulties involving time and setting. Currently, sleep endoscopy is most often performed during drug-induced sleep. This drug-induced sleep endoscopy (DISE) was introduced by Croft and Pringle in 1991 and enables a dynamic evaluation of the localization of flutter and collapse in patients with sleep-disordered breathing <sup>189</sup>. It uses a flexible nasopharyngoscope to visualize the upper airway under sedation, most commonly with midazolam and/or propofol, although the use of diazepam has also been described <sup>190-194</sup>.

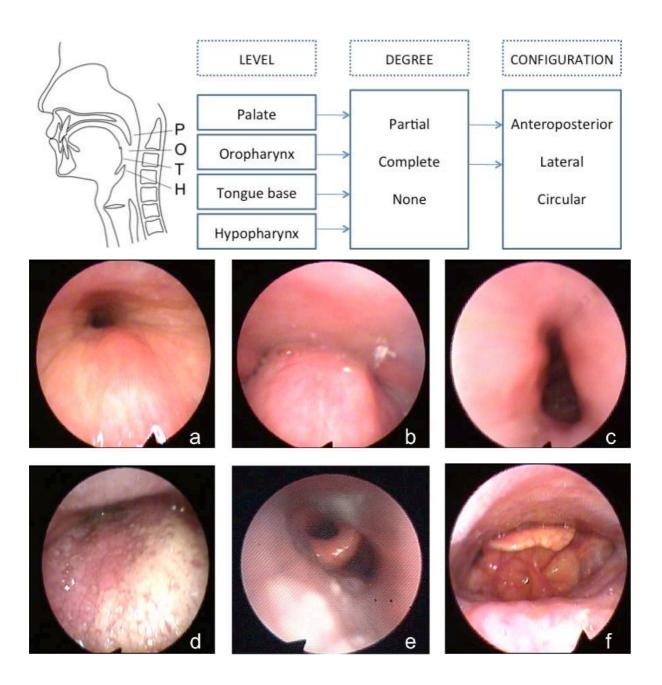
In the studies described in this thesis, sleep endoscopy was performed after administration of a bolus of midazolam, followed by target-controlled infusion (TCI) with propofol. Midazolam is considered well effective for induction of sleep and as background sedation, while propofol, with its rapid onset of action and recovery, can be used for finetuning <sup>195</sup>. In some clinics, in well-selected patients in good health and with an AHI<30, sleep endoscopy is performed with midazolam alone, administered intravenously by the ENT surgeon in an outpatient setting  $^{196,\,197}$ . However, especially in patients with higher American Society of Anesthesiologists (ASA) scores and/or more severe OSA, a more controlled setting is recommended. In general, monitoring for oxygen saturation and cardiac rhythms and presence of resuscitation facilities are recommended, emphasizing the need of anesthesiological support.

During DISE, a TCI system provides an objective (computer-controlled), reproducible and measured state of sedation, improving stability and accuracy of sedation <sup>193, 195, 198</sup>. To control the depth and stability of sedation, a bispectral monitoring (BIS) system can be used. The use of BIS can be especially interesting in study settings where strong intraindividual differences in depth of sedation are to be avoided <sup>194</sup>. When assessing the effects of the sedative agents, no relevant changes in main respiratory parameters such as AHI were detected, although literature did reveal an abolishment of rapid eye movement (REM) sleep <sup>199, 200</sup>. DISE may be contraindicated in patients with significant comorbidities, extreme severe OSA and/or severe obesity. The DISE examinator must be aware of the possible pitfall of overinducing muscle relaxation, which could lead to artifactual worsening of upper airway collapse <sup>190</sup>.

The different regions of the upper airway that can be investigated using DISE are the levels of the velopharynx (palate), oropharynx, tongue base, and hypopharynx (including the epiglottis). At each of these upper airway levels, the degree of collapse is reported as complete, partial, or none. The pattern of the obstruction is described as being circular (concentric), anteroposterior, or lateral <sup>191, 201, 202</sup>. This approach is visualized in main figure 1 (page 29).

In literature, several studies documented upper airway collapse patterns during DISE <sup>189, 191, 192, 197, 201, 203-209</sup> and recently, associations between DISE findings and baseline patient characteristics were reported <sup>210</sup>. Although several scoring systems have been introduced over the years <sup>200, 201, 206, 208, 211-215</sup>, no standard approach toward assessment and classification of DISE findings has been universally adopted yet. The validity and reliability of DISE in experienced observers have been demonstrated in the literature <sup>216-218</sup>, however, assessment is subjective and may vary based on clinical experience.

DISE has shown its value in optimizing patient selection for surgical upper airway interventions and can also be helpful in selecting patients for MAD treatment <sup>164, 219-222</sup>. For this purpose, several perioperative maneuvers were introduced, such as a chin lift or jaw thrust. It was demonstrated that DISE has a relevant influence on recommendations for treatment location when compared to awake assessment including endoscopic examination, in particular when considering MAD treatment or tongue base interventions <sup>218, 223-225</sup>.



Main figure 1. Upper airway evaluation during DISE, classified per upper airway level. Upper airway levels are demonstrated in the upper left panel (P: palate; O: oropharynx; T: tongue base; H: hypopharynx). Lower panels: a) partial circular palatal collapse, b) complete anteroposterior palatal collapse, c) partial lateral oropharyngeal collapse, d) complete anteroposterior tongue base collapse, e) partial circular hypopharyngeal collapse, f) complete anteroposterior epiglottis collapse

#### Outline of thesis and research questions

This thesis aims to discuss the following research questions:

- 1. What are the differences in DISE evaluation between experienced and nonexperienced ENT surgeons?
- 2. What insights do the results of DISE examinations in a large cohort of patients (N=1249) add to the current knowledge of upper airway behavior in sleep-disordered breathing?
- 3. Can the use of a simulation bite in a maximal comfortable protrusion during DISE improve patient selection for MAD therapy in OSA patients?
- 4. Does vertical opening of the mouth have favorable effects on upper airway dimensions as assessed during DISE?
- 5. Is DISE a valuable pre-treatment assessment technique for implantable upper airway stimulation for OSA?

This thesis focuses on the role of DISE as a tool for evaluating upper airway behavior in sleep-disordered breathing as well as for optimizing patient selection for non-CPAP therapies.

DISE is a relatively new procedure to most general ear, nose and throat (ENT) surgeons. Since further development and implementation of this procedure in the interdisciplinary field of sleep medicine is expected, assessment of the evaluation technique is imperative to promote its application. DISE is a useful, specific, and sensitive method of assessing patients with sleep-disordered breathing. Moreover, it has a good test-retest and a moderate to substantial interrater reliability among experienced ENT surgeons. In addition to these findings, chapter 2 focuses on calibration of findings obtained using DISE by experienced versus non-experienced observers. Observer agreement values were calculated in a cohort of 97 ENT surgeons, of whom 7 were experienced with DISE. Experienced ENT surgeons at the Antwerp University Hospital have been performing DISE in over 1200 patients routinely and in chapter 3, the results of 1249 DISE examinations are presented and discussed.

It is known from literature that DISE may be a valuable prognostic indicator of successful MAD treatment. In chapter 4, the prognostic value of DISE completed with a simulation bite in a maximal comfortable mandibular protrusion is assessed, in order to demonstrate its efficacy in predicting treatment response of MAD treatment. In addition to the DISE with simulation bite procedure, the upper airway effects of vertical opening are assessed, as the vertical dimension is one of the adaptable features of some types of MADs. These results are given in chapter 5. The application of DISE as a general pre-treatment assessment technique for implantable upper airway stimulation is discussed in chapter 6. The role of DISE in general is discussed in **chapter 7**.

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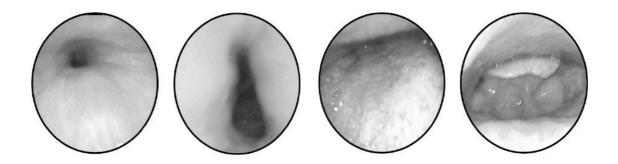
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## **Chapter 2**

Observer variation in drug-induced sleep endoscopy: experienced versus nonexperienced ENT surgeons

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## **ABSTRACT**

Study objective: To determine variations in interobserver and intraobserver agreement of drug-induced sleep endoscopy (DISE) in a cohort of experienced versus nonexperienced ear, nose, and throat (ENT) surgeons.

**Setting:** Ninety-seven ENT surgeons (90 nonexperienced with DISE; seven experienced) observed six different DISE videos and were asked to score the upper airway level, direction, and degree of collapse. Findings were collected and analyzed, determining interobserver and intraobserver agreement (overall agreement, specific agreement) and kappa values per upper airway level.

Measurement and results: In the nonexperienced group, overall interobserver agreement on presence of tongue base collapse (overall agreement = 0.63; kappa = 0.33) was followed by the agreement on epiglottis (overall agreement = 0.57; kappa = 0.23) and oropharynx collapse (overall agreement = 0.45; kappa = 0.09). Low overall interobserver agreement in this group was found for hypopharyngeal collapse (overall agreement = 0.33; kappa = 0.08). A similar ranking was found for degree of collapse. For direction of collapse, high interobserver agreement was found for the palate (overall agreement = 0.57; kappa = 0.16). Among the experienced observers, overall interobserver agreement was highest for presence of tongue base collapse (overall agreement = 0.93; kappa = 0.71), followed by collapse of the palate (overall agreement = 0.80; kappa = 0.51). In this group, lowest agreement was also found for hypopharyngeal collapse (overall agreement = 0.47; kappa = 0.03). Interobserver agreement on direction of collapse was highest for epiglottis collapse (overall agreement = 0.97; kappa = 0.97). Concerning the degree of collapse, highest agreement was found for degree of oropharyngeal collapse (overall agreement = 0.82; kappa = 0.66). Among the experienced observers a statistically significant higher interobserver agreement was obtained for presence, direction, and degree of oropharyngeal collapse, as well as for presence of tongue base collapse and degree of epiglottis collapse. Among the nonexperienced observers, high intraobserver agreement was found in particular for tongue base and epiglottis collapse. Among the experienced observers, high agreement was found for all levels but to a lesser extent for hypopharyngeal collapse. Intraobserver agreement was statistically significantly higher in the experienced group, for all upper airway levels expect for the hypopharynx.

**Conclusion:** This study indicates that both interobserver and intraobserver agreement was higher in experienced versus nonexperienced ENT surgeons. Agreement ranged from poor to excellent in both groups. The current results suggest that experience in performing DISE is necessary to obtain reliable observations.

## **CONTEXT**

Drug-induced sleep endoscpy (DISE) is a relatively new procedure to most general ear, nose and throat (ENT) surgeons. Because further development and implementation of this procedure in the interdisciplinary field of sleep medicine is expected, assessment of the evaluation technique could be of interest to improve its application. The purpose of the current study was to assess differences in DISE evaluation by experienced versus nonexperienced observers. Therefore, observer agreement values were calculated in a cohort of 97 ENT surgeons, of whom seven were experienced with DISE.

## **METHODS**

## Study design

This prospective study comprised a blinded multiobserver assessment of six DISE videos. These specific videos were selected because of the distinctive upper airway collapse patterns recorded. The DISE videos were shown to the observers twice in a randomized order, at two different time points.

#### **Patients**

The DISE videos originated from six different patients with OSA, who were reluctant about or non-responding to CPAP, or who had failed to use CPAP and underwent DISE (baseline characteristics shown in Table 1). Each DISE video represented one unique OSA patient. DISE was performed by an experienced ENT surgeon in a semidark and silent operating room with the patient lying in supine position in a hospital bed. Artificial sleep was induced by intravenous administration of midazolam (bolus injection of 1.5 mg) and propofol through a target-controlled infusion system (2.0 to 2.5 µg/mL). During the electrocardiography and oxygen saturation were continuously monitored. A fiberlaryngoscope (Olympus ENF-GP, diameter 3.7 mm, Olympus Europe GmbH, Hamburg, Germany) was used for videoscopic imaging, and simultaneous sound recording was performed.

Table 1. Baseline characteristics of patients

Variables	All patients (n=6)
Males (n, %)	5 (83.3%)
Age in years (mean ± SD)	51 ± 15
BMI in kg/m² (mean ± SD)	25 ± 3
AHI, per hour sleep (mean ± SD)	21 ± 10

BMI: Body mass index; AHI: apnea-hypopnea index; SD: standard deviation

#### **Observers**

The cohort consisted of 97 observers, who were invited to participate in this project during a 2-day conference. Ninety observers were general ENT surgeons with diverse clinical interests, who were nonexperienced with DISE. The other seven observers were experienced with DISE, as they perform the procedure on a regular basis in specialized sleep clinics and also conduct clinical research on this topic. A subset of observers was able to assess the DISE videos twice, as these observers were available on both days of the conference. All observers had no prior knowledge of patient history, including previous CPAP and non-CPAP treatment, polysomnography results, and findings on clinical examination or planned treatment. Each observer was asked to note his or her conclusions as to the level(s) of collapse and the degree and direction thereof, using a uniform scoring system (Main figure 1, page 29 of this thesis). The scoring system consisted of anatomic upper airway landmarks and was based on key elements of scoring systems recently proposed in the literature <sup>1-4</sup>.

## Statistical analysis

Data analysis was performed using R version 2.15.0 (R Foundation for Statistical Computing, Vienna, Austria). Descriptive statistics for clinical characteristics of patients were presented as means ± standard deviation (SD). Raw agreement among the observers was calculated by dividing the number of actual agreements by the total number of possible agreements. This was done for global agreement per upper airway level (overall agreement) and per specific response option (specific agreement) <sup>5</sup>. Additionally, Fleiss kappa values were determined to correct for chance agreement.

For the intraobserver agreement, raw agreement and kappa values were calculated per observer and averaged over all observers. For both interobserver and intraobserver agreement, 95% confidence intervals were obtained using bootstrap with 1,000 samples on the level of the observer 6, 7. For the nonexperienced observers this means that 1,000 samples, containing 90 × 6 videos, were taken with replacement from the 90 observers. Similarly, for the experienced observers, 1,000 samples were taken from seven observers. Bootstrap P values for the differences between experienced and nonexperienced raters were computed by pooling the experienced and nonexperienced raters together. Observers were then repeatedly artificially classified into experienced and nonexperienced in the same ratio as the original sample and the number of times the differences exceeded the observed value were counted.

## **RESULTS**

#### Interobserver variation

Specific and overall interobserver agreement values per upper airway level are shown in Tables 2 through 6. In the nonexperienced group (n = 90), overall interobserver agreement was highest for presence of palatal collapse (overall agreement = 0.88), although the kappa value for the presence of palatal collapse was lowest (-0.03). The agreement on the presence of tongue base collapse (overall agreement = 0.63; kappa = 0.33) was followed by the agreement on epiglottis (overall agreement = 0.57; kappa = 0.23) and oropharynx collapse (overall agreement = 0.45; kappa = 0.09). Low overall interobserver agreement in this group was found for hypopharyngeal collapse (overall agreement = 0.33; kappa = 0.08). A similar ranking was found for degree of collapse. For direction of collapse, high interobserver agreement was found for the palate (overall agreement = 0.57; kappa = 0.16).

In the experienced group (n = 7), no observers scored "not evaluable" for presence of collapse at the palate, oropharynx, or tongue base (marked with an asterisk in Tables 2 through 6). Overall interobserver agreement was highest for presence of tongue base collapse (overall agreement = 0.93; kappa = 0.71), followed by collapse of the palate (overall agreement = 0.80; kappa = 0.51). In this group, lowest agreement was also found for hypopharyngeal collapse (overall agreement = 0.47; kappa = 0.03). Interobserver agreement on direction of collapse was highest for epiglottis collapse (overall agreement = 0.97; kappa

= 0.97), followed by oropharynx (overall agreement = 0.82; kappa = 0.35). Among the experienced observers, several specific structure-configurations for direction of collapse were not observed (marked with double asterisks in Tables 2 through 6). Concerning the degree of collapse, highest agreement was found for degree of oropharyngeal collapse (overall agreement = 0.82; kappa = 0.66).

Among the experienced observers a statistically significant higher interobserver agreement was obtained for presence, direction, and degree of oropharyngeal collapse, as well as for presence of tongue base collapse and degree of epiglottis collapse.

#### Intraobserver variation

The intraobserver agreement per upper airway level is presented in Table 7. Among the nonexperienced observers, high intraobserver agreement was found in particular for tongue base and epiglottis collapse. Among the experienced observers, high agreement was found for all levels but to a lesser extent for hypopharyngeal collapse. Intraobserver agreement was statistically significantly higher in the experienced group, for all upper airway levels except for the hypopharynx. In total, 52 nonexperienced observers and five experienced observers were available to score the videos twice.

Table 2. Interobserver agreement on the palatal level

			Palate			
			Non	exp (N = 90)	E	xp (N = 7)
			N	Agreement	N	Agreement
Collapse	Specific	Collapse	369	0.94	26	0.85
	agreement			(0.91-0.96)		(0.68-0.98)
		No collapse	19	0.20	12	0.75
				(0.06-0.47)		(0.38-0.97)
		Not evaluable	3	0.01	0	#
				(0.00-0.05)		
	Overall agreement			0.88		0.80
	Overall agreement			(0.83-0.92)		(0.63-0.95)
	Карра			-0.03		0.51
	Карра			(-0.37-0.31)		(0.45-0.84)
Direction	Specific	Anteroposterior	174	0.64	13	0.60
	agreement			(0.56-0.71)		(0.30-0.86)
		Concentric	170	0.62	9	0.41
				(0.55-0.68)		(0.11-0.74)
		Lateral	10	0.05	0	##
				(0.01-0.11)		
	Overall agreement			0.57		0.44
	Overall agreement			(0.51-0.63)		(0.23-0.74)
	Карра			0.16		0.27
	Карра			(0.10-0.39)		(0.09-0.50)
Degree	Specific	Complete	262	0.73	17	0.72
	agreement			(0.68-0.78)		(0.47-0.92)
		Partial	91	0.39	8	0.44
				(0.30-0.48)		(0.11-0.79)
	Overall agreement	1		0.59		0.59
	Overall agreement			(0.55-0.65)		(0.36-0.85)
	Kanna			0.29		0.30
	Карра			(0.16-0.36)		(0.06-0.71)
	1	nalatal lovel (None	<u> </u>			vorce Evne

Interobserver agreement on the palatal level (Nonexp: nonexperienced observers; Exp: experienced observers), including 95% confidence intervals (in brackets). Single number sign indicates no experienced observers scored "not evaluable" for presence of palatal collapse; double number sign indicates none of them observed lateral palatal collapse.

Table 3. Interobserver agreement on the oropharyngeal level

				Oroph	harynx		
			None	xp (N = 90)	Ex	o (N = 7)	
	Γ		N	Agreement	N	Agreement	
Collapse	Specific	Collapse	249	0.68	17	0.75	
	agreement			(0.61-0.73)		(0.50-0.92)	
		No collapse	67	0.23	22	0.82	
				(0.17-0.31)		(0.59-0.96)	
		Not evaluable	25	0.08	0	#	
				(0.05-0.12)			
	Overall agreement	1		0.45		0.80*	
	orenan agreement		(0.39-0.52)		(0.63-0.94)		
	Карра			0.09		0.48*	
	Карра			(0.05-0.17)		(0.40-0.82)	
Direction	Specific	Anteroposterior	19	0.12	0	##	
	agreement			(0.05-0.22)			
		Concentric	112	0.44	2	0.92	
				(0.36-0.51)		(0.67-1.00)	
		Lateral	106	0.46	14	0.25	
				(0.38-0.54)		(0.00-0.84)	
	Overall agreement	1		0.33	0.82**		
				(0.28-0.39)		(0.42-1.00)	
	Карра			0.04		0.35*	
	Парра			(0.01-0.14)		(-0.47-1.00)	
Degree	Specific	Complete	65	0.36	4	0.93	
	agreement			(0.25-0.43)		(0.56-1.00)	
		Partial	165	0.57	12	0.60	
				(0.50-0.64)		(0.00-1.00)	
	Overall agreement		_	0.38		0.82*	
				(0.31-0.44)		(0.42-1.00)	
	Kanna			0.10		0.66**	
	Карра			(0.02-0.23)		(0.22-1.00)	
Interphserver agreement on the propharyngeal level (Noneyn: noneynerienced phservers:							

Interobserver agreement on the oropharyngeal level (Nonexp: nonexperienced observers; Exp: experienced observers), including 95% confidence intervals (in brackets). Single number sign indicates no experienced observers scored "not evaluable" for presence of oropharyngeal collapse; double number sign indicates none of them observed anteroposterior oropharyngeal collapse. The asterisk and double asterisk indicate significant differences in agreement between nonexperienced and experienced observers of < 0.05 or < 0.01, respectively.

Table 4. Interobserver agreement on the tongue base level

			Tongue base			
			No	nexp (N = 90)	E	xp (N = 7)
			N	Agreement	N	Agreement
Collapse	Specific	Collapse	276	0.79	29	0.96
	agreement			(0.74-0.84)		(0.83-1.00)
		No collapse	86	0.43	10	0.83
				(0.36-0.52)		(0.57-1.00)
		Not evaluable	4	0.01	0	#
				(0.00-0.05)		
	Overall agreement			0.63		0.93*
	Overall agreement			(0.57-0.70)		(0.80-1.00)
	Карра			0.33		0.71*
	Карра		(0.26-0.41)		(0.40-1.00)	
Direction	Specific	Anteroposterior	199	0.69	25	0.88
	agreement			(0.63-0.75)		(0.72-0.98)
		Concentric	60	0.33	0	##
				(0.25-0.43)		
		Lateral	4	0.02	0	##
				(0.00-0.06)		
	Overall agreement			0.51		0.76
	ŭ			(0.45-0.58)		(0.51-0.97)
	Карра			0.04		-0.14
				(-0.02-0.14)		(-0.36-0.26)
Degree	Specific	Complete	76	0.33	14	0.58
	agreement			(0.27-0.39)		(0.30-0.84)
		Partial	184	0.62	12	0.49
	Overall agreement			(0.56-0.68)		(0.24-0.78)
				0.45		0.50
				(0.40-0.52)		(0.32-0.75)
	Карра			0.12		0.03
	Kappa			(0.05-0.21)		(-0.01-0.58)
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Interobserver agreement on the tongue base level (Nonexp: nonexperienced observers; Exp: experienced observers), including 95% confidence intervals (in brackets). Single number sign indicates no experienced observers scored "not evaluable" for presence of tongue base collapse; double number sign indicates that none of them observed concentric or lateral tongue base collapse. Asterisk indicates significant differences in agreement between nonexperienced and experienced observers.

**Table 5.** Interobserver agreement on the hypopharyngeal level

			Hypopharynx			
			Non	exp (N = 90)		xp (N = 7)
	T		N	Agreement	N	Agreement
Collapse	Specific agreement	Collapse	166	0.51	10	0.45
				(0.44-0.58)		(0.16-0.72)
		No collapse	114	0.37	21	0.59
				(0.31-0.44)		(0.38-0.79)
		Not evaluable	43	0.11	5	0.016
				(0.08-0.16)		(0.00-0.42)
	Overall agreement			0.33		0.47
				(0.28-0.38)		(0.31-0.66)
	Карра			0.08		0.03
	Парра			(0.05-0.14)		(0.00-0.47)
Direction	Specific agreement	Anteroposterior	37	0.19	0	##
				(0.12-0.27)		
		Concentric	71	0.53	1	0.00
				(0.40-0.65)		(0.00-0.71)
		Lateral	45	0.21	8	0.71
				(0.14-0.27)		(0.25-1.00)
	Overall agreement			0.24		0.44
	Overall agreement			(0.17-0.31)		(0.14-0.95)
	Карра			0.02		0.05
	Карра			(0.00-0.12)		(-0.18-0.64)
Degree	Specific agreement	Complete	32	0.17	2	0.71
				(0.11-0.25)		(0.25-1.00)
		Partial	118	0.51	8	0.33
				(0.44-0.59)		(0.00-1.00)
	Overall agreement			0.28		0.54
				(0.22-0.35)		(0.20-0.98)
	Kanna			-0.06		0.09
	Карра			(-0.09-0.03)		(-0.19-0.68)

Interobserver agreement on the hypopharyngeal level (Nonexp: nonexperienced observers; Exp: experienced observers), including 95% confidence intervals (in brackets). Double number sign indicates that among the experienced observers, anteroposterior hypopharyngeal collapse was not observed.

**Table 6.** Interobserver agreement on the epiglottis level

			Epiglottis			
			Non	exp (N = 90)	E	Exp (N = 7)
			N	Agreement	N	Agreement
Collapse	Specific agreement	Collapse	189	0.71	14	0.82
				(0.63-0.78)		(0.53-0.97)
		No collapse	156	0.56	19	0.71
				(0.49-0.63)		(0.45-0.92)
		Not evaluable	13	0.19	5	0.67
				(0.06-0.47)		(0.00-1.00)
	Overall agreement			0.57		0.74
	green agreement			(0.51-0.63)		(0.57-0.92)
	Карра			0.23		0.51
	Марра			(0.16-0.34)		(0.41-0.77)
Direction	Specific agreement	Anteroposterior	153	0.82	12	1.00
				(0.75-0.88)		(1.00-1.00)
		Concentric	19	0.22	1	0.33
				(0.09-0.42)		(0.00-1.00)
		Lateral	8	0.13	0	##
				(0.02-0.73)		
	Overall agreement			0.63		0.97
				(0.53-0.73)		(0.72-1.00)
	Карра			-0.17		0.97
				(-0.25-0.15)		(0.71-1.00)
Degree	Specific agreement	Complete	77	0.51	9	0.75
				(0.42-0.61)		(0.35-1.00)
		Partial	98	0.48	4	0.40
				(0.40-0.57)		(0.00-1.00)
	Overall agreement			0.41		0.61
				(0.35-0.48)		(0.30-0.99)
	Карра			-0.05		0.61*
	ppu			(-0.08-0.19)		(-0.02-0.79)

Interobserver agreement on the epiglottis level (Nonexp: nonexperienced observers; Exp: experienced observers), including 95% confidence intervals (in brackets). Double number sign indicates that among the experienced observers, lateral epiglottis collapse was not observed. Asterisk indicates significant differences in agreement between nonexperienced and experienced observers.

 Table 7. Intraobserver agreement

		Nonexperie	enced (N=52	)		Experier	nced (N=5)		
	Raw agreement		Кај	ора	Raw agreement		Кар	Карра	
	Median	Bootstrap	Median	Bootstrap	Median	Bootstrap	Median	Bootstrap	
	Q1-Q3	Mean	Q1-Q3	Mean	Q1-Q3	Mean	Q1-Q3	Mean	
	(95%CI)	(95%CI)	(95%CI)	(95%CI)	(95%CI)	(95%CI)	(95%CI)	(95%CI)	
Р	1.0	0.92	0.00	-0.01	1.0	0.96	0.43	0.49***	
	(0.8-1.0)	(0.88-0.95)	(-0.05-0.00)	(-0.04-0.02)	(1.0-1.0)	(0.94–0.98)	(0.00-1.00)	(0.39-0.59)	
0	0.8	0.62	0.00	0.07	0.8	0.76	0.52	0.49**	
	(0.4-0.8)	(0.56-0.68)	(-0.11-0.17)	(-0.01-0.15)	(0.6–0.8)	(0.72–0.80)	(0.27-0.52)	(0.42-0.56)	
Т	0.8	0.74	0.40	0.38	1.0	0.92	1.00	0.81*	
	(0.6-1.0)	(0.69-0.80)	(0.00 - 0.64)	(0.28 - 0.48)	(0.8–1.0)	(0.90–0.94)	(0.52-1.00)	(0.75-0.87)	
Н	0.6	0.56	0.09	0.19	0.6	0.60	0.38	0.30	
	(0.2-0.8)	(0.48-0.64)	(-0.01-0.53)	(0.11-0.28)	(0.4–0.8)	(0.53–0.66)	(-0.10-0.52)	(0.20-0.41)	
Е	0.8	0.76	0.52	0.52	1.0	0.92	1.00	0.84*	
	(0.6-1.0)	(0.71-0.81)	(0.30-0.67)	(0.45-0.60)	(0.8–1.0)	(0.90–0.99)	(0.66-1.00)	(0.79-0.89)	

Intraobserver agreement on levels of upper airway collapse (Q: quartile; CI: confidence interval; P: palate; P: oropharynx; T: tongue base; H: hypopharynx; E: epiglottis). Asterisk, double asterisk, and triple asterisk indicate significant differences in agreement between nonexperienced and experienced observers of < 0.05, < 0.01, or < 0.001, respectively.

## **DISCUSSION**

This study describes variations in the interobserver and intraobserver agreement of DISE in a large cohort of ENT surgeons, consisting of both experienced and nonexperienced DISE observers. The current results indicate that as a rule, agreement is higher among experienced observers, and therefore experience in performing DISE is necessary to obtain reliable results. Training could be beneficial to ENT surgeons new to this emerging technique. Higher interobserver agreement was found in particular for oropharyngeal, tongue base and epiglottis collapse. Intraobserver agreement was higher among the experienced raters, also in particular for the oropharynx, tongue base and epiglottis (Table 7).

The difference in interobserver agreement on palatal collapse between the nonexperienced and experienced ENT surgeons might be due to a higher tendency of nonexperienced observers to see a collapse at this specific level, as it is the most common site of snoring<sup>8</sup> but does not necessarily implicate collapse. The differences in overall interobserver agreement for this specific upper airway level might thus be explained by an artificially high agreement among the nonexperienced observers, rather than a substantially lower agreement among the experienced raters. The low kappa value for presence of collapse of this specific upper airway level in the nonexperienced group might endorse this explanation. Least interobserver agreement was found for hypopharyngeal collapse in both the nonexperienced and experienced groups. General ENT surgeons regularly perform endoscopic upper airway procedures as part of their routine clinical practice but might be less accustomed to evaluation of the hypopharynx as an isolated entity of the upper airway tract. The low agreement for hypopharyngeal collapse in the experienced group might be attributed to the use of different scoring systems in specific specialized centers <sup>2, 9, 10</sup>, in which qualification of the hypopharynx is particularly subject to different approaches. Also, evaluation of the hypopharyngeal level in general can by hindered by collapse at a higher upper airway level where the tip of the nasopharyngoscope is positioned to observe the hypopharynx. This phenomenon is not present when assessing the palate, as the nasopharyngoscope is then positioned in the nasopharynx, not being a part of the collapsible segment of the upper airway. Furthermore, the hypopharynx has less defined structural boundaries, compared with

other upper airway levels, e.g,. the palate. The experienced observers appeared to find identification of the presence of upper airway collapse at the level of the palate, oropharynx and tongue base less cumbersome, having not scored "not evaluable" for these levels, unlike the nonexperienced observers. Also, the absence of certain structure-configurations in the ratings of the experienced observers is prominent. This is particularly true for the absence of lateral palatal collapse, anteroposterior oropharyngeal collapse, concentric or lateral tongue base collapse, anteroposterior hypopharyngeal collapse and lateral epiglottis collapse.

This study is the first to specifically describe differences in interobserver and intraobserver agreement between nonexperienced and experienced ENT surgeons. The current results on interobserver agreement in our subgroup of experienced ENT surgeons are in accordance with previous findings in the field, although study designs are only roughly comparable <sup>10, 11</sup>. Kezirian et al. found that the reliability of global assessment of obstruction was somewhat higher than the degree of obstruction, especially for the hypopharynx <sup>10</sup>. Rodriguez-Bruno found high interobserver and intraobserver agreement for obstruction at the level of the tonsils, followed by the epiglottis 11. There are major differences with the current study: the number of experienced observers (Kezirian et al. study: two; Rodriguez-Bruno et al. study: two; current study: seven), number of video segments shown (Kezirian et al. study: 108; Rodriguez-Bruno et al. study: 32; current study: six), and the type of scoring system used. Furthermore, Kezirian et al. found that among experienced surgeons, assessment of the palate, tongue, and epiglottis showed greater reliability than for other structures, whereas in the current study, higher agreement was found for palatal, oropharyngeal and tongue base collapse. As the palate and tongue base are better-defined upper airway structures, this might partially explain the findings of consistently better reliability on these specific levels.

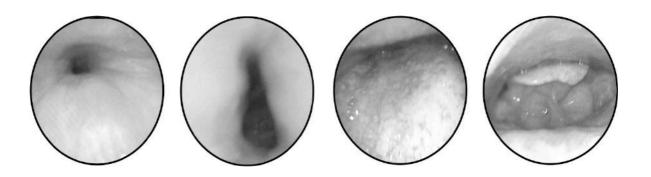
The current study provides important additional insights into what is known of interobserver and intraobserver variability in DISE, as it was conducted in a large cohort of general ENT surgeons, most of whom were nonexperienced with DISE and not yet specifically trained to assess DISE findings. All observers were blinded to baseline characteristics of the study participants, so no confounding effects of variables such as the apnea-hypopnea index or body mass index were to be expected. In recent literature on the value of DISE, it was suggested that DISE is most relevant when considering tongue base surgery or oral appliance therapy<sup>12</sup>; therefore, the high interobserver and intraobserver agreement found for tongue base collapse among the experienced ENT surgeons in the current study might be of particular importance. Furthermore, results on interobserver and intraobserver agreement in a cohort of both experienced and nonexperienced observers may help to detect differences in assessment for varying levels of training. A possible solution to the unreliability of DISE findings on particular levels could be training ENT surgeons with a set of standardized DISE videos to foster consistency for scoring the upper airway level variables. To do so, the use of a standardized and universally accepted DISE scoring system will also be essential.

There are several limitations to this study. Ideally, intraobserver agreement is to be determined based on more ratings, which was practically not feasible in the study setting. A fuller set of DISE samples, potentially including more different patterns, would have allowed more robust reliability testing of the scoring system. Furthermore, there were only seven observers in the experienced group. However, the current setting was considered sufficient to demonstrate and verify differences in agreement in experienced versus nonexperienced observers — the main goal of this study. As for the statistical analysis, it is to be mentioned that kappa coefficients have an important drawback in the current study design, because the kappa value is heavily dependent on the observed marginal frequencies. Some specific upper airway collapse configurations (i.e., lateral palatal collapse, anteroposterior oropharyngeal collapse) are generally rare or unlikely to be observed. This leads to lower kappa values and can therefore be severely misleading in interpreting the agreement among the observers. The observers participating in the current project were possibly acquainted with different DISE scoring systems at their home clinics. Using an unknown uniform study scoring system while assessing the DISE video segment may have been cumbersome. Furthermore, only segments of the DISE videos were shown, although this was considered a minor limitation, as the main goal was to assess interobserver and intraobserver variation and not to provide a treatment plan. The heterogeneity of the observer group is to be considered relative in this context. Indeed, there are differences in levels of experience within the subcategories of nonexperienced and experienced. However, this aspect reflects clinical reality and may help to emphasize the need for specific training in DISE assessment in daily clinical practice.

In conclusion, the reported findings on interobserver and intraobserver agreement in a cohort of ENT surgeons, both nonexperienced and experienced with DISE, demonstrate that overall observer agreement was higher in experienced versus nonexperienced ENT surgeons, suggesting that experience in performing DISE is necessary to obtain reliable observations. Training under guidance of an experienced surgeon might be helpful for those unexperienced with DISE. These findings are new to the field and add additional insights into the validity of the technique. If DISE is to be extended into general ENT practice, the need for a standardized scoring system increases.

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# Chapter 3

Drug-induced sleep endoscopy in sleep-disordered breathing: report on 1249 cases

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## **ABSTRACT**

Study objective: To describe upper airway collapse patterns during drug-induced sleep endoscopy (DISE) in a large cohort of patients with sleep-disordered breathing (SDB) and to assess associations with anthropometric and polysomnographic parameters.

Setting: 1,249 patients [age 47±10 y; apnea-hypopnea index (AHI) 18.9±15.3/h; body mass index (BMI) 27.2±3.7 kg/m<sup>2</sup>] underwent polysomnography and DISE. DISE findings were categorized to the following upper airway levels: palate, oropharynx, tongue base and hypopharynx. The degree of collapse was reported as complete, partial or none, and the pattern of the obstruction was described as anteroposterior, lateral or concentric. Associations between DISE findings and anthropometric and polysomnographic parameters were analyzed.

Measurements and results: Palatal collapse was seen most frequently (81%). The most frequently observed multilevel collapse pattern was a combination of palatal and tongue base collapse (25.5%). The prevalence of complete collapse, multilevel collapse and hypopharyngeal collapse increased with increasing severity of obstructive sleep apnea (OSA). Multilevel and complete collapse were more prevalent in obese patients and in those with more severe OSA. Both higher BMI and AHI values corresponded with a higher probability of complete concentric palatal collapse.

**Conclusion:** The current study provides an overview of upper airway collapse patterns in a large cohort of SDB patients who underwent DISE. The associations found in this study may improve insight into the pathogenesis of OSA but may also indicate that upper airway collapse patterns observed during DISE cannot be fully explained by selected baseline polysomnographic and anthropometric characteristics.

## **CONTEXT**

In literature, several studies documented upper airway collapse patterns during drug-induced sleep endoscopy (DISE) <sup>1-12</sup> and recently, associations between DISE findings and baseline patient characteristics were reported <sup>13</sup>. However, these results were restricted to only relatively small-scale studies. The present study describes the findings in a large cohort of patients with sleep-disordered breathing (SDB) who underwent DISE. The aims of this study were to provide an overview of collapse patterns and to assess the associations found between baseline patient characteristics and DISE findings.

## **METHODS**

## Study design

This observational study was conducted at the Antwerp University Hospital, where DISE was performed in 1,249 consecutive patients from 2007 to 2011. Polysomnography (PSG) was performed prior to DISE. The apnea—hypopnea index (AHI) was used to recommend either CPAP treatment (AHI>20 and mean arousal index (MAI)>30) or non-CPAP therapy (AHI<20), such as MAD or upper airway surgery. If non-CPAP therapy was advised, or if patients were reluctant to use, failed to tolerate, or were non-responsive to CPAP, a routine ENT examination and DISE were scheduled.

## Polysomnography (PSG)

The diagnosis of SDB was to be based on full-night polysomnography (PSG), with OSA being defined based on an AHI > 5/hour sleep. Sleep recordings were scored manually by a qualified sleep technician  $^{14}$ . Based on AHI the following levels of OSA severity are defined: mild sleep apnea with a score of 5 < AHI  $\leq$  15, moderate sleep apnea scored 15 < AHI  $\leq$  30, and severe sleep apnea with AHI > 30 events/hour sleep  $^{14}$ .

## Drug-induced sleep endoscopy (DISE)

DISE was performed by an experienced ENT surgeon in a semi-dark and silent operating room, with the patient lying in the supine position on a hospital bed. Artificial sleep was induced by intravenous administration of midazolam (bolus injection of 1.5 mg) and propofol through a target-controlled infusion system (1.5 to 3.0  $\mu$ g/mL). During the

procedure, electrocardiography, blood pressure and oxygen saturation were monitored continuously. Endoscopy was performed using a flexible, fibreoptic nasendoscopy (Olympus Europe GmbH, Hamburg, Germany). The procedure was performed in an outpatient setting.

Perioperative findings as to the level(s), degree, and direction of collapse were noted using a uniform scoring system (Main figure 1, page 29 of this thesis). Findings were classified as an isolated obstruction at the palate, oropharynx, tongue base or the hypopharynx (including the epiglottis) or combinations of these. The palate is defined as the portion of the upper airway at the level of the soft palate and uvula, while the oropharynx is defined as the pharyngeal region at the level of the tonsils (above the tongue base). The tongue base is defined as the retroglossal area, and the hypopharynx is defined as the pharyngeal region below the tongue base, including the tip of the epiglottis. Degree of narrowing and direction were evaluated, with degree classified as none, partial or complete and direction classified as anteroposterior, lateral or concentric. Upper airway obstruction was categorized as either unilevel or multilevel collapse.

# Statistical analysis

Data analysis was performed using R version 2.15.0 (R Foundation for Statistical Computing, Vienna, Austria). Descriptive statistics for clinical characteristics of patients are presented as means ± standard deviation (SD). Logistic regression models were used to assess the associations between the different levels of collapse and AHI and BMI while correcting for age and gender. For each configuration of collapse, a separate logistic regression model was constructed. A p-value of <0.05 was considered significant.

# **RESULTS**

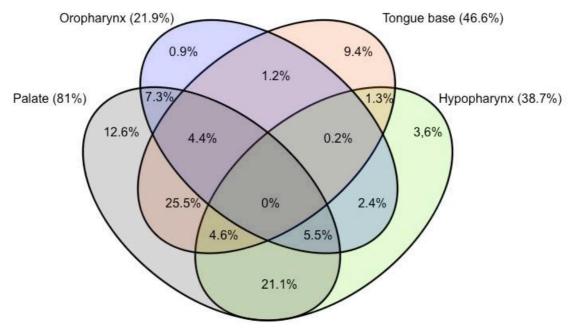
The majority of the study population was male, middle aged and slightly overweight (Table 1).

**Table 1.** Baseline patient characteristics

Variables	All subjects n=1249)
Males (n, %)	985 (79%)
Females	264 (21%)
Age in years (mean ± SD)	47 ± 10
BMI in kg/m² (mean ± SD)	27 ± 4
AHI, per hour sleep (mean ± SD)	17 ± 13

BMI: body mass index; AHI: apnea/hypopnoea index

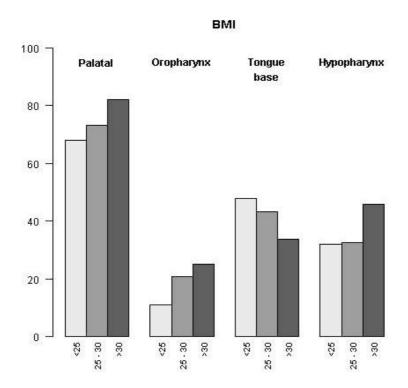
An overview of the upper airway collapse patterns in this study population is shown in a Venn diagram (Figure 2). Palatal collapse was seen most frequently (81%), followed by tongue base collapse (46.6%), then hypopharyngeal collapse (38.7%). The most frequently observed type of multilevel collapse was a combination of palatal and tongue base collapse in 25.5% of the patients.



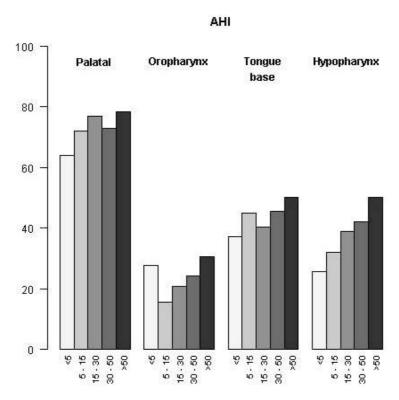
**Figure 2.** Venn diagram showing the prevalence of collapse per upper airway level and the combinations thereof.

The prevalence of collapse per upper airway level for different categories of BMI and AHI is depicted in Figures 3 and 4. The presence of palatal and oropharyngeal collapse becomes more prevalent as BMI increases (Figure 3), whereas the prevalence of tongue base collapse is lower in overweight and obese patients. The prevalence of hypopharyngeal collapse increases with OSA severity (Figure 4). The prevalence of the specific direction of collapse per upper airway level is shown in Figure 5.

A logistic regression model was constructed for in-depth analysis of the associations between BMI and AHI with specific collapse patterns, including degree and direction of collapse per upper airway level (Table 2). Increasing BMI values in particular correspond with a higher probability of complete concentric palatal collapse, partial lateral oropharyngeal collapse and partial lateral hypopharyngeal collapse (p<0.001). The opposite applies to complete anteroposterior tongue base collapse, where a higher probability was found with lower BMI values (p<0.001). Higher AHI values correspond with a higher probability of complete collapse, specifically complete concentric palatal collapse, complete concentric hypopharyngeal collapse and complete lateral hypopharyngeal collapse (p<0.001). Lower AHI values correspond with a higher probability of partial concentric palatal collapse (p<0.001).



**Figure 3.** Percentage of patients with upper airway collapse at a specific level for different categories of BMI (normal, overweight, obese)



**Figure 4.** Percentage of patients with upper airway collapse at a specific level per AHI category (no OSA, mild OSA, moderate OSA, severe OSA).

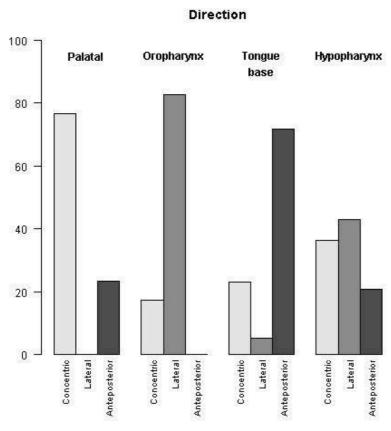


Figure 5. Percentage of patients with specific direction of collapse per upper airway level.

Table 2 (part 1). Associations between specific collapse patterns on the palatal and oropharyngeal levels with the body mass index (BMI) and apnea-hypopnea index (AHI); corrected for age and gender.

				Mean			Mean		
	COLLAPSE PATTERN		N	вмі	OR (95%CI)	р	АНІ	OR (95%CI)	р
				(SD)			(SD)		
	None		219	26.55	0.93	0.003	17.82	1.00	0.964
				(3.46)	(0.89,0.98)		(12.84)	(0.99,1.01)	
		Conc	293	27.44	1.03	0.088	14.15	0.96	< 0.001 <sup>†</sup>
				(3.71)	(0.99,1.08)		(10.06)	(0.95,0.97)	
	Part	Lat							
tal		AP	85	26.50	0.93	0.062	17.86	1.00	0.811
Palatal		Ar	83	(3.90)	(0.87,1.00)	0.002	(15.47)	(0.98,1.02)	
		Conc	393	28.00	1.08	< 0.001 <sup>†</sup>	20.87	1.02	< 0.001 <sup>†</sup>
		Conc	393	(3.83)	(1.04,1.12)	< 0.001	(15.46)	(1.01,1.03)	
	Compl	Lat							
		АР	124	26.47	0.92	0.007 <sup>§</sup>	22.14	1.02	0.024*
				(3.44)	(0.86,0.98)		(15.17)	(1.00,1.03)	
	None		88	27.01	0.92	< 0.001	18.02	0.99	0.184
				(3.66)	(0.88,0.96)		(13.46)	(0.98,1.00)	
	Part	Conc	9	26.48	0.95	0.710	14.63	0.98	0.620
				(2.78)	(0.74,1.23)		(10.22)	(0.91,1.06)	
		Part Lat	120	28.42	1.09	< 0.001 <sup>†</sup>	18.47	1.00	0.957
×			120	(3.50)	(1.04,1.15)	< 0.001	(13.16)	(0.98,1.02)	0.557
Oropharynx		AP							
oph	Compl	Conc	33	29.06	1.12	0.036*	23.92	1.01	0.252
ŏ				(4.14)	(1.01,1.24)		(20.11)	(0.99,1.04)	
		Lat	81	27.93	1.05	0.174	21.00	1.01	0.123
				(4.28)	(0.98,1.12)		(17.80)	(1.00,1.03)	0.125
		AP							
		A-P	172	26.09	0.89	< 0.001 <sup>†</sup>	20.31	1.01	0.029
				(3.47)	(0.84,0.94)		(14.71)	(1.00,1.03)	
<u> </u>			<u> </u>	<u> </u>					

Part: partial; Compl: complete. Conc: concentric; Lat: lateral; AP: anteroposterior. \*p<0.05,  ${}^{\$}p<0.01$ ,  ${}^{\dagger}p<0.001$ . Shaded boxes reflect the fact that a specific structure-configuration was not observed. Light grey text corresponds to low prevalence of the specific collapse pattern.

Table 2 (part 2). Associations between specific collapse patterns on the tongue base and hypopharyngeal levels with the body mass index (BMI) and apnea-hypopnea index (AHI); corrected for age and gender

р	OR (95%CI)	Mean AHI (SD)	p	OR (95%CI)	Mean BMI (SD)	N	COLLAPSE PATTERN		
0.641	1.00	18.34	< 0.001	1.08	27.72	606	None		
	(0.99,1.01)	(13.58)		(1.04,1.12)	(3.89)				
0.837	1.00	17.65	0.831	1.01	27.32	70	Conc		
	(0.98,1.02)	(13.63)		(0.94,1.09)	(3.79)				
0.333	1.01	19.48	0.944	1.00	27.26	20	Lat	Part	
	(0.99,1.05)	(11.98)		(0.88,1.13)	(2.97)	20	Luc	Ture	e,
0.003 <sup>§</sup>	0.98	16.07	0.142	0.97	26.83	206	A-P		pas
	(0.96,0.99)	(13.83)	0.142	(0.92,1.01)	(3.28)	200	A-r		Tongue base
0.220	1.01	21.55	0.745	1.02	27.63	52	Cons		To
0.229	(0.99,1.03)	(16.91)	0.715	(0.93,1.11)	(3.57)	52	Conc		
0.159	1.03	25.84	0.875	0.98	27.18	7	Lat	Compl	
	(0.99,1.07)	(17.20)		(0.76,1.26)	(4.01)			Compl	
0.029	1.01	20.31	< 0.001 <sup>†</sup>	0.89	26.09	172	A-P		
	(1.00,1.03)	(14.71)		(0.84,0.94)	(3.47)				
0.016	0.99	17.25	0.106	0.97	27.10	697	None		
0.010	(0.98,1.00)	(13.11)		(0.94,1.01)	(3.53)	097			
0.766	1.00	18.36	0.619	0.98	27.04	84	Conc		
	(0.98,1.02)	(14.37)	0.019	(0.92,1.05)	(4.11)				
0.486	0.99	19.41	< 0.001 <sup>†</sup>	1.12	28.68	154	Lat	Part	
0.460	(0.98,1.01)	(14.80)	< 0.001	(1.07,1.17)	(4.09)				×
0.197	0.97	14.75	0.163	0.90	26.09	20	A D		arynx
	(0.93,1.02)	(9.93)	0.163	(0.77,1.04)	(2.87)	29	A-P		Hypoph
< 0.001 <sup>†</sup>	1.03	26.20	0.023*	0.91	26.60	74	Conc	Compl	
< 0.001	(1.01,1.04)	(17.43)		(0.85,0.99)	(3.21)				
0.001	1.03	27.35	0.022*	1.11	29.04	33	Lat		
	(1.01,1.05)	(15.06)		(1.02,1.22)	(4.82)				
0.000	1.00	17.75	0.093	0.91	26.35	-P 62	A-P		
0.909	(0.98,1.03)	(13.61)		(0.82,1.02)	(3.74)				
	(0.93,1.02) 1.03 (1.01,1.04) 1.03 (1.01,1.05) 1.00	(9.93) 26.20 (17.43) 27.35 (15.06) 17.75	0.022*	(0.77,1.04) 0.91 (0.85,0.99) 1.11 (1.02,1.22) 0.91	(2.87) 26.60 (3.21) 29.04 (4.82) 26.35	33	Lat	Compl	Нурорhа

Part: partial; Compl: complete. Conc: concentric; Lat: lateral; AP: anteroposterior. \*p<0.05, §p<0.01, <sup>†</sup>p<0.001. Light grey text corresponds to low prevalence of the specific collapse pattern.

# **DISCUSSION**

The present study provides a description of upper airway collapse patterns in a large cohort of patients with SDB. Palatal collapse was most frequently observed, followed by collapse of the tongue base, hypopharynx and the oropharynx. The high prevalence of palatal collapse may be due to the fact that snoring, which most often originates from palatal vibration, is a common complaint among patients with SDB. In addition, this study assessed the associations between certain upper airway collapse patterns and anthropometric and polysomnographic parameters. In the reported population, both increasing BMI and AHI values corresponded with a higher probability of complete concentric palatal collapse. Lower BMI values corresponded with a higher probability of complete anteroposterior tongue base collapse.

Upper airway collapse patterns in patients with SDB have been previously described in literature. In contrast to previous studies, the large population size of the present study made it possible to construct logistic regression models for each upper airway collapse configuration and correct for age and gender. In general, finding palatal collapse to be the most frequently observed level of collapse (81%) in the present study confirms previous findings <sup>1, 4, 6, 8, 10, 12, 13, 15</sup>. Ravesloot et al. previously reported on upper airway collapse patterns in a cohort of 100 OSA patients and also assessed the associations between AHI, BMI and upper airway collapse patterns <sup>13</sup>. The authors found that palatal collapse was seen most frequently (83%), followed by tongue base (56%), epiglottis (38%) and oropharyngeal collapse (7%). A similar ranking was found in the present study, although oropharyngeal collapse (21.9%) was more frequently observed. In Ravesloot's study, mean BMI and AHI were higher when complete concentric palatal collapse was present. These findings were confirmed in the present study, as both higher BMI and AHI values corresponded to a higher probability of complete concentric palatal collapse. Ravesloot found a tendency for lower BMI when tongue base collapse was present, and this association was also found to be statistically significant in our study. This may be due to the fat accumulation in the lateral pharyngeal walls, as previously described in literature <sup>16-18</sup>. In the current study, a higher BMI and AHI were associated with a higher probability of complete concentric palatal collapse. Furthermore, the probability of complete concentric palatal collapse rose with increasing BMI. A high BMI

and AHI also corresponded to a higher probability of complete lateral hypopharyngeal collapse, which also may be explained by the fat accumulation at the lateral (para)pharyngeal walls.

The aim of upper airway evaluation is not only to gain better insight into the different upper airway collapse patterns, but also to improve treatment success rates by selecting the most appropriate therapeutic option for the individual patient <sup>19</sup>. As non-CPAP treatment modalities aim to resolve upper airway collapse at specific levels, evaluation of the upper airway is essential to obtain insight into the individual patient's specific collapse patterns. Various techniques of upper airway assessment have been introduced over the years, including X-ray cephalometry, computed tomography (CT) scanning, magnetic resonance imaging (MRI), pressure measurements and sleep endoscopy. In the present study, DISE was used to assess upper airway collapse patterns. An advantage of this approach is that DISE is a dynamic, safe, and feasible procedure that can be performed in an outpatient setting <sup>6</sup>.

Furthermore, DISE is likely to detect anatomical upper airway abnormalities, which in lean or young subjects explain a major part of the variance in AHI and are likely to play an important role in the pathophysiology <sup>20</sup>. Also, in contrast to conventional diagnostics for SDB, DISE can add valuable information about the direction of collapse in a dynamic setting, especially in more complex multilevel collapse patterns. The differentiation of the direction of collapse also may reflect underlying pathophysiological mechanisms and may be of importance in assessing the effects of therapy on the upper airway collapse patterns, although further research is needed to determine this.

In line with previous findings in literature, the present findings indicate that multilevel collapse patterns are more prevalent in patients with higher AHI values, making adequate assessment of the levels of obstruction compulsory to compose an adequate multilevel surgical plan <sup>21</sup>. Complete collapse is seen more often with higher AHI values, which also may limit the success of non-CPAP therapy, as complete collapse may be more difficult to eradicate with surgery or oral appliance therapy than partial collapse. In addition, there is some preliminary evidence that the outcome of a specific treatment option, such as upper airway stimulation (UAS) therapy, will be dependent on upper airway collapse patterns as documented during DISE <sup>22, 23</sup>. Recently, the absence of complete concentric palatal collapse was found to be of possible predictive value towards therapeutic success with implanted UAS and regarding this specific issue, it is important to highlight the high prevalence of concentric palatal collapse, in particular when compared to the obviously relatively low prevalence of anteroposterior palatal collapse, in the current cohort.

Furthermore, with regard to the ongoing process of developing a standardized universal DISE scoring system, in approximately 20% of the current cohort, assessed by trained ENT surgeons, a concentric collapse of the tongue base was described. This is a direction of tongue base collapse that is not recognized to exist in all currently available scoring systems <sup>24</sup>. This once again emphasizes the need for a pluripotent system that not automatically excludes certain configurations and may even leave room for describing anatomical abnormalities.

There are several limitations to the present study. Although the validity and reliability of DISE have been demonstrated <sup>25-27</sup>, DISE findings remain subjectively assessed. A key factor is the training of general ENT surgeons for this procedure, as higher intra- and interobserver agreement has been found among ENT surgeons experienced with performing DISE <sup>28</sup>. In the present study, DISE findings were assessed by different ENT surgeons; however, all of them were experienced with DISE and trained at the same institute. The performing ENT surgeons were not blinded for the baseline patient characteristics while assessing DISE. A clinic-specific scoring system familiar to the performing ENT surgeons was used for the assessment of DISE, so the present data may not be automatically translated into other settings were other scoring forms are applied <sup>24, 29</sup>. Nevertheless, the scoring system used in this study was based on anatomically defined items, a fast growing trend in DISE reporting 24, 29. The development of a universal DISE scoring system is a point of interest for future research. Other research in the field of DISE should focus on optimization of objective assessment of DISE findings as well as the implementation and optimization of DISE as a patientselection tool for non-CPAP therapies. An interesting attempt has been recently described by Borek et al., who performed quantitative analysis of upper airway changes during DISE in the work-up for transoral robotic surgery for OSA <sup>30</sup>.

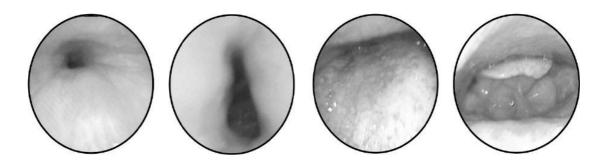
The current findings of DISE in a large cohort of patients demonstrate that palatal collapse was most frequently observed. The prevalence of complete or multilevel upper airway collapse increases with the severity of OSA and in overweight and obese patients. Both increasing BMI and AHI values correspond with a higher probability of complete concentric palatal collapse. These findings indicate that upper airway collapse patterns as observed during DISE can be explained in part by selected baseline characteristics and that additional evaluation of the upper airway remains essential to obtain insight into the specific collapse patterns of the individual patient.

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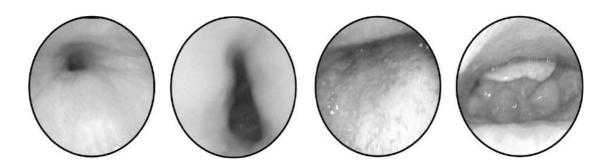
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# Chapter 4

Drug-induced sleep endoscopy with simulation bite



# Chapter 4.1

The procedure of drug-induced sleep endoscopy with simulation bite

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Operative Techniques in Otolaryngology 2011;22:175-182

#### **ABSTRACT**

Mandibular advancement devices (MADs) are currently the most widespread and valuated type of oral appliance used to treat obstructive sleep apnea (OSA). Although oral appliance therapy usually reduces snoring, it is not always as effective in treating OSA. The methods that have been described to predict treatment outcome with oral appliance therapy mostly have relied on retrospective analysis and there is a significant lack of uniformity concerning the predictive models. Therefore, the ability to predict treatment outcome of oral appliance therapy prospectively in the individual patient and, thereby, preselecting suitable OSA patients for oral appliance therapy, is still limited in clinical practice. The site of upper airway obstruction can be assessed by sleep nasendoscopy or 'drug-induced sleep endoscopy' (DISE). Generally, a decision is made after performing the so-called 'chin-lift' maneuver, whereby the mandible is brought forward maximally. Although allowing for a visual inspection of the effect of mandibular protrusion, the position itself is not reproducible and it remains to be determined to what extent it is physiologically tenable by the patient. Furthermore, the chin-lift maneuver requires a further opening of the mouth simply for allowing the dental sleep professional the possibility to grasp and protrude the mandible. At our multidisciplinary dental sleep clinic at the Antwerp University Hospital, we started using a bite simulation approach to investigate the patient's protrusive characteristics prior to the modified multipart DISE procedure. This specific technique using a simulation bite, custom-made for each individual patient, during DISE is described in detail in this article.

# **CONTEXT**

The mechanism by which mandibular advancement devices (MADs) counteract obstructive sleep apnea (OSA) is still a subject of research. Improved insight into the mechanism of action could contribute to the identification of the complex of factors determining treatment outcome <sup>1</sup>. Predictors of treatment outcome are of importance in selecting patients who might benefit from MAD treatment <sup>2</sup>. Various anthropometric and polysomnographic predictors have been described in the literature, including lower apnea-hypopnea index (AHI), lower body mass index (BMI), lower age, female gender and supine-dependent OSA <sup>3</sup>. Using cephalometry, Tsuiki et al. concluded that an anteriorly titrated mandibular position reduced obstructive sleep apnea severity, enlarged the velopharynx and diminished the curvature of the anterior velopharyngeal wall in good responders <sup>4</sup>. Functional imaging using computational fluid dynamics on computerized tomography (CT)-images of head and neck could be of predictive value in predicting treatment success, with a decrease in upper airway (UA) resistance and in an increase in UA volume correlating with both a clinical and an objective improvement <sup>5</sup>. The role of flow-volume curves has also been described, although it was suggested that this functional assessment could be of improved predictive value when combined with a structural assessment of the UA with imaging modalities <sup>6</sup>.

However, most of the reported variables that correlate with increased effectiveness come with significant shortcomings. First, the methods that have been described to predict treatment outcome with oral appliance therapy mostly have relied on retrospective analysis. Second, there is a significant lack of uniformity concerning the predictive models. Therefore, the ability to predict treatment outcome of oral appliance therapy prospectively in the individual patient and, thereby, preselecting suitable OSA patients for oral appliance therapy, is still limited in clinical practice.

Drug-induced sleep endoscopy (DISE) has been suggested as a valuable prognostic indicator of successful oral appliance treatment in the individual patient 7, 8. A so-called "chin-lift"-maneuver can be added to the DISE procedure, whereby the mandible is actively guided forward by 'grasping' it and advancing it to a maximal protruded position. Although allowing a visual inspection of the effect of mandibular protrusion, the position itself is not reproducible and it remains to be determined to

what extent it is physiologically tenable by the patient. Furthermore, the chin-lift maneuver requires a further opening of the mouth simply for allowing the dental sleep professional the possibility of grasping and protruding the mandible. It has been demonstrated recently that DISE, completed with a jaw thrust maneuver, shows a relevant influence on the location of treatment recommendation, especially when considering MAD treatment or tongue base interventions <sup>9</sup>. A possible criticism of the reported study is that a non-reproducible and non-titratable mandibular protrusion maneuver has been performed during DISE, also not accounting for vertical opening while closing the mouth <sup>10</sup>.

At our multidisciplinary dental sleep clinic at the University Hospital, Antwerp, we started using a bite simulation approach to investigate the patient's protrusive characteristics prior to the modified multipart DISE procedure, as described below in its different steps.

#### **PROCEDURE**

# Technique of DISE completed with a simulation bite and chin-lift maneuver

The actual procedure of DISE with simulation bite approach is preceded by the registration of a specific simulation bite, custom-made for each individual patient. A dedicated registration fork was made (Ostron Blue; GCEurope, Belgium) (Figure 1A). The thickness of this instrument equals the interincisive distance required for future MAD fitting. First, the upper arch of the fork is covered with a registration material (Futar D; Kettenbach GmbH & Co, Germany) and left to cure once placed against the upper jaw. On the extension, sliding calipers are then placed and the patient is guided into habitual occlusion and this "baseline" position is marked by fixating 1 caliper (Figure 1B). The patient is then asked to protrude the mandible maximally followed by a slow retraction of the mandible until a position is reached that the patient describes as the maximal comfortable protrusive position (Figure 1C, 1D). This is further referred to as the maximal comfortable protrusion (MCP). The measurements are repeated 3 times and averaged. This position is now transferred to the registration fork and fixed by the second caliper. Next the lower surface is covered with the registration material and the patient is guided into the MCP until curing (Figure 1D). The registration bite in MCP is then ready to be used during the DISE procedure (Figure 1E, 1F); thereby, it is guaranteed that it corresponds to a position that the patient is really able to tolerate, and that the DISE is performed at an exact reproducible position while it can still be extended to a maximal protrusion by removing the simulation bite and performing a chin-lift maneuver.

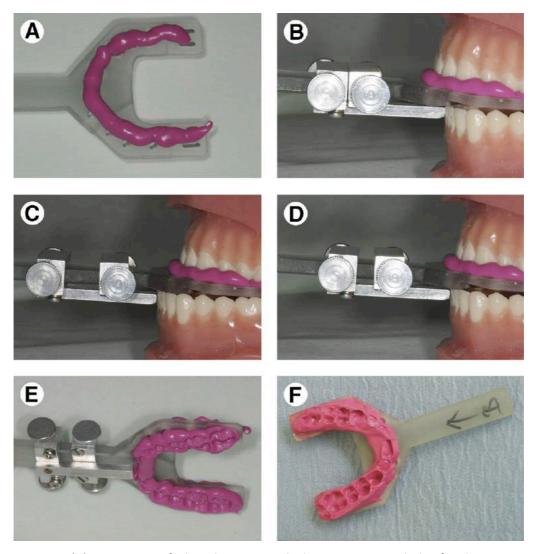


Figure 1. (A) Registration fork with constant thickness, retention holes for the registration paste, extension for measuring calipers, and registration paste applied to the upper arch. (B) Registration fork in situ, with patient in habitual occlusion and sliding calipers fixed in "baseline" position. (C) The patient is then repetitively asked to maximally protrude; this position is referred to as "maximal protrusion." (D) Thereafter, the patient retracts until the MCP is reached and this position is also registered. (E) After curing, the calipers are removed and the simulation bite is ready for DISE. (F) The simulation bite as used during DISE.

Prior to the start of the DISE procedure, patients are preoperatively examined by the anesthesiologist at the start of their short-stay hospitalization in the day care center. The DISE procedure is performed by the ENT surgeon in a semi-dark and silent operating theater in a multidisciplinary setting together with the dental sleep professional, the operation nurses, and the anesthesiologist. During DISE, the patient is in the supine position and under continuous monitoring of cardiac rhythms and oxygen saturation <sup>11</sup>. Artificial sleep is induced by intravenous administration of midazolam with a bolus injection of 1.5 mg and with Propofol using a target-controlled infusion system at a target of 2.0 or 2.5 g/mL (Figure 2).



Figure 2. Target-controlled infusion of propofol at the start of the procedure (left panel), and at plateau" phase during the procedure (right panel).

#### Step 1: Simulation bite approach

The first step of our modified multipart DISE procedure contains the particular part of the sleep endoscopy with intraoral positioning of the simulation bite. The main reason for this order of rank is that in the opposite rank, wanting to have the simulation bite intraorally in the second part of DISE, the teeth, and dental arches might be clamped making placement and positioning of the simulation bite more intrusive with the inherent risk of waking up the patient.

Prior to the intravenous administration of the sedative drugs, the simulation bite is fitted into the mouth of the conscious patient by the dental sleep professional (Figure 3). Thereafter, the dental sleep professional gently holds the lower jaw against the simulation bite to avoid the patient opening the mouth while falling asleep. Meanwhile, the ENT introduces the flexible fiberoptic nasopharyngoscope before the patient is completely unconscious to avoid irritation <sup>12</sup>. Once the plateau phase of propofol is

reached, the upper airway collapse is investigated endoscopically during at least 5 consecutive minutes with the simulation bite in situ (Figure 3). Meanwhile the images are continuously recorded using digital video recording and, in addition, diagnostically relevant image stills are captured.

# **Step 2: Baseline DISE**

After the first part of the procedure, DISE with simulation bite approach, the simulation bite is removed by the dental sleep professional. The simulation bite is only removed out of the mouth of the patient once the patient has remained sufficiently long on the "plateau" phase, and meanwhile, the flexible fiberoptic nasopharyngoscope is kept in place.

Doing so, the effects on the upper airway can be studied in a normal baseline setting without any mandibular repositioning. Again, during this second part of our multipart procedure, upper airway collapse is assessed and analyzed according to the classical grading systems. During this part of the DISE procedure, the upper airway collapse at the different pharyngeal levels can be visualized and examined without the mandibular protrusion effect, again during at least 5 consecutive minutes of plateau phase of propofol.

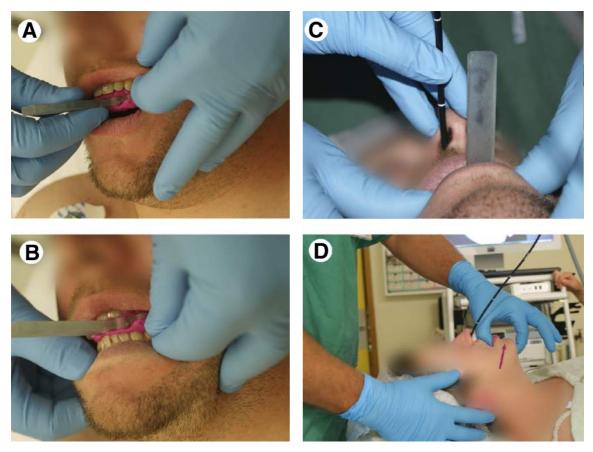


Figure 3. Insertion of the simulation bite: (A) starting with the upper teeth, and then (B) guiding of the mandible into the lower arch impressions of the simulation bite. (C) Situation during procedure: flexible fiberoptic nasopharyngoscope and simulation bite registration inserted. (D) Performing chin-lift maneuver: positioning and lifting of the mandible.

# **Step 3: DISE with chin-lift maneuver**

Preferably during an obstructive apnea, the dental sleep professional finally brings the mandible in the maximal protrusive position (Figure 3), again with the flexible fiberoptic nasopharyngoscope in place but without simulation bite. This part allows studying the effect of maximal protrusive positioning on the upper airway collapsibility. However, the increased vertical opening of the mouth due to the positioning of the fingers of the dentist lingually of the lower jaw incisives should be taken into account.

# Step 4: Decision-Making

The final step of DISE completed with simulation bite approach is that the peroperative findings during the different phases of the investigation are noted in the patient's medical file. A review is performed of the video recordings and still captures (Figures 4, 5, and 6). For each upper airway level, the baseline collapse (green square) is compared to the degree of collapse with simulation bite approach (yellow square) and during chinlift maneuver (purple square), respectively. A decision on future treatment planning is then discussed. When upper airway collapse is completely resolved using the bite simulation approach including chin-lift, at that stage, the patient is considered a suitable candidate for MAD treatment. The flow chart and decision scheme are shown in Figure Contraindications include insufficient mouth opening (<25 mm), insufficient mandibular protrusion (<5-6 mm) and untreated periodontal disease or substantial tooth mobility <sup>13, 14</sup>. Furthermore, a sufficient number of healthy teeth are required, with a particular need for posterior teeth to obtain a solid intraoral fixation <sup>14</sup>. Relative contraindications include active moderate to severe temporomandibular joint disease <sup>15</sup>.

The described technique of DISE completed with simulation bite approach provides the use of a reliable and reproducible mandibular position during the examination. A major advantage of the excellent reproducibility is that the simulation bite approach is made applicable for use during other investigations with possible clinical utility in predicting the outcome of treatment of OSA with MAD. Therefore, the simulation bite approach can be used, not only during DISE, but also during nasopharyngoscopic evaluation during wakefulness <sup>16, 17</sup>, or during functional imaging studies using computer methods for the evaluation of the upper airway in patients with sleep disordered breathing 5, 18.

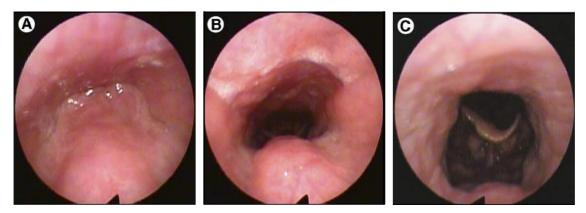


Figure 4. Multipart DISE procedure (at the palatal level). Baseline (A): complete anteroposterior collapse of the palate, with simulation bite approach; (B) partial reopening of the upper airway at the level of the palate, performing chin-lift maneuver; (C) relief of the palatal collapse.

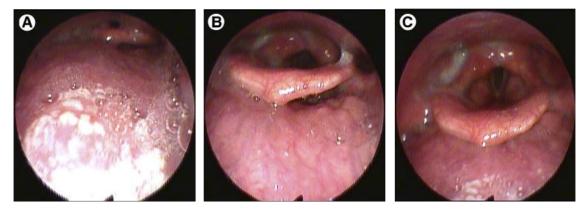


Figure 5. Multipart DISE procedure (level of the tongue base). Baseline (A): complete anteroposterior collapse of the tongue base, with simulation bite approach; (B) partial reopening of the upper airway at the level of the tongue base, performing chin-lift maneuver; (C) relief of the tongue base collapse.

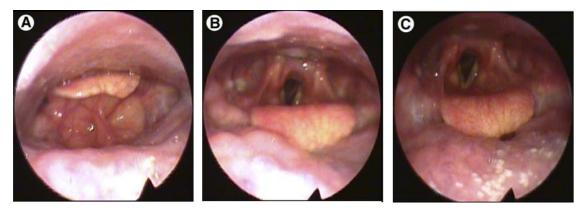


Figure 6. Multipart DISE procedure (at the level of the epiglottis). Baseline (A): complete anteroposterior collapse of the epiglottis, with simulation bite approach; (B) significant reopening of the upper airway at the level of the epiglottis, performing chin-lift maneuver; (C) relief of the epiglottis collapse.

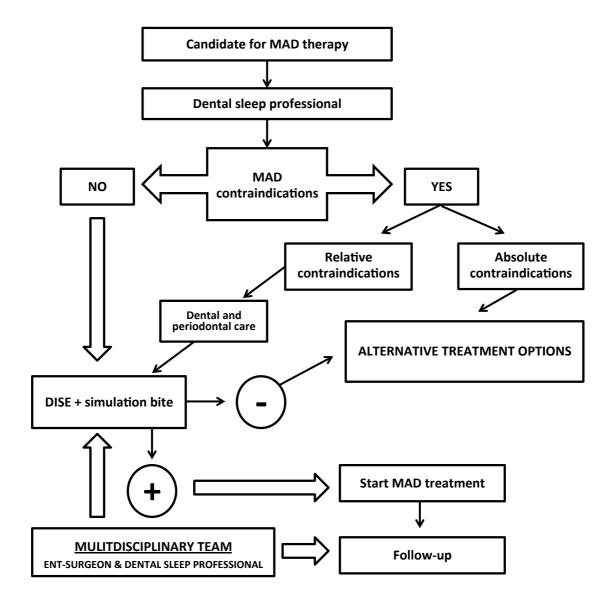
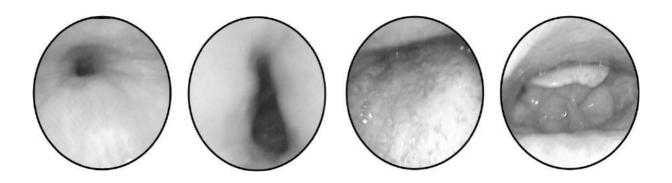


Figure 7. Flow chart on the decision-making performing DISE with bite simulation approach including chin-lift.

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# Chapter 4.2

Sleep endoscopy with simulation bite for prediction of oral appliance treatment outcome

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#### **ABSTRACT**

Study objective: To assess the value of drug-induced sleep endoscopy (DISE) using a custom-made simulation bite in maximal comfortable protrusion (MCP) of the mandible, in the prediction of treatment outcome for obstructive sleep apnea (OSA) with a mandibular advancement device (MAD).

Methods: Two hundred patients (74% male; age 46±9 years; apnea-hypopnea index (AHI) 19±13/hour sleep; BMI 27±4 kg/m²) with sleep-disordered breathing underwent DISE with a simulation bite in MCP. One hundred thirty-five patients with an established diagnosis of OSA commenced MAD treatment. The associations between the findings during DISE with simulation bite and treatment outcome were evaluated. Treatment response was defined as a reduction in AHI following MAD treatment of ≥ 50% compared to baseline.

**Results:** Overall MAD treatment response in the studied population was 69%. The results of this study demonstrated a statistically significant association between a positive effect of the simulation bite on the upper airway patency during DISE and treatment response with MAD (p<0.01).

Conclusion: The results of this study suggest that the use of a simulation bite in maximal comfortable protrusion (MCP) of the mandible, as used during DISE in patients with OSA, tends to be effective in predicting treatment response of MAD treatment.

# **CONTEXT**

In the present study, the prognostic value of the drug-induced sleep endoscopy (DISE) procedure with simulation bite in maximal comfortable protrusion (MCP), as described in Chapter 4.1, is assessed in terms of treatment outcome with mandibular advancement device (MAD).

#### **METHODS**

#### Study subjects

Two hundred consecutive adult patients with sleep disordered breathing (SDB) referred for oral appliance treatment, were included in the study. Baseline characteristics are shown in Table 1.

The reported study was conducted in accordance with the institutional guidelines of the ethical committee and all patients gave written informed consent.

# Polysomnography (PSG)

The diagnosis of SDB was to be based on polysomnography (PSG), with obstructive sleep apnea (OSA) being defined as an apnea-hypopnea index (AHI) > 5/hour sleep. For this purpose, a standard full-night PSG was performed (Brain RT software, OSG, Belgium). Sleep recordings were scored manually in a standard fashion by a qualified sleep technician <sup>1</sup>. The sleep technician had no knowledge of DISE prediction results. Based on AHI the following levels of OSA severity are defined: mild sleep apnea with a score of 5 < AHI ≤ 15, moderate sleep apnea scored 15 < AHI ≤ 30, and severe sleep apnea with AHI > 30 events/hour sleep <sup>1</sup>.

# Drug-induced sleep endoscopy (DISE) with simulation bite

The actual procedure of DISE with simulation bite was preceded by the registration of a specific simulation bite, custom-made for each individual patient. This novel procedure has been extensively described by our group (chapter 4.1 of this thesis). Peroperative findings as to the presence and the level(s) of collapse were noted in the patient's medical file, using a standard scoring system (Main figure 1, page 29 of this thesis). The palate is defined as the particular portion of the upper airway at the level of the soft palate and uvula, while the oropharynx is defined by the pharyngeal region at the levels of the tonsils (above the tongue base). The tongue base is defined as the retroglossal area, and the hypopharynx is defined as the upper airway region below the tongue base, including of the tip of the epiglottis. Examples of upper airway collapse patterns are shown in figure 2.

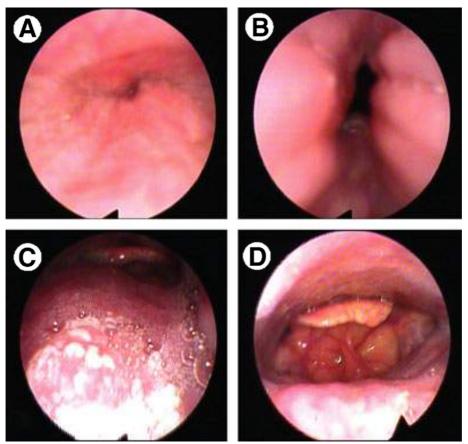


Figure 2. Complete circular collapse at the level of the palate (A); partial lateral collapse at the level of the oropharynx (B); partial anteroposterior collapse of the tongue base (C); complete anteroposterior collapse of the epiglottis (D).

When upper airway collapse was completely resolved (no residual collapse at any upper airway level) using the simulation bite, the patient was considered a "well suitable" candidate for MAD treatment. If only partial resolution was achieved (improvement, but with residual collapse at one or more upper airway levels) this was qualified as "partially suitable". Patients were considered "not suitable" when upper airway collapsibility increased or remained unchanged with the simulation bite *in situ*. A similar classification was applied for the chin-lift maneuver.

# Mandibular advancement device (MAD)

A custom-made, titratable, duobloc MAD (RespiDent Butterfly® MAD, Orthodontic Clinics NV, Antwerp, Belgium) was fitted for each patient starting MAD treatment (Fig. 3) <sup>2</sup>. The MAD consists of two dental clips that are attached to each other with an attachment for adjustment of the mandibular protrusion in the frontal teeth area, enabling titration. Acclimatization occurred over a period of 3 months, during which the appliance was titrated to either a maximal comfortable protruded position of the mandible or a resolution of the snoring, daytime sleepiness and/or apneas as witnessed by the bed partner, based on titration instructions as provided and demonstrated by the dental sleep professional. The dental sleep professional had no knowledge of DISE prediction results.



**Figure 3.** Lateral view of the RespiDent Butterfly® MAD intraorally; the device consists of two dental clips with attachments that allow adjustment of the mandibular protrusion in the frontal teeth area.

#### **Evaluation**

At baseline evaluation, the Epworth Sleepiness Scale (ESS) and the Visual Analogue Scale (VAS) for snoring were assessed, to evaluate daytime sleepiness and nighttime snoring, respectively <sup>3, 4</sup>. Patients with OSA at baseline and commencing MAD treatment were evaluated polysomnographically with the MAD in situ after an adaptation and titration period of 3 months, allowing 'target protrusion' of the mandible, defined as the final and most effective protrusion, to be attained. An outpatient clinic appointment was scheduled to discuss the polysomnography results and the changes in subjective assessment, including the ESS and the VAS for snoring.

The associations between findings during DISE and treatment outcome were assessed. Treatment outcome was based on polysomnographic results with MAD. Treatment response was defined as a reduction in AHI following MAD treatment of ≥ 50% compared to baseline, non-response was defined as a reduction in AHI of < 50%<sup>5</sup>. Compliance failure was defined as a discontinuation of treatment due to medical or nonmedical reasons.

# Statistical analysis

Data analysis was performed using R version 2.15.0 (R Foundation for Statistical Computing, Vienna, Austria. Descriptive statistics for clinical characteristics of patients are presented as means ± standard deviation (SD). Normality of distribution was assessed using Q-Q plots. Unpaired t-tests were used to compare the maximal comfortable protrusion between responders and non-responders. Paired t-tests were used to compare measurements at baseline and at evaluation with MAD when data were distributed normally. Non-parametric tests were used in case the data were not normally distributed. Categorical data were analyzed using chi-square tests. A multiple logistic regression model was built to evaluate the prognostic values of the baseline characteristics on treatment response, allowing adjustment for gender, age and BMI. Odds ratios (OR) together with confidence intervals (CI) and P-values are reported. A Pvalue of <0.05 was considered significant.

# **RESULTS**

A total of 200 patients (baseline characteristics outlined in table 1) underwent DISE with simulation bite and chin-lift maneuver. Patient flow is depicted in figure 4. Fifty-two out of 200 patients did not start treatment as they were considered "not suitable" and other treatment options could be offered. Thirteen patients were considered not to have OSA, as their AHI was below 5/hour sleep. As a result, 135 patients (75% male; age 46±8 years; AHI 21±13/hour sleep; BMI 27±4 kg/m²) with an established diagnosis of OSA commenced MAD treatment. Twenty-five patients were lost to follow-up, as they did not show up for dental control visits and the polysomnographic evaluation with MAD, despite the appointment reminders. Of the 110 remaining patients, the majority of patients suffered mild OSA (53.6%), while 23 patients (20.9%) and 28 patients (25.5%) had moderate and severe OSA, respectively. PSG with MAD was performed in 103 out of 110 patients and compliance failure was noted in the remaining seven cases. The reasons for non-compliance were the following: unable to tolerate the device throughout the night (two patients), choking sensations (one patient) or side effects such as tooth tenderness (one patient) and dry mouth (one patient) or a combination of thereof (one patient), and in one case, claustrophobia during MAD wear.

#### Upper airway collapse pattern

An overview of the upper airway collapse patterns in this study population is shown in the Venn diagram (Fig. 5). As noted per level, a collapse at the level of the palate was seen most frequently, followed by the tongue base and the epiglottis, while the oropharyngeal level was scored least frequently. There were frequently observed combinations of collapse levels, with the most frequent collapse pattern being a combination of palatal and tongue base collapse (34.4%). Multilevel collapse in general was noted in 87.2% of all patients.

Table 1. Baseline patient characteristics

Variables	All subjects (n=200)
Males (n, %)	148 (74%)
Age in years (mean ± SD)	46 ± 9
Height in cm (mean ± SD)	176 ± 9
Weight in kg (mean ± SD)	84 ± 14
BMI in kg/m² (mean ± SD)	27 ± 4
AHI, per hour sleep (mean ± SD)	19 ± 13

BMI: body mass index; AHI: apnea/hypopnea index.

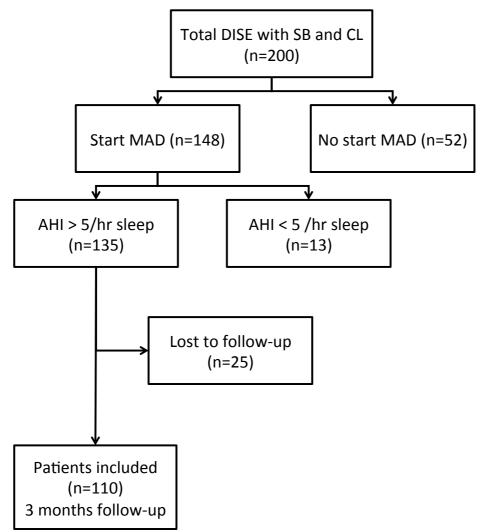
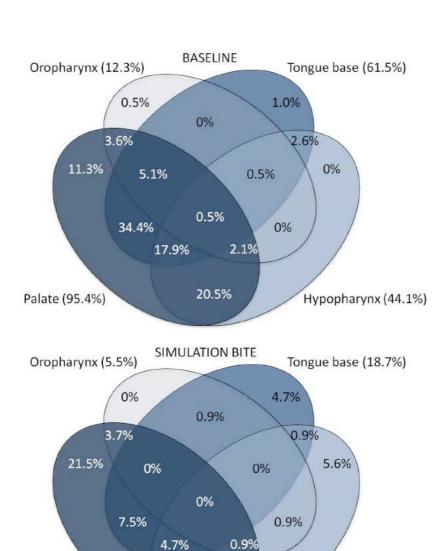
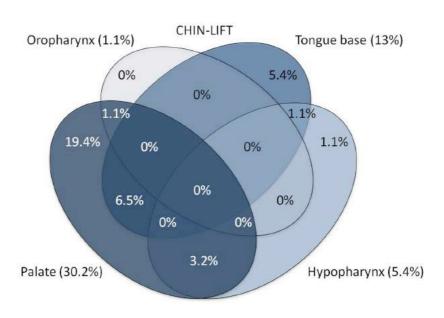


Figure 4. Patient flowchart. DISE: drug-induced sleep endoscopy; SB: simulation bite; CL: chin-lift maneuver; MAD: mandibular advancement device; AHI: apnea/hypopnea index.

61.3% of all cases, there was no upper airway collapse). Decreased transparency corresponds to higher incidence of collapse. during baseline evaluation, with the simulation bite in situ (in 43.9% of all cases, there was no upper airway collapse), with chin-lift maneuver (in Figure 5. Venn diagrams showing the percentages per upper airway level, and combinations thereof, contributing to the complex of collapse patterns

Palate (43%)





4.7%

Hypopharynx (17.7%)

#### **Treatment outcome**

Treatment response with MAD application was achieved in 71/103 (68.9%) of patients; with a mean AHI improving from 21.4 to 8.9/hour sleep. ODI, ESS and VAS also significantly decreased, as is shown in Table 2. A non-responder rate of 31.1% was noted (32 patients).

**Table 2.** Baseline versus MAD treatment outcome parameters.

N=103	Baseline	Evaluation with MAD after titration	P value
AHI, per hour sleep (mean ± SD)	21.4 ± 13.3	8.9 ± 9.7	p<0.001
ODI (mean ± SD)	6.8 ± 7.6	3.2 ± 4.0	p<0.001
ESS (mean ± SD)	10 ± 5	8 ± 5	p<0.001
VAS for snoring (mean ± SD)	7 ± 2	3 ± 2	p<0.001

MAD, mandibular advancement device; AHI, apnea-hypopnea index; ODI, oxygen desaturation index; ESS, Epworth Sleepiness Scale; VAS, visual analogue scale.

# Prediction of treatment outcome

In the present cohort, patients marked as "well suitable" for MAD treatment based on findings of upper airway patency changes during DISE procedure with simulation bite, have a higher chance of treatment response with MAD than patients marked as only "partially suitable" or "not suitable" [odds ratio (OR): 4.9619; 95% confidence interval (CI): 1.7301-14.2311; P value: 0.0029]. The presence of palatal collapse at baseline evaluation was also associated with treatment response, albeit with a wider confidence interval (OR 8.6822; 95% CI: 1.5643-48.1894; P value: 0.0135). Presence of hypopharyngeal collapse at baseline evaluation showed a tendency towards an association with a less favorable treatment outcome. These associations remained significant after adjustment for gender, age, BMI, AHI, and positional dependency. An overview of these findings is shown in Table 3. No statistical association was found between the effect of chin-lift maneuver on upper airway caliber and treatment response (p=0.64). The receiver operating characteristic (ROC) curve (Fig. 6) shows a high predictive value of this procedure (area under curve: 0.82). With a cut-off level of 0.50, the sensitivity is 0.91, the specificity is 0.53, the positive likelihood ratio is 1.96 and the negative likelihood ratio is 0.16. Maximal comfortable protrusion did not differ between responders (mean: 8.1 mm) and non-responders (mean: 8.4 mm) (p=0.54). The effect of the simulation bite per outcome category is shown in Table 4, with "predicted response" being based on the number of patients marked as "well suitable" for MAD treatment. The middle column and right column consist of the patients who were categorized as "partially suitable" and "not suitable", respectively. The results show that in the "predicted response" group, a majority of patients were responders (83.3%).

**Table 3.** Multiple logistic regression model (combined model with all parameters).

	Multiple logistic regression			Adjuste	•	r, age, BMI, <i>A</i> endency	AHI, supine	
		95% C	l for OR			95% C	I for OR	
	OR	Lower	Upper	Pr(> Z )	OR	Lower	Upper	Pr(> Z )
Effect SB	4.9619	1.7301	14.2311	0.0029	4.7791	1.5334	14.8950	0.0070
Collapse level:								
Palate	8.6822	1.5643	48.1894	0.0135	8.2699	1.3776	49.6433	0.0209
Oropharynx	3.6712	0.5156	26.1421	0.1941	3.2503	0.3854	27.4149	0.2786
Tongue base	0.7576	0.2734	2.0996	0.5935	0.6373	0.2014	2.0162	0.4433
Hypopharynx	0.3185	0.1170	0.8670	0.0251	0.2968	0.0984	0.8947	0.0310

SB: simulation bite; OR: odds ratio; CI: confidence interval; P: p value; BMI: body mass index; AHI: apnea/hypopnea index.

Table 4. Prediction of treatment outcome and treatment outcome on polysomnography with the mandibular advancement device (MAD)

Outcome	Predicted response	Predicted improvement	Predicted non- response	Total
Treatment response	35	34	2	71
Treatment failure	7	21	4	32
Total	42	55	6	103

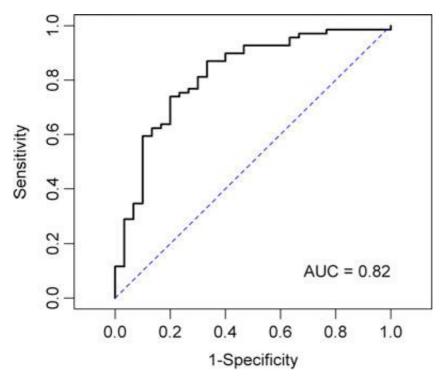


Figure 6. Receiver Operating Characteristic (ROC) – curve. The area under curve is 0.82. With a cut-off level of 0.50, the sensitivity is 0.91, the specificity is 0.53, the positive likelihood ratio is 1.96 and the negative likelihood ratio is 0.16.

# **DISCUSSION**

This study is the first to describe the effects of a custom-made simulation bite in maximal comfortable protrusion (MCP) of the mandible during DISE for the prospective prediction of MAD treatment outcome in the individual patient. The results of this study demonstrate that patients in whom upper airway patency improved substantially with the presence of the simulation bite in MCP during DISE are more likely to be treated successfully with MAD treatment. The described DISE technique completed with the simulation bite provides a reliable and reproducible mandibular position during the DISEexamination. A major advantage of the reproducibility is that the simulation bite can also be used during other investigations with possible clinical utility in predicting the outcome of treatment of OSA with oral appliance therapy, such as computed tomography (CT), magnetic resonance imaging (MRI), awake endoscopy, cephalometry and two-dimensional (2D) videofluoroscopy <sup>6, 7</sup>. Accordingly, Johal et al. demonstrated that significant changes occur in the pharyngeal airway of OSA patients following insertion of an oral appliance in MCP when assessed using videofluoroscopy 8.

The results of the present study indicate that the chin-lift maneuver in maximal protrusion may be clinically less relevant for therapeutic decision-making than generally considered. Manually mimicking MAD use may be indicative to a certain extent 9, 10, but this approach does not account for the given thickness of a particular MAD, whereas each oral appliance inherently causes a certain amount of vertical mouth opening. In addition, this maneuver is not reproducible in terms of the degree of mandibular advancement <sup>11</sup>. Furthermore, both the jaw thrust (Esmarch) and chin-lift maneuvers can be disturbing stimuli during DISE, potentially provoking an arousal by awakening of the patient during the procedure.

DISE with simulation bite being of predictive value for MAD treatment outcome is a key finding, particularly as the prediction of MAD treatment outcome continues to be an important research topic throughout the field. Retrospective analysis of factors such as AHI and body position has shown that these parameters are of potential influence on treatment outcome, as are BMI, neck circumference, gender and age <sup>5, 12, 13</sup>. Using cephalometry, Mostafiz et al. found a larger tongue size in complete responders to MAD treatment in relative terms <sup>13</sup>. Chan et al. suggested that the palate is important in

determining treatment outcome with MAD <sup>7</sup>. In the present study, a statistically significant association was found between the presence of palatal collapse and treatment response with MAD, confirming these previous findings. Although the odds ratio for this association is higher than for the association between the simulation bite effect and treatment response, the variability is higher, hindering direct clinical conclusions. Furthermore, it must be noted that in the present study, a palatal collapse was seen most frequently as a part of a multilevel collapse (Fig. 5). In other recent literature, it was found that oropharyngeal collapse has been related to a better outcome with MAD treatment, using multisensory catheters to determine upper airway closing and the site(s) of upper airway collapse <sup>14</sup> or phrenic nerve stimulation <sup>15</sup>. Comparison of these studies is limited, as mainly population sizes (Ng study: N=12; Bosshard study: N=33; present study: N=110) and evaluation technique differ (Ng study: upper airway catheters; Bosshard study: upper airway catheter; present study: DISE). Further studies combining advanced diagnostic technologies and individually tailored treatment could contribute to a better understanding of the role of the upper airway in the pathophysiology of OSA and treatment thereof <sup>16</sup>.

When considering treatment that is not certain to positively affect all potentially collapsible upper airway levels, identifying patterns of upper airway collapse is a crucial element in the diagnostic work-up. Although time-consuming, DISE provides information that is less likely to be collected otherwise, especially taking into account the multifactorial nature of upper airway obstruction <sup>11, 17-19</sup>. In evaluating the collapse patterns in the present study population, the quasi-omnipresent palatal collapse (95.4%) is remarkable, as is depicted clearly in the Venn diagram (Fig. 5). Also, multilevel collapse was noted in the majority of patients. These findings are in accordance with recent literature <sup>20</sup>.

This study has several limitations. It is obvious that the assessment of the upper airway during DISE is based on subjective findings. Concerning the subjective nature of the observations during DISE, presence of an interrater variability component is to be expected to a certain extent, although the interrater reliability has been labeled moderate to substantial and the test-retest reliability of DISE appears to be good, especially in the evaluation of the hypopharyngeal airway <sup>21, 22</sup>. Furthermore, it is not

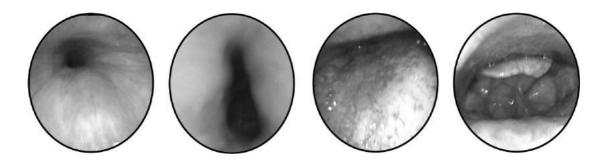
known to what extent the upper airway patency needs to change in order to counteract upper airway collapse effectively. Further studies will need to investigate such types of effect on the predictive value of the screening approach applied. In the present study, a standard DISE scoring system was used, with configuration of collapse as a standard component (main figure 1 on page 29 of this thesis). However, the present study population was considered too small to perform proper statistical analysis assessing the associations of the combinations of level-degree-configuration with treatment response. Another important issue is the quantification of the cross-sectional upper airway areas during DISE. Although adequate quantified measurement techniques in propofolanaesthetized subjects are described in the literature <sup>23, 24</sup>, visual estimation of the upper airway during DISE is still common practice. Also in this study, no specific measurements of the cross-sectional upper airway areas were performed, which can be considered a limitation that needs to be addressed in further research on the role of DISE in predicting MAD therapy outcome. Another potential limitation of the study is the generalizability and accessibility of DISE in routine clinical practice. As DISE generally requires administration of propofol, the procedure has to be performed in a controlled setting with specialized health care professionals. This may be cumbersome as the accessibility may not be optimal throughout all practices. Finally, another important drawback concerns the negative predictive value of the reported DISE with simulation bite procedure. Previous studies on prediction of MAD treatment outcome found negative predictive values of 78% and 45%, respectively <sup>25, 26</sup>. In the present study, the majority of patients who were considered "not suitable" for MAD treatment did not start MAD treatment. For this reason, the negative predictive value of the use of the simulation bite could was hard to assess in this study. Future research in this field should also focus on the false negative proportion, as this may constitute a large group of patients.

Ideally, patient selection is based on prospective elements. Specific diagnostic procedures that are potentially well suitable for this purpose must also be feasible, easily accessible, time and cost effective and well tolerable for the patient. At the same time, different relative anatomical and functional effects are to be expected in different patients; therefore proper individual assessment in a setting that resembles MAD use most accurately will be necessary. The DISE approach complemented with the use of a simulation bite in maximal comfortable protrusion is likely to meet this criterion closely.

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# Chapter 5

Effects of vertical opening on pharyngeal dimensions in patients with obstructive sleep apnea

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Parts of this study were presented as a poster at the Annual Congress European Respiratory Society, 27 September 2011, Amsterdam

Sleep Medicine 2012 Mar; 13(3): 314-6

#### **ABSTRACT**

Background: It is still subject to controversy if an increased vertical opening is beneficial in oral appliance therapy for the treatment of obstructive sleep apnea. Each oral appliance has a given thickness causing vertical opening. Therefore, evaluation of the effects of the amount of vertical opening on pharyngeal dimensions is mandatory.

**Methods:** The effects of vertical opening on the cross-sectional area of the upper airway at the level of the tongue base during sleep endoscopy were scored and categorized.

Results: The figures demonstrate the possible effects of vertical opening on pharyngeal collapse relative to the baseline cross-sectional area and the maximal comfortable protrusion of the mandible. Thirty-two patients (80%) showed an adverse effect of vertical opening (Fig. 1), one patient (2.5%) had a positive effect (Fig. 2), and seven patients (17.5%) demonstrated an indifferent effect (Fig. 3).

**Conclusion:** Based on literature, the effect of vertical opening on pharyngeal collapse is unclear and the therapeutic impact of vertical opening is not determined. The results of the present study indicate that the effect of vertical opening on the degree of pharyngeal collapse as assessed during sleep endoscopy tends to be adverse, causing an increase in collapsibility in the majority of patients.

# **CONTEXT**

It is still controversial whether or not an increased vertical opening is beneficial in oral appliance therapy <sup>1-4</sup>. Each oral appliance has a given thickness causing vertical opening. Therefore, evaluation of the effects of the amount of vertical opening on pharyngeal dimensions is mandatory.

In the present study the effect of vertical opening on pharyngeal collapsibility was assessed video-endoscopically during sleep endoscopy. Images of sleep endoscopies in 40 patients (80% male; mean age 48±9 years; mean apnea/hypopnea index 16±12/h sleep; mean body mass index 26±3 kg/m²) were registered. During sleep endoscopy, an experienced dental sleep professional induced vertical opening of up to 20 millimeters (mm), by manual downwards movement of the mandible starting from an initial vertical opening of 6.8±1.0 mm and a mean maximal comfortable protrusion of 7.2±1.8 mm (n = 40). The effects of vertical opening on the cross-sectional area of the upper airway at the level of the tongue base were scored and categorized as: adverse (narrowing), positive (widening) or indifferent (no change in pharyngeal dimensions).

## **IMAGE ANALYSIS**

Figures 1 to 3 demonstrate the possible effects of vertical opening on pharyngeal collapse relative to the baseline cross-sectional area and the maximal comfortable protrusion of the mandible.

Thirty-two patients (80%) showed an adverse effect of vertical opening (Fig. 1), one patient (2.5%) had a positive effect (Fig. 2) and seven patients (17.5%) demonstrated an indifferent effect (Fig. 3).



Figure 1. Adverse effect of vertical opening on pharyngeal dimensions: baseline (left panel), maximal comfortable protrusion (middle panel), vertical opening (right panel).



Figure 2. Positive effect of vertical opening on pharyngeal dimensions: baseline (left panel), maximal comfortable protrusion (middle panel), vertical opening (right panel).



Figure 3. Indifferent effect of vertical opening on pharyngeal dimensions: baseline (left panel), maximal comfortable protrusion (middle panel), vertical opening (right panel).

# **DISCUSSION**

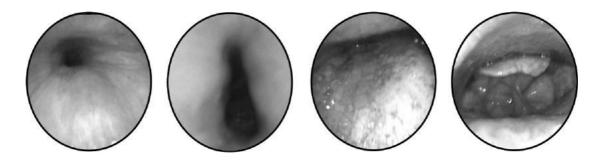
This study found that an increase in vertical opening tends to have an adverse effect on pharyngeal cross-sectional area at the level of the tongue base, as assessed during sleep endoscopy. In the majority of patients (80%), vertical opening led to a decrease in pharyngeal cross-sectional area.

There are several reports in the literature on the effects of increased vertical opening on the efficacy and side-effects of oral appliance therapy for OSA <sup>2-4</sup>. One study indicated that the amount of vertical opening did not affect treatment efficacy, but that patients preferred oral appliances with minimal vertical opening as they were more comfortable <sup>4</sup>. Another study reported that OSA is more effectively treated with increased vertical opening <sup>2</sup>. However, Ferguson et al. concluded that the effect of vertical opening on efficacy of oral appliance therapy remains unclear <sup>1</sup>. Meurice et al. suggested that mouth opening was associated with a significant increase in total respiratory resistance, which could lead to increased collapsibility of the upper airways <sup>3</sup>.

The present results are of primary clinical relevance, as vertical opening is a variable characteristic in oral appliance construction. A vertical opening maneuver, although not yet standardized, can easily be added to a sleep endoscopy, which is one of the evaluation techniques used to identify the pattern of pharyngeal obstruction. The present results indicate that increased vertical opening in oral appliance therapy has an adverse effect on pharyngeal dimensions in most patients.

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# Chapter 6

Evaluation of drug-induced sleep endoscopy as a patient selection tool for implanted upper airway stimulation for obstructive sleep apnea

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Parts of this study were presented as a poster at the SLEEP 2012 26th Annual Meeting of the Associated Professional Sleep Societies (APSS), 11 June 2012, Boston, MA (USA)

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#### **ABSTRACT**

Study Objectives: To study the possible predictive value of drug-induced sleep endoscopy (DISE) in assessing therapeutic response to implanted upper airway stimulation for obstructive sleep apnea (OSA).

Methods: During DISE, artificial sleep is induced by midazolam and/ or propofol, and the pharyngeal collapse patterns visualized using flexible are а fiberoptic nasopharyngoscope. The level (palate, oropharynx, tongue base, hypopharynx/ epiglottis), the direction (anteroposterior, concentric, lateral), and the degree of collapse (none, partial, or complete) were scored in a standard fashion.

Results: We report on the correlation between DISE results and therapy response in 21 OSA patients (apnea-hypopnea index [AHI] 38.5±11.8/h; body mass index [BMI] 28±2 kg/m<sup>2</sup>, age 55±11 years, 20 male/1 female) who underwent DISE before implantation of an upper airway stimulation system. Statistical analysis revealed a significantly better outcome with upper airway stimulation in patients (n = 16) without palatal complete concentric collapse (CCC), reducing AHI from 37.6±11.4/h at baseline to 11.1±12.0/h with upper airway stimulation (p < 0.001). No statistical difference was noted in AHI or BMI at baseline between the patients with and without palatal CCC. In addition, no predictive value was found for the other DISE collapse patterns documented.

**Conclusions:** The absence of palatal CCC during DISE may predict therapeutic success with implanted upper airway stimulation therapy. DISE can be recommended as a patient selection tool for implanted upper airway stimulation to treat OSA.

# **CONTEXT**

The aim of this study was to perform a detailed assessment of the possible predictive value of drug-induced sleep endoscopy (DISE) in the evaluation of therapeutic response to implanted upper airway stimulation therapy for obstructive sleep apnea (OSA).

# **METHODS**

We report on OSA patients who underwent a DISE before upper airway stimulation system implantation <sup>1</sup>. Patients with moderate to severe OSA (apnea-hypopnea index [AHI] ≥15/h sleep) and body mass index (BMI) <35 kg/m² were selected for upper airway stimulation system implantation if they failed or were intolerant of continuous positive airway pressure (CPAP) treatment. Exclusion criteria included chronic obstructive pulmonary disease, New York Heart Association class III or IV congestive heart failure, neuromuscular diseases, or prior upper airway surgeries not related to OSA. The trial was approved by the institutional review boards or ethics committees at all participating centers, and informed consent was obtained from all study subjects.

#### **Polysomnography**

An 18-channel in-laboratory polysomnography examination was conducted according to the American Academy of Sleep Medicine (AASM) guidelines  $^2$ . Hypopneas were scored according to the AASM 2007 Rule 4a: a nasal pressure drop  $\geq$ 30% of baseline, duration >10 sec,  $\geq$ 4% desaturation from baseline, and  $\geq$ 90% of the event duration must meet the amplitude reduction criteria for hypopnea.

#### Drug-induced sleep endoscopy (DISE)

The DISE procedure was performed by an ENT surgeon in a semi-dark and silent operating room with the patient in supine position <sup>3, 4</sup>. Continuous monitoring of cardiac rhythms and oxygen saturation was provided <sup>3</sup>. Unconscious sedation was induced by intravenous administration of midazolam with a bolus injection of 1.5 mg and/or with propofol using a target-controlled infusion system at a target of 2.0 to 3.0 g/mL. During DISE, the level (palate, oropharynx, tongue base, hypopharynx/ epiglottis), the direction (anteroposterior [AP], concentric, lateral), and degree of upper airway collapse (none,

partial, or complete) were scored in a standard fashion (Main figure 1, page 29 of this thesis) <sup>3-7</sup>. The palate is defined as the particular portion of the upper airway at the level of the soft palate and uvula, while the oropharynx is defined by the pharyngeal region at the levels of the tonsils (above the tongue base). The tongue base is defined as the retroglossal area, and the hypopharynx is defined as the upper airway region below the tongue base, including of the tip of the epiglottis. The collapse patterns were assessed during inspiration. All ENT surgeons who performed DISE in the present study were experienced with this procedure, and the DISE videos were assessed by the ENT surgeon who performed the procedure. The mean duration of the procedure was 25±18 minutes.

### **Upper airway stimulation system**

The upper airway stimulation system consists of a respiration sensor, a programmable implanted pulse generator, and stimulating electrodes (Inspire Upper Airway Stimulation therapy, Inspire Medical Systems, Minneapolis, MN, USA). The Inspire II Upper Airway Stimulation system (Inspire Medical Systems, Maple Grove, MN) consisted of a respiration sensor, programmable implanted pulse generator (IPG), and stimulating electrodes. The sensor detected respiratory efforts from the chest that were analyzed by the IPG. From the sensor signal, the IPG predicted the onset of inspiration, delivering stimulation pulses between the end of expiration and the beginning of the next expiratory phase of each respiratory cycle. The electrical pulses were applied to the hypoglossal nerve through platinum/ iridium electrodes. The patient was given a programming device capable of initiating and terminating the upper airway stimulation therapy. The operative technique of the implantation of the upper airway stimulation system used in this study has been described in detail previously <sup>1, 8</sup>.

## **Definition of treatment success**

The present study used the criteria established by Sher et al. to define treatment success as AHI <20/h after treatment and an AHI reduction ≥50% as compared to baseline 9. Additionally, success rates were assessed for a success definition of AHI <15/h sleep. To assess daytime sleepiness, patients filled out the Epworth Sleepiness Scale (ESS) 10.

# Statistical analysis

The pre-implantation AHI was compared to AHI 6 months after implantation. Statistical analysis was performed using MATLAB (The Mathworks, Natick, MA, USA) and Excel (Microsoft Corp, Redmond, WA, USA). A Wilcoxon signed-rank test was used to compare the pre-implantation AHI to the post-implantation AHI. Differences were considered statistically significant if the p-value was less than 0.05. Results were presented as means and standard deviations.

#### **RESULTS**

# **Subjects**

DISE videos were recorded for 21 patients with an established diagnosis of moderate to severe OSA before the implantation of the upper airway stimulation system. Patients were predominantly male, with an average age of 55±11 years, a baseline AHI of  $38.5\pm11.8$  /h, and a BMI of  $28\pm2$  kg/m<sup>2</sup> (Table 1).

Table 1. Patient demographics, including baseline differences between patients with and without complete concentric collapse (CCC) at the level of the palate

	Baseline AHI	ВМІ	Age	Gender
	(events/hour)	(kg/m²)	(years)	(M / F)
All patients (n=21)	38.5 ± 11.8	28 ± 2	55 ± 11	20 / 1
Palatal non-CCC (n=16)	37.6 ± 11.4	28 ± 2	55 ± 11	15 / 1
Palatal CCC (n=5)	41.54 ± 13.8	29 ± 2	55 ±9	5 / 0

#### **DISE** analysis

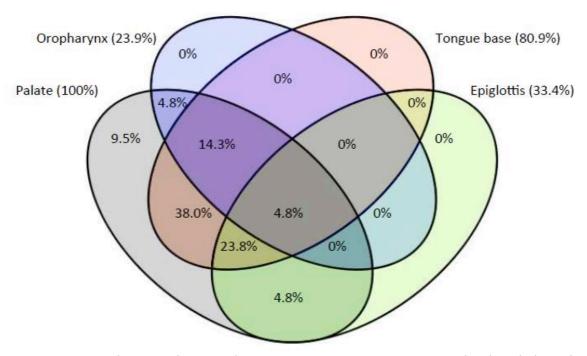
An overview of the distribution of the levels of upper airway collapse for all patients included in this study based on DISE scoring is provided in Figure 1 and Table 2. The majority of patients (91%) had multilevel collapse, predominantly at the palatal and tongue base levels and rarely at the oropharyngeal and hypopharynx/ epiglottis levels (Fig. 1). The most common upper airway collapse patterns noted in this study were AP collapse at the levels of the palate (76.2%) and the tongue base (71.4%) (Table 2).

Sixteen patients were categorized as having predominant AP palatal collapse, and 5 were categorized as having complete concentric collapse (CCC) at the palatal level (Fig. 2). There was no significant difference in baseline AHI, BMI, or age between patients with and without palatal CCC (Table 1).

In this patient group, 19 of 21 patients had multilevel collapse. All patients had at least a collapse at the level of the palate (Fig. 1), whereas tongue base, hypopharynx/ epiglottis, and oropharynx collapse were noted in 80.9%, 33.4%, and 23.9% of patients, respectively (Fig. 1). Conversely, no patients had tongue base collapse without palatal collapse (Fig. 1). The most common combination of multilevel collapse was the combination of AP palatal and AP tongue base collapse without epiglottis collapse, which occurred in 33% of the patients.

**Table 2.** Overview of the distribution of the levels of upper airway collapse including the corresponding direction of upper airway collapse based on DISE scoring (n = 21)

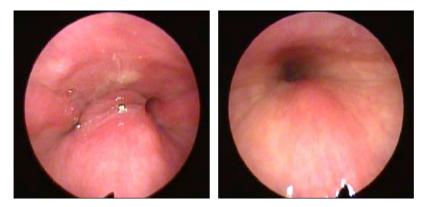
	Palate	Oropharynx	Tongue Base	Hypopharynx / Epiglottis
Anterior-posterior	76.2%	4.8%	71.4%	28.6%
Concentric	23.8%	4.8%	4.8%	4.8%
Latero-lateral	0.0%	14.3%	4.8%	0.0%
None	0.0%	76.2%	19.0%	66.7%



**Figure 1.** Venn diagram showing the percentages per upper airway level including the percentages of overlap between the different levels in case of multi-level collapse.

### Upper airway stimulation effect on various collapse types

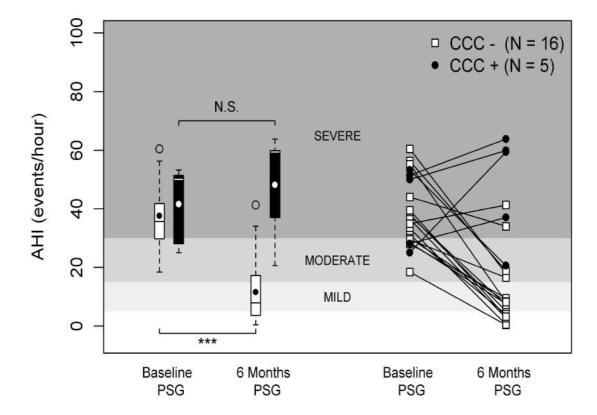
Patients with palatal CCC did not have a significant change in AHI with upper airway stimulation 6 months after implantation, as baseline AHI was  $41.5\pm13.8/h$  and AHI with upper airway stimulation was  $48.1\pm18.7/h$ , (p = 0.44; Fig. 3). The patients without palatal CCC had a significant improvement in AHI with upper airway stimulation despite multilevel collapse at the palate and tongue base. For this subset of patients, AHI went from  $37.6\pm11.4/h$  at baseline to  $11.6\pm11.7/h$  with upper airway stimulation (p < 0.001; Fig. 3). Thirteen patients with both palatal AP and tongue base AP collapse had a significant improvement in the AHI, decreasing from  $38.0\pm10.3$  at baseline to  $13.6\pm12.1$  with upper airway stimulation (p < 0.001).



**Figure 2.** Example of anteroposterior (left) versus concentric (right) collapse at the level of the palate during DISE.

## **Treatment success analysis**

The overall upper airway stimulation treatment success rate for all 21 patients included in this study using Sher's criteria was 62% (13/21). Treatment success in the subset of patients without CCC collapse at the level of the palate was 81% (13/16), while treatment success could not be achieved in any patient with CCC collapse at the level of the palate in this study (0/5). When assessing the success rates specifically for AHI <15, overall success would be achieved in 11/21 (52.4%) patients. In patients without palatal CCC success would be achieved in 11/16 patients (68.8%); in patients with palatal CCC this would be 0/5 (0%). There was no significant difference in BMI between baseline and 6 months in either group. Overall, ESS improved significantly from baseline  $8.2\pm5.0$  to  $6.4\pm4.3$  (p = 0.02; n = 18).



**Figure 3.** Apnea-hypopnea index (AHI) in patients with (black color) and without (white color) complete concentric collapse (CCC) at the level of the palate 6 months after upper airway stimulation implantation during stimulation as compared to baseline without upper airway stimulation; the different grey scales represent the distinction between normal nocturnal breathing (AHI <5/h sleep), mild OSA (AHI 5-15/h), moderate OSA (AHI 15-30/h), and severe OSA (AHI >30/h).

Left panel: boxplots showing the 75th and 25th percentiles by the upper and lower margins, the mean values by the closed circle, and the median values by the horizontal line. Whiskers represent the maximum value (top) and the minimum value (bottom) of the dataset; this range includes all data except the outliers. Outliers are represented by an open circle.

Right panel: the individual patient response data are plotted in line graphs, with the white squares being the AHI values in patients without CCC and the black circles being the AHI values in patients with CCC.

N.S.: not significant; \*\*\* p < 0.001

#### **DISCUSSION**

This study evaluates DISE as a patient selection tool for implanted upper airway stimulation therapy to treat OSA. The results of this study indicate that the absence of CCC at the level of the palate as documented during DISE may predict therapeutic success for OSA patients with implanted upper airway stimulation therapy. These finding are highly relevant to the field, as previous studies have indicated that the application of hypoglossal nerve stimulation in non-selected OSA patients leads to high interindividual variation in therapeutic effectiveness <sup>1, 11-14</sup>.

The role of DISE in patient selection for implanted upper airway stimulation therapy was recently addressed; however, the present study population consists of 5 additional subjects and provides specific demographics of the various combinations of multilevel upper airway collapse in this population. Patients with palatal CCC did not have a significant change in AHI with upper airway stimulation 6 months after implantation (AHI 41.5±13.8/h at baseline versus 48.1±18.7/h with upper airway stimulation), suggesting that the tongue protrusion resulting from the upper airway stimulation therapy is not sufficient to overcome the airway obstruction in patients with CCC at the level of the palate.

The results of this study also suggest that the stimulation at the base of tongue can potentially overcome AP obstruction not only at the base of tongue level but also at the palatal level. A statistically significant reduction in AHI was seen in patients with both AP palatal and tongue base collapse, suggesting that upper airway stimulation can resolve multilevel collapse. One possible explanation might be that an AP palatal collapse is due to a tongue base obstruction pushing back the soft palate. In this concept, upper airway stimulation is able to maintain airway patency as the tongue base is directly hindered from obstruction that keeps the palate in an anterior position.

These results showing that palatal CCC prohibits therapeutic success with upper airway stimulation might indicate that an AP movement induced by hypoglossal nerve stimulation cannot resolve a concentric collapse of the upper airway. Thus, the actual effects of upper airway muscle activation on upper airway shape are dependent on both the upper airway region and cross-sectional area <sup>15</sup>. Further research on DISE as a patient selection tool for implanted upper airway stimulation may focus on upper airway behavior during upper airway stimulation as assessed during DISE. In a recent study by Goding et al., cross-table fluoroscopic images were obtained during hypoglossal nerve stimulation in 26 subjects while two-dimensional changes in the AP dimensions of both the retropalatal and the retrolingual airway spaces were recorded <sup>16</sup>. The results of this fluoroscopy study indicate that during hypoglossal nerve stimulation, an opening of the upper airway at the level of the palate occurs in a majority of cases, confirming the beneficial effect of hypoglossal nerve stimulation on the AP upper airway dimensions <sup>16</sup>.

There is great interest in the prospective prediction of treatment outcome of non-CPAP options such as surgery and oral appliance therapy  $^{\rm 3,\ 17}.$  DISE provides an alternative method of studying the upper airway in OSA patients while performing a fiberoptic endoscopy during sedation. The lack of uniformity in the methods used for sedation during DISE as well as the fact that a consensus on DISE scoring systems has not yet been established, are clear limitations to this study 3, 4, 18, 19. Recent studies that address the test-retest and the intra- and interobserver variability in DISE scoring indicate that the reliability of both are moderate to fair, and that inter-observer agreement is higher in ENT surgeons who are experienced with DISE <sup>20-23</sup>. The limitations of this study also include the fact that DISE was performed only in the supine position, whereas upper airway collapse patterns should ideally be assessed in both the supine and non-supine position <sup>24</sup>.

It is well known that the probability of a multilevel collapse is significantly associated with the severity of OSA, as higher AHI values are correlated with a higher percentage of multilevel collapse <sup>6, 19, 25</sup>. This finding might explain the high prevalence of multilevel collapse in our study (91%) given the relatively high overall baseline AHI of 38.5±11.8/h. Upper airway collapse at the level of the palate was the most common level of collapse in this study, with collapse at the level of the tongue base being the second most common (Fig. 1). Again, these findings are in line with previous studies <sup>19, 25</sup>.

Two recent studies have shown a correlation between a patient's BMI and the therapeutic response to upper airway stimulation <sup>1, 16</sup>. In addition, a baseline AHI ≤50/h turned out to be a predictor of upper airway stimulation therapy response <sup>1</sup>.

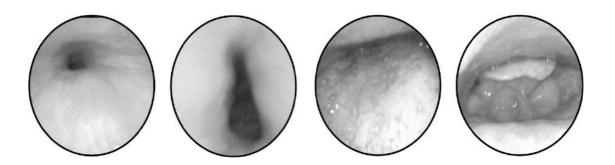
Although the number of patients included in this study was relatively low, a clinically and statistically significant difference in AHI was detected between the two groups of OSA patients (those with versus those without palatal CCC; Fig. 3). According to Sher's criteria, treatment success in the patients without palatal CCC was 81%, while no patients with CCC at the level of the palate could be treated successfully with upper airway stimulation. The correlation between the absence of CCC at the level of the palate and treatment success with upper airway stimulation turned out to be independent from baseline AHI and the patient's BMI (Table 1). Given that both parameters were previously described as predictors of therapeutic outcome with hypoglossal nerve stimulation for OSA, the fact that the absence of palatal CCC remains highly predictive independent from AHI and BMI certainly adds to the power of these findings.

In conclusion, based on the results of the reported study, DISE can be recommended as a patient selection tool for implanted upper airway stimulation to treat OSA. Further analysis of the predictive value of DISE in assessing therapeutic response to upper airway stimulation therapy needs to be performed in larger multicenter trials that are currently ongoing.

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# Chapter 7

General discussion

#### **GENERAL DISCUSSION**

This thesis focuses on drug-induced sleep endoscopy (DISE) as an evaluation method for upper airway behavior in obstructive sleep apnea (OSA) and as a tool for improved patient selection when non-CPAP therapy is considered. This chapter provides a comprehensive overview of the current status of DISE with its specific pros and cons, put into perspective of the findings of the present thesis.

## **Evaluation of upper airway obstruction**

Identifying the pathophysiological mechanisms underlying OSA in the individual patient remains a challenge. Upper airway collapse is a complex process and is influence by a wide range of factors <sup>1</sup>. Identifying the individual risk factor profile is becoming more essential. In the following paragraph, the factors promoting upper airway collapse and the role of DISE regarding this issue will be discussed.

Abnormalities of the upper airway anatomy in OSA may include skeletal factors such as hypoplasia or retroposition of the maxilla and/or mandible, or increased volume of soft tissues. Based on its inherent endoscopic nature, DISE may offer no direct improvement of recognition of the maxillar and/or mandibular abnormalities as compared to clinical examination or radiological imaging. A recent study compared DISE and lateral cephalometry and found these two largely distinct upper airway evaluation techniques to be of complementary value <sup>2</sup>. There was little association between DISE and lateral cephalometry findings on velum-related obstruction, although significant associations were identified between tongue-related obstruction during DISE and airway measurements posterior to the tongue base as assessed by lateral cephalometry. As pointed out by the authors, it is important to stress that DISE provides a threedimensional evaluation of the airway during unconscious sedation, often performed with individuals in the supine position, whereas lateral cephalometry is a two-dimensional evaluation performed during wakefulness with individuals in the upright sitting position.

Providing a dynamic endoscopic assessment of the upper airway, DISE also has an additional value in the identification of soft tissue abnormalities and their contribution to the complex of upper airway collapse, such as epiglottis malformation or tonsil hypertrophy. Narrowing of the airway by the lateral pharyngeal walls is in particular an important determinant of OSA, followed by enlargement of the tonsils, uvula enlargement and tongue enlargement <sup>3</sup>. Unlike most other evaluation techniques, DISE provides an excellent real-time identification of the direction of collapse, i.e. anteroposterior; lateral; and concentric (Main figure 1, page 29 of this thesis). Key findings relating to this differentiation in collapse patterns in a large cohort of patients are extensively described in chapter 3 of this thesis. Palatal collapse was seen most frequently (81%), with multilevel collapse noted in 68.2% of all patients. The most frequently observed multilevel collapse pattern was a combination of palatal and tongue base collapse, occurring in one out of four subjects. The prevalence of complete collapse, multilevel collapse and hypopharyngeal collapse increased with increasing severity of OSA. Multilevel and complete collapse were more prevalent in obese patients and in those with more severe OSA. Both higher BMI and AHI values corresponded with a higher probability of complete concentric palatal collapse. The associations found in this study provide an answer to research question 2 ("What insights do the results of DISE examinations in a large cohort of patients add to the current knowledge of upper airway behavior in sleep-disordered breathing?"), as the results indicate that upper airway collapse patterns observed during DISE cannot be fully explained by selected baseline polysomnographic and anthropometric characteristics, indicating that additional upper airway evaluation is essential in the diagnostic work-up.

Although DISE provides an assessment of the upper airway lumen only, the effects of surrounding tissue and its forces on the upper airway may well be indirectly evaluated. Pharyngeal muscle factors are known to contribute to upper airway behavior in sleep-disordered breathing: insufficient reflexes, impaired strength or endurance of dilators and increased upper airway collapsibility may contribute to OSA. This may be complemented by parapharyngeal fat accumulation in obese subjects and in particular centripetal obesity patterns in males. Measurements of the cross-sectional area can improve an objective approach and recent research indicates that DISE also allows for objective upper airway measurements <sup>4</sup>. This may even be extended to the use of DISE with and without treatment, allowing for objective assessment of changes in upper airway dimensions.

Being an endoscopic ENT procedure, DISE not only provides an evaluation of the upper airway collapse patterns, but may also reveal anatomical deformities of the upper airway, e.g. epiglottis deformation, that may be less obvious when investigated otherwise. On the other hand, a potential disadvantage of DISE may be the inability to visualize the entire upper airway simultaneously, in contrast to radiological imaging. This may hinder integral evaluation, although the implications of this aspect are yet to be determined. Furthermore, the use of sedatives inducing muscle relaxation may potentially cause an artifactual worsening of upper airway collapse, so the depth of sedation must be actively guarded.

## Assessment and interpretation of DISE

DISE is a safe and easy to perform procedure that provides real-time information on upper airway collapse, including macroscopic inspection of soft tissue structures. However, assessment is based on subjective evaluation. In chapter 2 of this thesis, it is demonstrated that the reliability of DISE findings varies based on clinical experience and agreement on DISE findings improves when assessed by experienced ENT surgeons. So although ENT surgeons are generally well acquainted to endoscopic upper airway procedures, it may not be assumed that the level of DISE evaluation skills is perfectly comparable among ENT surgeons in general. Observer agreement also differs per upper airway level, with higher agreement on upper airway levels with well-defined structural boundaries, such as the oropharynx, tongue base, and epiglottis. This provides an answer to research question 1: "What are the differences in DISE evaluation between experienced and nonexperienced ENT surgeons?".

A possible solution to the unreliability of DISE findings on particular levels could be training ENT surgeons with a set of standardized DISE videos to foster consistency for scoring the upper airway level variables. To do so, the use of a standardized and universally accepted DISE scoring system will also be essential. Although several scoring systems have been introduced over the years 5-13, no standard approach towards assessment and classification of DISE findings has been universally adopted. In the author's opinion, a scoring system should preferably consist of an easy-to-use and uncomplicated algorithm based on anatomical landmarks, clear enough to avoid confusion but at the same time allowing for registration of more rare collapse patterns or anatomical peculiarities.

As mentioned previously, quantification of the cross-sectional upper airway areas may improve the objective assessment of DISE. Although adequate quantified measurement techniques in propofol-anaesthetized subjects are described in literature <sup>4</sup>, <sup>14, 15</sup>, visual estimation of the upper airway during DISE is still common practice. This should preferably be replaced by objective assessment, e.g. cross-sectional upper airway measurements, and may be further improved by combining DISE with simultaneous other upper airway evaluation techniques.

Ideally, a DISE work-up for OSA includes a uniform sedation protocol, standard calibrated quantification, assessment through a universal scoring system and a treatment-targeted approach.

## **Patient selection**

Key factor within the continuum of treatment options for OSA is preventing upper airway collapse, be it by applying a pneumatic splint through CPAP, surgical removal of tissues prone to collapse, or transposing upper airway structures by oral appliance treatment or surgical procedures.

A diagnostic ENT work-up in case of suspected OSA obviously starts off with a clinical examination. This in itself already provides a considerable amount of information on the upper airway, but additional procedures are necessary and essential to further unravel OSA pathophysiology and improve treatment outcome. Recent literature addresses the additional value of DISE and it was stated that DISE provides more clinical information to assess airway function and collapse than awake endoscopy alone and assists in the surgical planning 16, 17. Another recent study investigated if locations of treatment recommendations given after DISE are different to those made after clinical ENT examination <sup>18</sup>. The results of this study might suggest that DISE is most relevant when considering tongue base surgery or MAD therapy; and that DISE might turn out to provide less added value for the identification of indications for the treatment of the tonsils <sup>18, 19</sup>. When discussing these results in the light of the findings in chapter 2 of this thesis, it can only be emphasized once again that DISE is to be performed by an experienced ENT surgeon, as in particular agreement on tongue base collapse is higher among experienced ENT surgeons when compared to less experienced ENT surgeons. The physician should above all strive to provide an appropriate treatment plan for the individual patient – especially when considering surgical interventions is often irreversible.

Recently, a large randomized trial compared CPAP and MAD, being the two leading forms of OSA treatment and although CPAP demonstrated superior efficacy in terms of AHI reduction, self-reported compliance with MAD was higher and the resulting effects on clinically important moderate to severe OSA-related health outcomes were either equivalent or better with MAD <sup>20</sup>. These findings challenge the current practice of recommending MAD only for mild to moderate OSA or in patients who refuse or fail to use CPAP. However, patient selection for MAD and other non-CPAP therapies in general remains a key issue. Ideally, patient selection for a particular therapy is based on validated prospective elements. Specific diagnostic upper airway evaluation procedures that are potentially well suitable for this purpose must also be feasible, easily accessible, time and cost effective and well tolerable for the patient. At the same time, different relative anatomical and functional effects are to be expected in different patients; therefore proper individual assessment in a setting that most accurately resembles the non-CPAP therapy will be necessary. For MAD therapy, the approach of DISE complemented with the use of a simulation bite in maximal comfortable protrusion, as described in chapter 4, is likely to closely meet this criterion, thereby providing an answer to research question 3 ("Can the use of a simulation bite during DISE improve patient selection for MAD therapy in OSA patients?"). The results of this study indicate that mimicking mandibular advancement during DISE in a similar way to that of a MAD but without the accompanying cost of a real MAD - may improve treatment outcome with MAD. Additional gradual advancement during DISE may improve insights into the effects of MAD titration. Recent research already revealed that the use of a remotely controlled mandibular positioner during an overnight PSG can accurately predict therapeutic success and in addition, among the study participants predicted to be therapeutically successful with MAD, the effective target protrusive position provided efficacious mandibular protrusion in the majority <sup>21</sup>. This encourages further investigation of this specific aspect of optimizing MAD patient selection.

DISE has the advantage of being a dynamic procedure that allows for other perioperative manipulations, such as adjustment of the mandibular position in a vertical plane. This specific aspect is important in assessing the effects of MAD therapy as this implies both horizontal and vertical movement, since every MAD has a given thickness. In the study population described in chapter 5, vertical opening caused adverse effects on the pharyngeal dimensions in the majority of patients. This provides an answer to research question 4 ("Does vertical opening of the mouth have favorable effects on upper airway dimensions as assessed during DISE?").

DISE has also shown its predictive value for implanted upper airway stimulation, as addressed in chapter 6. Again, the differentiation between different directions of collapse is a key issue. For this specific therapy, the absence of complete circular palatal collapse during DISE may predict therapeutic success and DISE can be recommended as a patient selection tool, answering research question 5 ("Is DISE a valuable pre-treatment assessment technique for implantable upper airway stimulation for OSA?"). The therapy in question is still in an experimental phase, but has been proven safe and efficacious in a select group of patients with moderate to severe OSA who cannot or will not use CPAP as primary treatment <sup>22-24</sup>. Further analysis of the predictive value of DISE in assessing therapeutic response to upper airway stimulation therapy needs to be performed in larger multicentre trials that are currently ongoing.

## **Conclusions**

DISE covers the evaluation of a variety of upper airway behavior aspects in OSA and results on prediction of treatment outcome with non-CPAP therapies are promising. Endoscopic upper airway evaluation is first and foremost an essential item in the ENT work-up of OSA and when executed by experienced ENT surgeons it provides additional information that is not likely to be easily derived otherwise. It must be recognized that there still are a significant number of diagnostic challenges in the identification of upper airway obstruction to be addressed, to maintain equilibrium between functional effects, mechanistic concepts and financial aspects.

## **Future perspectives**

Over time, individualized work-up and treatment planning have become key issues in the field of OSA. An optimized combination of different upper airway evaluation techniques may eventually be of the strongest predictive value. Interest in combined treatment is considerably anticipated by an increase in research activities in this field and we are only a few steps away from expanding the treatment range with exciting new options. Appropriate upper airway evaluation will remain important, as "trial and error" treatment planning should preferably be avoided.

Further studies combining advanced diagnostic technologies and individually tailored treatment could contribute to a better understanding of the role of the upper airway in the pathophysiology of OSA and treatment thereof.

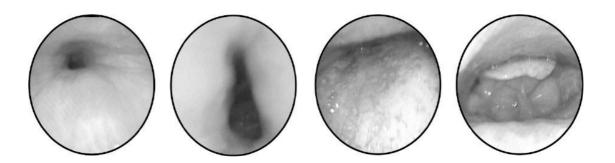
The development of a standardized and universally accepted DISE scoring system remains a point of interest for future research. In the author's opinion, a scoring system should preferably consist of an easy-to-use and uncomplicated algorithm based on anatomical landmarks, clear enough to avoid confusion but at the same time allowing for registration of more rare collapse patterns, anatomical peculiarities, and the effect of maneuvers and therapy (simulation). Ideally, DISE assessment would more and more include solid and objective upper airway measurements – if you cannot measure it, you cannot manage it.

In conclusion, a DISE work-up for OSA should preferably include a uniform sedation protocol, standard calibrated quantification, assessment through a universal scoring system and a treatment-targeted approach.

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# Chapter 8

Summary

#### **SUMMARY**

## Chapter 1

This chapter provides an overview of the history, definitions, epidemiology, pathogenesis risk factors and health effects of obstructive sleep apnea (OSA). The current evaluation and treatment options are discussed, from diagnosis onwards and up to specific upper airway assessment and individualized treatment. Following on from this, we present the aims of the studies and the outline of this thesis.

This thesis aims to discuss the following research questions:

- 1. What are the differences in drug-induced sleep endoscopy (DISE) evaluation between experienced and nonexperienced ear, nose and throat (ENT) surgeons?
- 2. What insights do the results of DISE examinations in a large cohort of patients (N=1249) add to the current knowledge of upper airway behavior in sleep-disordered breathing (SDB)?
- 3. Can the use of a simulation bite in a maximal comfortable protrusion during DISE improve patient selection for mandibular advancement (MAD) therapy in OSA patients?
- 4. Does vertical opening of the mouth have favorable effects on upper airway dimensions as assessed during DISE?
- 5. Is DISE a valuable pre-treatment assessment technique for implantable upper airway stimulation for OSA?

## **Chapter 2**

DISE is a subjective assessment and findings may vary based on clinical experience. The objective of this study was to determine variations in interobserver and intraobserver agreement of DISE in a cohort of experienced versus nonexperienced ENT surgeons. Ninety-seven ENT surgeons (90 non-experienced with DISE; 7 experienced) observed six different DISE videos and were asked to score the upper airway collapse patterns.

In the nonexperienced group, overall interobserver agreement on the presence of tongue base collapse was followed by the agreement on epiglottis and oropharynx

collapse. Low overall interobserver agreement in this group was found for hypopharyngeal collapse. Among the experienced observers, overall interobserver agreement was highest for presence of tongue base collapse, followed by collapse of the palate. In this group, lowest agreement was also found for hypopharyngeal collapse. Among the experienced observers a statistically significant higher interobserver agreement was obtained for the presence, direction and degree of oropharyngeal collapse, as well as for the presence of tongue base collapse and degree of epiglottis collapse. Intraobserver agreement was statistically significantly higher in the experienced group, for all upper airway levels expect for the hypopharynx.

In conclusion, both interobserver and intraobserver agreement was higher in experienced versus nonexperienced ENT surgeons. Agreement ranged from poor to excellent in both groups. The present results suggest that experience in performing DISE is necessary to obtain reliable observations.

## **Chapter 3**

DISE provides an evaluation of the localization of flutter and collapse in patients with SDB. During the procedure, upper airway collapse patterns can be assessed when treatment alternatives to continuous positive airway pressure (CPAP) are considered. In this chapter, the upper airway collapse patterns during DISE in a large cohort of patients with SDB are described. In addition, associations with anthropometric and polysomnographic parameters are assessed.

1249 patients underwent polysomnography and DISE. The most frequently observed multilevel collapse pattern was a combination of palatal and tongue base collapse (25.5%). Palatal collapse was seen most frequently (81%). The prevalence of complete collapse, multilevel collapse and hypopharyngeal increased with increasing OSA severity. Multilevel and complete collapse patterns were more prevalent in obese patients and in those with more severe OSA. Both increasing body mass index (BMI) and apnea-hypopnea index (AHI) values corresponded with a higher probability of complete concentric palatal collapse.

In conclusion, the current study provides an overview of upper airway collapse patterns in a large cohort of SDB patients. The associations as found in this study may improve insight into pathogenesis of OSA, but may also indicate that upper airway collapse patterns as observed during DISE, cannot be fully explained by certain baseline polysomnographic and anthropometric characteristics.

#### Chapter 4

The ability to predict treatment outcome of MAD therapy prospectively in the individual patient and, thereby, preselecting suitable OSA patients for MAD therapy, is still limited in clinical practice. In chapter 4.1, the procedure of DISE with a simulation bite for the prediction of the outcome of treatment of OSA with MAD is described. In chapter 4.2 the results of this approach in 200 OSA patients are presented.

One hundred thirty-five patients with an established diagnosis of OSA commenced MAD treatment. The associations between the findings during DISE with simulation bite and treatment outcome were evaluated. Overall MAD treatment response (defined as a reduction in AHI following MAD treatment of  $\geq$  50% compared to baseline) in the studied population was 69%. The results of this study demonstrated a statistically significant association between a positive effect of the simulation bite on the upper airway patency during DISE and treatment response with MAD (p<0.01).

In conclusion, the use of a simulation bite in maximal comfortable protrusion (MCP) of the mandible, as used during DISE in patients with OSA, tends to be effective in predicting treatment response of MAD treatment.

### **Chapter 5**

It is still subject to controversy if an increased vertical opening is beneficial in oral appliance therapy for the treatment of OSA. Each oral appliance has a given thickness causing vertical opening. Therefore, evaluation of the effects of the amount of vertical opening on pharyngeal dimensions is mandatory. The effects of vertical opening on the cross-sectional area of the upper airway at the level of the tongue base during DISE were scored and categorized.

The figures demonstrate the possible effects of vertical opening on pharyngeal collapse in relation to the baseline cross-sectional area and the maximal comfortable

protrusion of the mandible. The majority of patients (80%) showed an adverse effect of vertical opening.

Based on literature, the effect of vertical opening on pharyngeal collapse is unclear and the therapeutic impact of vertical opening is not determined. The results of the present study indicate that the effect of vertical opening on the degree of pharyngeal collapse as assessed during sleep endoscopy tends to be adverse, causing an increase in collapsibility in the majority of patients.

## Chapter 6

Upper airway stimulation therapy, which uses electrical stimulation of the hypoglossal nerve, has been previously reported to be safe and efficacious in a select group of OSA patients who cannot or will not use CPAP as primary treatment. In non-selected OSA patients undergoing upper airway stimulation therapy, a large interindividual difference in response to stimulation is observed. In this chapter, we study the possible predictive value of DISE in assessing therapeutic response to implanted upper airway stimulation for OSA.

We report on the correlation between DISE results and therapy response in 21 OSA patients who underwent DISE before implantation of an upper airway stimulation system. Statistical analysis revealed a significantly better outcome with upper airway stimulation in patients without palatal complete concentric collapse (CCC), significantly reducing the AHI. No statistical difference was noted in AHI or BMI at baseline between the patients with and without palatal CCC. In addition, no predictive value was found for the other DISE collapse patterns documented.

In conclusion, the absence of palatal CCC during DISE may predict therapeutic success with implanted upper airway stimulation therapy. DISE can be recommended as a patient selection tool for implanted upper airway stimulation to treat OSA.

## **Chapter 7**

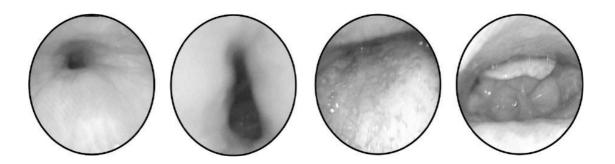
In this chapter, the main findings of the studies in this thesis are presented in the light of relevant literature in the field. Furthermore, clinical implications and suggestions for future research are discussed.

This thesis focuses on DISE as an evaluation method for upper airway behavior in OSA and as a tool for improved patient selection when non-CPAP therapy is considered.

DISE covers the evaluation of a variety of upper airway behavior aspects in OSA and results on prediction of treatment outcome with non-CPAP therapies are promising. Endoscopic upper airway evaluation is first and foremost an essential item in the ENT work-up of OSA and when executed by experienced ENT surgeons it provides additional information that is not likely to be easily derived otherwise.

Further studies combining advanced diagnostic technologies and individually tailored treatment could contribute to a better understanding of the role of the upper airway in the pathophysiology of OSA and treatment thereof. Ideally, this would more and more include a standardized and universally accepted scoring system as well as solid and objective upper airway measurements — if you cannot measure it, you cannot manage it.

In conclusion, a DISE work-up for OSA should preferably include a uniform sedation protocol, standard calibrated quantification, assessment through a standardized and universal scoring system and a treatment-targeted approach.



# Chapter 9

Samenvatting

#### **SAMENVATTING**

### Hoofdstuk 1

In dit hoofdstuk wordt een overzicht gegeven van de geschiedenis, definities, epidemiologie, pathogenese, risicofactoren en gezondheidseffecten van het obstructief slaapapneusyndroom (OSAS). De huidige onderzoeks- en behandelmogelijkheden worden besproken, evenals het traject van diagnose via niveauspecifieke bovenste luchtwegevaluatie naar een op maat gemaakte behandeling. Hieruit vloeien de doelstellingen van dit proefschrift voort, toegesneden op de toepassing van slaapendoscopie als een onderzoek voor zowel de evaluatie van de bovenste luchtweg bij patiënten met slaapgebonden ademhalingsstoornissen als voor de selectie van de optimale therapie voor de individuele patiënt.

De volgende onderzoeksvragen worden besproken:

- 1. Wat zijn de verschillen in beoordeling van slaapendoscopie tussen ervaren en minder ervaren keel-, neus en oor (KNO)-artsen?
- 2. Welke verdere inzichten brengt de analyse van slaapendoscopie bevindingen in een grote groep van patiënten met slaapgebonden ademhalingsstoornissen?
- 3. Kan het gebruik van een simulatiebeet in een maximaal comfortabele protrusie van de onderkaak tijdens slaapendoscopie een bijdrage leveren aan de selectie van patiënten voor behandeling met een mandibulair repositie apparaat?
- 4. Wat zijn de effecten van mondopening op de bovenste luchtweg dimensies zoals beoordeeld tijdens slaapendoscopie?
- 5. Heeft slaapendoscopie een meerwaarde als vooronderzoek bij de selectie van patiënten voor bovenste luchtweg stimulatietherapie?

## Hoofdstuk 2

Slaapendoscopie is een subjectief onderzoek waarvan de bevindingen kunnen variëren naar gelang de mate van ervaring van de endoscopist. Het doel van deze studie was het in kaart brengen van de overeenstemming in beoordeling van zes

slaapendoscopiefragmenten in een groep KNO-artsen, waarvan er 90 relatief onervaren en 7 ervaren waren in het uitvoeren van slaapendoscopieën. Hierbij werd gekeken naar de overeenstemming tussen de verschillende KNO-artsen (interindividuele overeenstemming) en naar de overeenstemming per KNO-arts voor de twee afzonderlijke momenten van beoordeling (intraindividuele overeenstemming).

In de onervaren groep was de interindividuele overeenstemming het hoogst voor aanwezigheid van tongbasiscollaps, gevolgd door overeenstemming over epiglottis- en orofarynxcollaps. In deze groep was er een lage overeenstemming voor hypofaryngeale collaps. Onder de ervaren KNO-artsen was de interindividuele overeenstemming ook het hoogst voor tongbasiscollaps, gevolgd door de overeenstemming voor palatale collaps. In deze groep was er ook de laagste interindividuele overeenstemming voor hypofaryngeale collaps. In de ervaren groep was er een significant hogere interindividuele overeenstemming voor de aanwezigheid, richting en mate van orofaryngeale collaps, alsook voor de aanwezigheid van tongbasiscollaps en de mate van collaps ter hoogte van de epiglottis. Intraindividuele overeenstemming was significant hoger in de ervaren groep voor alle niveaus van de bovenste luchtweg, met uitzondering van de hypofarynx.

Er kan gesteld worden dat zowel interindividuele als intraindividuele overeenstemming aangaande de beoordeling van slaapendoscopie hoger is onder ervaren KNO-artsen. De gevonden resultaten wijzen erop dat ervaring een belangrijke rol speelt bij de betrouwbaarheid van de resultaten van dit specifieke endoscopische onderzoek.

#### Hoofdstuk 3

Slaapendoscopie geeft een beeld van de niveaus van vibratie en obstructie bij patiënten met slaapgebonden ademhalingsstoornissen. Met behulp van dit onderzoek kunnen de alternatieven voor CPAP-therapie, zoals chirurgische of tandheelkundig ondersteunde behandeling, worden geëvalueerd. In dit hoofdstuk wordt een overzicht gegeven van de collapspatronen in een grote groep patiënten met een slaapgebonden ademhalingsstoornis, die allen een slaapendoscopie ondergingen. Verder werden ook de verbanden met antropometrische en polysomnografische parameters onderzocht.

Het meest geziene multilevel collapspatroon omvatte een combinatie van palatale en tongbasiscollaps, in een kwart van de gevallen. Palatale collaps, al dan niet als onderdeel van een multilevel collapspatroon, werd het meest frequent gezien, in 81% van de gevallen. Het voorkomen van complete collaps, multilevel collaps en hypofaryngeale collaps steeg naarmate de ernst van OSAS toenam. Multilevel en complete collaps werden vaker gezien bij obese patiënten en bij patiënten met ernstiger OSAS. Zowel toename in body mass index (BMI) als apneu-hypopneu index (AHI) gingen gepaard met een hogere kans op complete circulaire palatale collaps.

Deze studie geeft een overzicht van de bovenste luchtweg collapspatronen in een grote groep van patiënten met een slaapgebonden ademhalingsstoornis. De verbanden die in deze studie werden gevonden dragen bij aan het verdere inzicht in de mechanismen die ten grondslag liggen aan OSAS, maar geven ook aan dat de collapspatronen, zoals die gezien kunnen worden tijdens een slaapendoscopie, niet volledig verklaard kunnen worden op basis van polysomnografische antropometrische gegevens.

### Hoofdstuk 4

In de dagelijkse praktijk is de mogelijkheid om het therapiesucces met een mandibulair repositie apparaat voor een individuele patiënt te voorspellen nog beperkt. In dit hoofdstuk wordt de rol van slaapendoscopie bij de selectie van patiënten voor behandeling met een mandibulair repositie apparaat verder uitgediept. In hoofdstuk 4.1 wordt de procedure van slaapendoscopie met gebruik van een zogenaamde simulatiebeet, een afdruk van de tanden in een maximaal comfortabele voorwaartse verplaatsing van de onderkaak, vergelijkbaar met die van een mandibulair repositie apparaat, in detail toegelicht. In hoofdstuk 4.2 worden de resultaten van deze toepassing voor een groep van 200 patiënten met een slaapgebonden ademhalingsstoornis beschreven. Van deze groep zijn 135 OSAS-patiënten gestart met een mandibulair repositie apparaat.

Uit de resultaten blijkt dat de slaapendoscopie met simulatiebeet een betere voorspellende waarde heeft voor de behandeluitkomst met een mandibulair repositie apparaat, dan de slaapendoscopie alleen, al dan niet met het uitvoeren van een zogenaamde chinlift manoeuvre.

#### Hoofdstuk 5

De rol van mondopening bij de behandeling met een mandibulair repositie apparaat wordt nog volop onderzocht. Resultaten van eerdere studies hieromtrent zijn niet eenduidig en daarom werd in deze studie het effect van mondopening op de bovenste luchtwegstructuren tijdens slaapendoscopie geëvalueerd. In de meerderheid van de patiënten (80%) werd er tijdens slaapendoscopie een averechts effect van mondopening op de diameter van bovenste luchtweg vastgesteld.

Het is dus van belang ook dit aspect te onderzoeken bij selectie van patiënten waarbij een behandeling met een mandibulair repositie apparaat wordt overwogen.

#### Hoofdstuk 6

Stimulatietherapie van de bovenste luchtwegen, waarbij de nervus hypoglossus wordt gestimuleerd teneinde bovenste luchtwegcollaps te voorkomen, werd eerder al veilig en doeltreffend bevonden in een geselecteerde groep patiënten, bij wie CPAP therapie geen optie (meer) was. Een belangrijk punt bij het overwegen van deze behandeling is een adequate patiëntenselectie. In deze studie worden de resultaten beschreven van 21 patiënten, die een slaapendoscopie ondergingen als diagnostisch onderzoek voorafgaand aan de implantatie van de stimulator.

Uit de analyse bleek dat de afwezigheid van een volledige concentrische collaps ter hoogte van het palatum een positief voorspellende waarde heeft voor de uitkomst van stimulatietherapie van de bovenste luchtwegen. Slaapendoscopie kan dus een rol spelen bij het selecteren van de geschikte patiënten voor deze therapie.

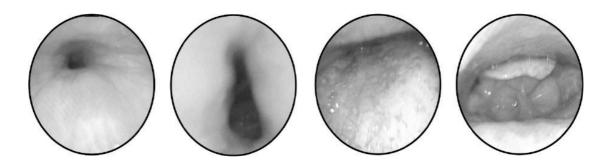
#### Hoofdstuk 7

In dit hoofdstuk wordt een overzicht gegeven van de belangrijkste bevindingen van de studies in dit proefschrift en worden deze gekaderd in het licht van de relevante literatuur. Ook worden de klinische implicaties en toekomstperspectieven besproken.

Dit proefschrift is toegespitst op de rol van slaapendoscopie als een onderzoek van de bovenste luchtweg bij patiënten met slaapgebonden ademhalingsstoornissen en tevens als een middel tot de patiëntenselectie voor operatieve of tandheelkundig ondersteunde behandeling.

De toepassing van slaapendoscopie als een onderzoek voor zowel de evaluatie van de bovenste luchtweg bij patiënten met slaapgebonden ademhalingsstoornissen als voor de selectie van de optimale therapie voor de individuele patiënt blijkt in de handen van ervaren KNO-artsen een belangrijke meerwaarde te hebben.

Toekomstige studies die zich richten op de verschillende diagnostische procedures en op maat gemaakte behandeling kunnen bijdragen aan een beter begrip van de precieze rol van de bovenste luchtweg en optimalisatie van de behandeling van OSAS. Verder dient er ook aandacht besteed te worden aan de ontwikkeling van een uniform en algeheel geaccepteerd slaapendoscopie-scoresysteem en de kwantificatie van de bevindingen tijdens slaapendoscopie.



## Appendices

List of abbreviations

List of publications

## LIST OF ABBREVIATIONS

**AASM** : American Academy of Sleep Medicine

AHI : apnea-hypopnea index

ΑP : anteroposterior

ASA : American Society of Anesthesiologists

AUC : area under the curve

BMI : body mass index

CCC : complete concentric collapse

CFD : computational fluid dynamics

CI : confidence interval

CT : computed tomography

**CPAP** : continuous positive airway pressure

DISE : drug-induced sleep endoscopy

**ECG** : electrocardiography

**EDS** : excessive daytime sleepiness

EEG : electroencephalometry

**EMG** : electromyography

**ENT** : ear, nose and throat

EOG : electrooculography

ESS : Epworth Sleepiness Scale

**FOT** : forced oscillation technique

kg : kilogram

: meter m

: mandibular advancement device MAD

**MCP** : maximal comfortable protrusion

MinSaO2 : lowest oxyhemoglobulin saturation during sleep

MMA : maxillomandibular advancement

MRI : magnetic resonance imaging

NS : not significant

ODI : oxygen desaturation index OR : odds ratio

: obstructive sleep apnea (syndrome) OSA(S)

: critical closing pressure Pcrit

PSG : polysomnography

: rapid eye movement REM

: radiofrequency RF

SD : standard deviation

: sleep-disordered breathing SDB

: upper airway stimulation UAS

: uvulopalatopharyngoplasty UPPP

: visual analogue scale VAS

## LIST OF PUBLICATIONS

Vanderveken OM, Vroegop AV, Van de Heyning PH, Braem MJ. Drug-induced sleep endoscopy completed with a simulation bite approach for the prediction of the outcome of treatment of obstructive sleep apnea with mandibular repositioning appliances. Operative Techniques in Otolaryngology - head and neck surgery, 2011, 22: 175-182.

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**Vroegop AV**, Braem MJ, Dieltjens M, Hamans E, Van de Heyning PH, Vanderveken OM. Drug-induced sleep endoscopy predictors for oral appliance treatment outcome. *Manuscript in preparation.*