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# **Three-dimensional analysis of the upper airway in obstructive sleep apnea patients**

**Hui Chen**

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VRIJE UNIVERSITEIT

# Three-dimensional analysis of the upper airway in obstructive sleep apnea patients

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# **Chapter 1**

## **General Introduction**





## General Introduction

Obstructive sleep apnea (OSA) is a sleep-related breathing disorder, often associated with oxygen desaturations and arousals from sleep [1]. The most common complaints of OSA patients are excessive daytime sleepiness, unrefreshing sleep, poor concentration, and fatigue [2]. Snoring is a typical feature of OSA, which may disturb the patient's bed partner during sleep [3]. Snoring is often the main reason for patients to seek help for their OSA condition. OSA is a major public health problem, affecting a significant portion of the population. Approximately 3-7% of adult men and 2-5% of adult women have OSA [4-7]. It is estimated that approximately 80-90% of people meeting the criteria of at least moderate OSA remain undiagnosed [8]. OSA has a range of deleterious long-term consequences which include increased cardiovascular morbidity, neurocognitive impairment, and overall mortality [9-12]. As untreated OSA is associated with serious long-term consequences, it is necessary to recognize, diagnose, and treat OSA patients in an early stage.

Polysomnography (PSG) is the gold standard for the diagnosis of OSA. In 2016, the American Academy of Sleep Medicine reported the rules, terminology and technical specifications for the scoring of sleep and associated events [13]. Apnea was defined as cessation of airflow  $\geq 90\%$  for at least 10 seconds. Hypopnea was defined as a decrease in airflow of more than 30% for at least 10 seconds, and an oxygen desaturation greater than 3% [13]. The apnea-hypopnea index (AHI) is defined as the number of apneas and hypopneas per hour of sleep. An OSA diagnosis is based on an AHI of  $\geq 5$  events/hour of sleep and the presence of excessive daytime sleepiness and/or fatigue that is not explained by other factors [10, 14]. Based on the AHI obtained from a PSG recording, the American Academy of Sleep Medicine (AASM) Task Force classified OSA as mild (AHI 5-15), moderate (AHI 15-30), and severe (AHI  $> 30$ ) [10].

The most common treatment modalities for OSA are continuous positive air pressure (CPAP) [15], mandibular advancement devices (MADs) [16], and surgery [17]. MADs are prescribed for patients with mild to moderate OSA [18-20]. Although an MAD is a promising treatment modality, the reported success rates with MADs are limited and variable, ranging from 21% to 54% [21]. In most studies, patients are considered as responder if  $AHI < 10$ /hour with MADs in situ or non-responder if  $AHI \geq 10$ /hour with MADs in situ [18, 19]. To obtain the optimal mandibular position, the MAD is titrated either based on the patient's subjective

evaluation of improvement [20] or by following an overnight MAD titration procedure [21].

It is assumed that both anatomical and neuromuscular factors are of significance in the pathogenesis of upper airway obstruction in OSA [1]. Previous studies using different imaging techniques, such as multi-detector row computed tomography (MDCT), cone beam computed tomography (CBCT), or magnetic resonance imaging (MRI), suggest that an abnormal anatomy of the upper airway is a key factor in the development of OSA [22-24]. Nowadays, CBCT has become available to analyze the upper airway anatomy three dimensionally, with its advantages of a lower radiation dose and lower costs compared to MDCT and MRI [25]. On the basis of these 3D imaging techniques, different aerodynamic methods, such as particle image velocimetry (PIV) [26] and computational fluid dynamics (CFD) [27], have been introduced to simulate air flow characteristics in OSA patients [28, 29]. In previous studies on the analysis of the upper airway in OSA patients, there is a large variation in the definition of the upper airway boundaries, the imaging modalities, and the software programs applied in these studies. Based on the literature, we still do not know how accurate the imaging modalities are for the analysis of the upper airway [30, 31]. Similarly, it is not clear how accurate and reliable the software programs are for the analysis of the upper airway [25]. Therefore, we determined in this thesis: (1) whether the methodology of landmark localization and upper airway measurements in clinical trials is reliable (**Chapter 2**); (2) how accurate three-dimensional imaging modalities, such as MDCT and CBCT, are for the analysis of the upper airway (**Chapter 3**); and (3) if the software programs used for the analysis of the upper airway are accurate and reliable (**Chapter 4**).

Since an important role in the pathogenesis of OSA is played by anatomical abnormalities of the upper airway [32], there are many studies focusing on the analysis of the anatomy of the upper airway of OSA patients [22-24, 33-35]. Compared with non-OSA patients, OSA patients have in general a smaller upper airway [36], an oval airway shape [37], and a longer upper airway [38]. However, no consensus has been reached regarding the question which anatomical characteristics of the upper airway are the most relevant ones in the pathogenesis of OSA. Therefore, we performed a systematic review of the literature to assess the most relevant anatomical characteristics of the upper airway related to the pathogenesis of OSA by analyzing the three-dimensional upper airway anatomy (**Chapter 5**). Moreover, using aerodynamic methods, such as CFD and PIV, we can simulate the airflow during respiration, which can further improve our understanding of upper airway

obstruction in OSA. However, there is only a limited number of studies on the comparison of aerodynamic characteristics between OSA patients and their controls [39]. In **Chapter 6** of this thesis, using CFD, we aimed to determine the difference in aerodynamic characteristics of the upper airway between OSA patients and their controls as to better understand the pathogenesis of OSA from the perspective of aerodynamics.

One ongoing clinical challenge is to recognize the characteristics of responders and non-responders in OSA patients prior to starting an MAD treatment. An early recognition of non-responders will result in improvement of the cost-effectiveness of this therapy and will avoid an ineffective treatment of this patient group. Therefore, in **Chapter 7**, based on CBCT images, we aimed to assess the differences in craniofacial anatomical structures between responders and non-responders to MAD treatment within a large group of OSA patients. Besides, previous studies using CFD concluded that the ventilation of the air in the upper airway was improved during and after treatment [29, 40]. Since the optimal aim of a therapy is to prevent the collapse of the upper airway, which allows an unimpeded passage of the airflow along the upper airway, it is necessary to know how the treatment modalities (i.e., Surgery, MADs) influence the airflow in the upper airway. Therefore, we performed another systematic review to assess how the aerodynamic characteristics in the upper airway change during and after treatment (**Chapter 8**). Moreover, it is still unclear how different positions of an MAD influence the aerodynamic characteristics of the upper airway. Therefore, using PIV, we studied a single case and evaluated the aerodynamic characteristics in the upper airway of an OSA patient at different protrusion positions (**Chapter 9**).

## Synopsis

The overall aim of this thesis was to determine the role of the upper airway characteristics in the pathogenesis of OSA and in mandibular advancement device treatment outcome in OSA patients. Therefore, the objectives per chapter were:

1. To assess the intra- and inter-observer reliability of the localization of both hard-tissue and soft-tissue landmarks of the upper airway on CBCT images; and to assess the intra- and inter-observer reliability of three-dimensional measurements of the upper airway based on these landmarks. (**Chapter 2**)

2. To assess the accuracy of five different computed tomography scanners (GE®, Siemens®, Newtom5G®, Accuitomo®, Vatech®) for the evaluation of the upper airway morphology. **(Chapter 3)**
3. To assess the reliability and accuracy of three different kinds of imaging software (Amira®, 3Diagnosys®, and Ondemand3D®) for three-dimensional analysis of the upper airway based on cone beam CT (CBCT). **(Chapter 4)**
4. To systematically review the literature to assess the most relevant anatomical characteristics of the upper airway related to the pathogenesis of OSA by analyzing the three-dimensional upper airway anatomy. **(Chapter 5)**
5. To determine the most relevant aerodynamic characteristic of the upper airway related to the collapse of the upper airway in OSA patients. **(Chapter 6)**
6. To assess the differences in craniofacial anatomical structures between responders and non-responders to MAD treatment within a large group of OSA patients based on CBCT images. **(Chapter 7)**
7. To determine the effects of various non-continuous positive airway pressure (non-CPAP) therapies on the aerodynamic characteristics of the airflow in the upper airway of OSA patients. **(Chapter 8)**
8. To evaluate the airflow characteristics in the upper airway of an OSA patient at different protrusion positions using PIV. **(Chapter 9)**

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## Chapter 2

# Reliability of three-dimensional measurements of the upper airway on cone beam computed tomography images

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## **Reliability of three-dimensional measurements of the upper airway on cone beam computed tomography images**

### **Abstract**

**Aim:** To assess intra- and inter-observer reliability of the localization of anatomical landmarks of the upper airway on cone beam computed tomography (CBCT) images; (2) and to assess intra- and inter-observer reliability of the three-dimensional measurements of the upper airway based on these landmarks.

**Methods:** Fifteen NewTom 5G CBCT data sets were randomly selected from the archives of Department of Oral Radiology, Academic Centre for Dentistry Amsterdam (ACTA). Three observers localized six anatomical landmarks that are relevant for upper airway analysis twice with a 10-day interval using 3Diagnosys® software. Subsequently, the observers performed upper airway volume measurement based on those landmarks twice as well, again with a 10-day interval using Amira® software. The upper airway measurements also included the minimum cross-sectional area ( $CSA_{min}$ ), location of the  $CSA_{min}$ , and anterior-posterior and lateral dimensions of the  $CSA_{min}$ .

**Results:** Both intra- and inter-observer reliability were excellent for the localization of the anatomical landmarks of the upper airway (Intraclass correlation coefficients (ICC)=0.97-1.00) as well as for the three-dimensional upper airway measurements (ICC=0.78-1.00).

**Conclusion:** The methodology of landmark localization and upper airway measurements used in this study shows an excellent reliability and can thus be recommended in the upper airway analysis on CBCT images.

## **Introduction**

The upper airway is an important and complex anatomical structure in respiratory medicine. It is suggested that anatomical and functional abnormalities of the upper airway play an important role in the pathogenesis of obstructive sleep apnea (OSA) [1]. Recently, the use of cone beam computed tomography (CBCT) in dentistry has increased considerably. Due to its high spatial resolution, adequate contrast between the soft tissue and empty space, and the relatively low radiation dose compared to CT, CBCT has been used to analyze the upper airway anatomy three-dimensionally [2].

Based on CBCT data sets, previous studies have shown a high reliability of the localization of some anatomical landmarks [3-5], however, there are some limitations. For example, most of the anatomical landmarks chosen in these studies are cephalometric, using only the hard-tissue landmarks, excluding hereby, the soft-tissue landmarks related to the upper airway [3, 6, 7]. It has been recommended that the reliability of the soft-tissue landmarks based on CBCT data sets needs to be investigated [8].

After the landmark localization, the upper airway can be segmented based on these landmarks for further analysis. At this moment, there are several studies that tested the reliability of upper airway measurements [9-13]. Some studies showed a good reliability [9-12], but another study demonstrated that certain upper airway measurements are unreliable [13]. Moreover, most studies only focused on the reliability of the volume of the upper airway, without testing the reliability of the area measurement of the upper airway or that of the linear measurement of the upper airway [9, 11, 12]. Therefore, the aims of this study were: (1) to assess the intra- and inter-observer reliability of the localization of both hard-tissue and soft-tissue landmarks of the upper airway on CBCT images; (2) and to assess the intra- and inter-observer reliability of the three-dimensional measurements of the upper airway based on these landmarks.

## **Materials and methods**

### *Power calculation*

The power calculation recommended by Walter et al. for reliability studies was followed [14]. The null hypothesis was defined as  $H_0: \rho_0 \leq 0.6$  and the alternative hypothesis was defined as  $H_1: \rho_1 \geq 0.8$ . The rate of type I error ( $\alpha$ ), which equals to the criterion for significance, was set at 0.05. The rate of type II error ( $\beta$ ), which is related to the power of a test ( $1-\beta$ ), was set at 0.2. After checking table II in Walter's study, the proposed sample size was set at 15 patients.

### *CBCT images*

CBCT images of 15 patients were randomly and retrospectively selected from available scans of the Department of Oral and Maxillofacial Radiology of the Academic Centre for Dentistry Amsterdam (ACTA), The Netherlands. These patients were referred to the Department of Oral Kinesiology of the Academic Centre for Dentistry Amsterdam (ACTA), The Netherlands, for an examination of the temporomandibular joints between April 1st, 2013 and July 1st, 2014. (Approved by Medical Ethics Committee of the VU University, Amsterdam, protocol number: NL18726.029.07). The inclusion criteria were: age > 18 years; and CBCT images covering the entire upper airway from the level of the hard palate to the base of the epiglottis. The exclusion criteria were: presence of a palatal cleft, presence of a craniofacial syndrome and/or craniofacial surgery in the past.

The procedure of randomization was as follows: 1. 36 CBCT data sets of the patients fulfilled the inclusion criteria. 2. These patients were put in random order using the excel "RAND" function. 3. The first 15 datasets of the random list were selected in this study.

The CBCT data sets used in this study have been obtained using the NewTom 5G (QR systems, Verona, Italy), according to the standard imaging protocol of the department. During the imaging procedure, the patients were positioned in a supine position with the Frankfort horizontal (FH) plane perpendicular to the floor. They were instructed to maintain maximum intercuspation and to avoid swallowing and other movements during the scanning period. The exposure settings were 110 kV, 4 mA, 18\*16 cm field of view (FOV), 0.3 mm voxel size, 3.6 seconds exposure time (pulsed radiation), and 18-36 seconds scanning time depending on the size of the patient. For further analysis, the images were saved as digital imaging and communications in medicine (DICOM) files, and these data sets were imported into 3Diagnosys® software (v5.3.1, 3diemme, Cantu, Italy) for anatomical landmark localization

and into Amira® software (v4.1, Visage Imaging Inc., Carlsbad, CA, USA) for upper airway measurements.

### *Procedure of measurements*

Two maxillofacial radiologists and an orthodontist were trained as observers, using two data sets that were not included in this study. After training, each observer independently localized the anatomical landmarks defined in Table 1, using the axial, sagittal and coronal planes of the CBCT data sets (Figure 1).

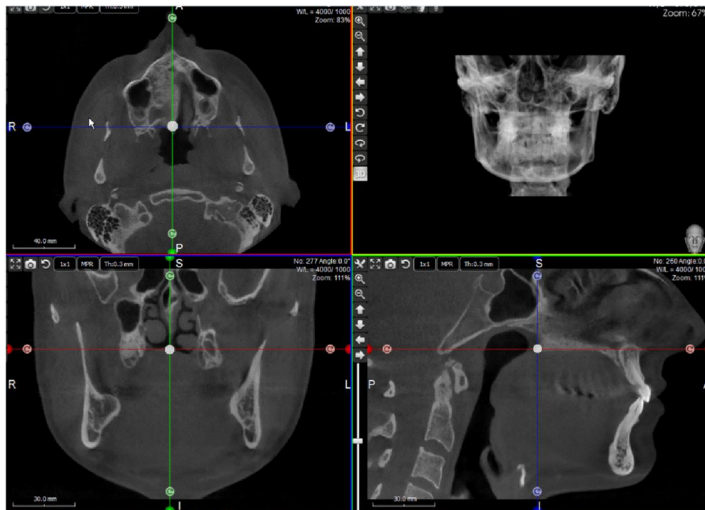


Figure 1. Localization of the posterior nasal spine on the axial, sagittal and coronal planes of the CBCT images.

Based on these landmarks, the upper airway was segmented. Then, the observers measured the upper airway variables shown in Table 2. The observers performed the landmark localization and upper airway measurements twice, with a 10-day interval. The order of the CBCT images was established randomly prior to the measurements. The observers were blinded to patients' information during the measurements and did not have access to their own previous results at the second measurement.

Table 1 Definitions of the anatomical landmarks in three dimensions

Landmark	Definition	Sagittal (X)	Coronal (Y)	Axial (Z)
Posterior nasal spine (PNS)	Tip of the sharp posterior end of the nasal crest of the hard palate	Most posterior point	First slice to show PNS (from posterior to anterior)	Mid-posterior point
Anterior nasal spine (ANS)	Tip of bony projection formed by the union of the two premaxillae	Most anterior point	First slice to show ANS (from anterior to posterior)	Mid-anterior point
Anterior-inferior aspect of the vertebral body of 2nd cervical vertebra (AICV)	Middle inferior point of the second cervical vertebra	Most inferior point	Mid-inferior point	First slice to show second cervical vertebra (from inferior to superior)
Tip of the uvula (TUV)	Inferior point of caudal margin of the uvula at the mid-sagittal plane	Inferior-anterior point	Mid-inferior point	Mid-posterior point
Tip of the epiglottis (TEP)	Mid-superior point of the epiglottis	Most superior point	Mid-superior point	First slice to show epiglottis (from superior to inferior)
Base of epiglottis (BEP)	Bottom of epiglottis crypt	Most inferior point	Mid-inferior point	First slice to show epiglottis crypt (from inferior to superior)

Table 2 Definitions of the upper airway measurements

Variable	Definition
Volume of the upper airway	Volume of the upper airway with threshold ranging from -1000 to -500
Minimum cross-sectional area ( $CSA_{min}$ )	At axial view, the minimum cross-sectional area ( $CSA_{min}$ ) of upper airway
Location of the $CSA_{min}$	The number of the axial slice where $CSA_{min}$ was located
Lateral dimension of the $CSA_{min}$	At coronal view, width of $CSA_{min}$
Anterior-posterior dimension of the $CSA_{min}$	At sagittal view, length of $CSA_{min}$

Six anatomical landmark localizations (Figure 2) and five upper airway measurements (Table 2) were obtained for each CBCT data set. The landmarks used were: posterior nasal spine (PNS) and anterior nasal spine (ANS) to define the hard palate plane; the tip of the uvula (TUV) and the tip of the epiglottis (TEP) to define the retroglottal region of the upper airway;



the base of the epiglottis (BEP), to define the lower boundary of the upper airway; and finally the anterior-inferior aspect of the vertebral body of 2nd cervical vertebra (AICV) to define the oropharyngeal region of the upper airway. The locations of the landmarks were recorded in an orthogonal coordinate system (X, Y, Z), using the 3Diagnosys® software, and exported into Microsoft Excel® (2007; Microsoft Corporation, Redmond, USA). The final location ( $P_i$ ) of each landmark (i) was calculated using the following formula:  $P_i = \sqrt{X_i^2 + Y_i^2 + Z_i^2}$  for each observer and for each session.



Figure 2. Location of the anatomical landmarks on the cone beam computed tomography (CBCT) images on the mid-sagittal plane, identified to enable upper airway measurements (1: PNS, posterior nasal spine; 2: ANS, anterior nasal spine; 3: AICV, anterior-inferior aspect of the vertebral body of 2nd cervical vertebra (AICV); 4: TUV, tip of the uvula; 5: TEP, tip of the epiglottis; 6: BEP, base of epiglottis.)

The automatic process of the upper airway segmentation, using the Amira® software, was performed as follows: first, a voxel set was built to include all of the information of the upper airway; second, a new mask was built with its thresholds ranging from -1000 to -500; and third, the superior boundary (i.e., the plane across the posterior nasal spine parallel to the FH plane) and the inferior boundary (i.e., the plane across the base of the epiglottis parallel to the FH plane) of the upper airway were selected in the corresponding axial planes and put into the voxel set. Finally, all of the slices between the upper and lower boundaries were selected and put into the voxel set. In this way, the upper airway from the hard palate to the base of epiglottis was segmented by the observers (Figure 3a). The software then calculated the total upper airway volume and the cross-sectional area (CSA) of every axial

slice automatically. Based on these results, the minimum cross-sectional area ( $CSA_{min}$ ) and its location (axial slice number) were identified. On the specific slice where the  $CSA_{min}$  was located, the anterior-posterior dimension and lateral dimension of  $CSA_{min}$  were measured by the observer, using the linear measuring tool integrated in the software (Figure 3b).

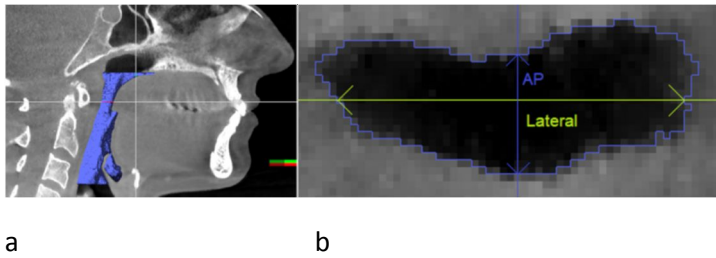


Figure 3a. The segmented upper airway. b. The minimum cross-sectional area ( $CSA_{min}$ ) on the axial slice of the CBCT image. AP: anterior-posterior dimension of  $CSA_{min}$ ; Lateral: lateral dimension of  $CSA_{min}$ .

### *Statistical methods*

Data were imported into Microsoft Excel® (2007; Microsoft Corporation, Redmond, USA) and statistically evaluated using the IBM Statistical Package for Social Sciences for Windows (SPSS® version 21, Chicago, IL, USA). Intraclass correlation coefficients (ICCs) were calculated to determine the intra- and inter-observer reliability of the landmark localization and of the three-dimensional upper airway measurements. Statistical significance was established at  $\alpha=0.05$ . Reliability was divided into three categories: poor ( $ICC<0.40$ ); fair to good ( $0.40\leq ICC\leq 0.75$ ); excellent ( $ICC>0.75$ ) [15].

### **Results**

ICCs of intra- and inter-observer reliability of the anatomical landmark localization and of the upper airway measurements are shown in Table 3 and Table 4, respectively. Both the intra-observer reliability and inter-observer reliability of the landmark localization were excellent ( $ICC=0.97-1.00$ ). Similar results were found for the upper airway measurements,

wherein, both the intra-observer reliability and inter-observer reliability of the upper airway measurements were excellent (ICC=0.78-1.00). Descriptive data of the upper airway measurements are also shown in table 4.

Table 3 Intra-observer and inter-observer reliability of the localization of different landmarks of the upper airway, estimated by intraclass correlation coefficients (ICCs)

Variable	Intra-observer reliability			Inter-observer reliability
	Observer 1	Observer 2	Observer 3	
PNS	1.00	1.00	0.99	0.99-1.00
ANS	1.00	1.00	1.00	0.99-1.00
AICV	1.00	1.00	0.97	0.98-1.00
TUV	1.00	0.97	0.99	0.97-0.99
TEP	1.00	1.00	1.00	1.00
BEP	1.00	0.99	0.99	0.99

PNS, posterior nasal spine; ANS, anterior nasal spine; AICV, anterior-inferior aspect of the vertebral body of 2nd cervical vertebra; TUV, tip of the uvula; TEP, tip of the epiglottis; BEP, base of epiglottis.

Table 4 Intra-observer and inter-observer reliability of the upper airway measurements estimated by intraclass correlation coefficients (ICCs)

Variable	Intra-observer reliability			Inter-observer reliability
	Observer 1	Observer 2	Observer 3	
	Mean±SD (ICC)	Mean±SD (ICC)	Mean±SD (ICC)	
Volume (cm <sup>3</sup> )	10.28±2.96 (0.99)	10.34±2.98 (0.99)	10.22±2.86 (0.97)	10.28±2.90 (0.97-0.99)
CSA <sub>min</sub> (mm <sup>2</sup> )	101.06±44.12 (1.00)	101.09±44.11 (1.00)	102.14±44.40 (1.00)	101.46±43.72 (0.99-1.00)
Location	1.00	0.99	0.99	0.85-1.00
AP (mm)	6.90±3.00 (0.97)	6.83±2.85 (0.99)	6.88±3.08 (0.83)	6.87±2.95 (0.83-0.98)
Lateral (mm)	17.24±3.59 (0.96)	16.90±3.28 (0.98)	16.85±4.15 (0.85)	17.00±3.65 (0.78-0.97)

CSA<sub>min</sub>; minimum cross-sectional area; AP, anterior-posterior dimension of CSA<sub>min</sub>; Lateral, lateral dimension of CSA<sub>min</sub>.

## Discussion

In our study, both intra- and inter-observer reliability were excellent for both anatomical landmark localization and three-dimensional upper airway measurements on CBCT images. This study showed that the methodology of both the anatomical landmark localization and the upper airway measurements used in this study can be applied in future research in a reliable way. Although no gold standard was used in this study to test the accuracy of the measurements, a previous study showed that three-dimensional measurements obtained from CBCT images, such as the volume of the upper airway, give an accurate representation of the anatomical dimensions [9].

CBCT is playing an increasingly important role in the diagnosis of morphological abnormalities in the oral and maxillofacial region [16]. Although it does not have the same excellent soft tissue contrast as magnetic resonance imaging (MRI), in our study, it was shown that there was an excellent reliability of the localization of the soft-tissue landmarks, such as the tip of the uvula (ICC=0.97-1.00) and the tip of the epiglottis (ICC=1). Therefore, it is suggested that NewTom 5G CBCT can be used for the localization of these soft-tissue landmarks related to the upper airway with high reliability, which is consistent with previous studies [17, 18]. Besides, NewTom 5G CBCT scans were taken in the supine position, it would be interesting to investigate if the methodology of the landmark localizations is reliable in an upright CBCT set up in the future.

The landmarks used in this study were: posterior nasal spine (PNS) and anterior nasal spine (ANS) to define the hard palate plane, which can be used to determine the upper boundary of the upper airway; the tip of the soft palate (TSP) and the tip of the epiglottis (TEP) to define the retroglossal segment of the upper airway; and the base of the epiglottis (BEP) [19] or the anterior-inferior aspect of the vertebral body of 2nd cervical vertebra (AICV) [20, 21] to define the lower boundary of the upper airway. The localization of these landmarks is essential for the segmentation of the upper airway. This methodology of upper airway measurements can be used in future studies investigating the role of the upper airway morphology in the pathogenesis of many breathing disorders, such as obstructive sleep apnea (OSA) [1].

Six landmarks used in other studies for the segmentation of the upper airway were selected in this study [19, 20, 22]. Landmarks such as posterior nasal spine (PNS) and anterior nasal spine (ANS), which are also used for two-dimensional cephalometric analysis in orthodontic treatment planning, have an excellent reliability (ICC=0.99-1.00) in our study, which is consistent with other studies [5, 7]. As the position of the uvula can be influenced by the respiratory phase, it is possible that the anatomical characteristics of the uvula do not allow for a consistent localization in all patients [23]. However, in our study, the reliability of the tip of the uvula as an anatomical landmark was excellent (ICC=0.97-1.00), suggesting that the definition of the soft tissue landmarks applied in this study can be applied in future studies in a reliable way.

The superior boundary of the upper airway was defined as the axial plane across the posterior nasal spine (PNS) parallel to the FH plane, and the inferior boundary of the upper airway was defined as the axial plane across the base of the epiglottis (BEP) parallel to the FH plane. Therefore, the upper airway measurements (e.g., volume) are depending on the reliability of these landmark localizations (both PNS and BEP). As the ICCs of PNS and BEP demonstrated an excellent inter- and intra-observer reliability, the segmentation of the upper airway based on these two landmarks could be considered as reliable. This is consistent with the results of the reliability analysis of the measurements (e.g., volume) of the upper airway (ICC=0.97-1.00) found in this study.

The upper airway assessments by three observers showed a high reliability for the volume measurements (ICC=0.97-1.00), which is consistent with the results of other studies [9, 10, 13]. However, Mattos et al., [13] reported some unreliable measurements, such as the  $CSA_{min}$ , which is not consistent with our results. This difference may arise from the different software program used in that study. In our study, after the segmentation of the upper airway, the calculation of the cross-sectional area of every axial slice was performed automatically, which makes it convenient to detect the  $CSA_{min}$  and measure its area.

Although the observers had different backgrounds and different experiences with the use of the software, they showed good inter-observer reliabilities (ICC=0.78-1.00) in all of the measurements of the upper airway. This finding can be explained by several reasons. First, the landmark localization and upper airway measurements were well defined and the

observers were trained before doing the measurements. Second, the upper airway from the hard palate to the base of epiglottis was semi-automatically segmented, using proper landmarks (e.g. PNS and BEP), and the reliability of these landmarks was excellent. Third, a fixed threshold ranging from -1000 to -500 was used for the selection of the upper airway. In this way, the observer's subjectivity in upper airway segmentation could be eliminated. Therefore, it is recommended to choose automatic or semiautomatic segmentation of the region of interest in studies assessing characteristics of the upper airway in order to improve the reliability of the measurements.

Two different software programs (3Diagnosis® and Amira®) were used in this study. 3Diagnosis® provides an orthogonal coordinate system (X, Y, Z) which makes it efficient for the observers to localize the landmarks. Amira® produces the cross-sectional area of the segmented upper airway of every axial slice automatically, which makes it easy to identify the minimum cross-sectional area ( $CSA_{min}$ ) of the upper airway and its location (axial slice number). However, the accuracy of these two software programs has not been determined yet. Besides, there are a lot of different software programs available on the market. Therefore, the reliability and accuracy of the software programs including 3Diagnosis® and Amira® will be investigated in future studies at our department.

## **Conclusion**

The intra- and inter-observer reliability of the localization of the anatomical landmarks of the upper airway and that of three-dimensional upper airway measurements on CBCT images were excellent. Therefore, the methodology of the landmark localization and upper airway measurements used in this study is recommended in future studies in the upper airway analysis on CBCT images.

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## Chapter 3

### **Accuracy of MDCT and CBCT in three-dimensional evaluation of the oropharynx morphology**

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## Accuracy of MDCT and CBCT in three-dimensional evaluation of the oropharynx morphology

### Abstract

**Aim:** To assess the accuracy of five different computed tomography (CT) scanners for the evaluation of the oropharynx morphology.

**Methods:** An existing cone-beam computed-tomography (CBCT) dataset was used to fabricate an anthropomorphic phantom of the upper airway volume that extended from the uvula to the epiglottis (oropharynx) with known dimensions (gold standard). This phantom was scanned using two multi-detector row computed-tomography (MDCT) scanners (GE Discovery CT750 HD, Siemens Somatom Sensation) and three CBCT scanners (NewTom 5G, 3D Accuitomo 170, Vatech PaX Zenith 3D). All CT images were segmented by two observers and converted into standard tessellation language (STL) models. The volume and the cross-sectional area of the oropharynx were measured on the acquired STL models. Finally, all STL models were registered and compared with the gold standard.

**Results:** The intra- and inter-observer reliability of the oropharynx segmentation was fair to excellent. The most accurate volume measurements were acquired using the Siemens MDCT (98.4%; 14.3 cm<sup>3</sup>) and Vatech CBCT (98.9%; 14.4 cm<sup>3</sup>) scanners. The GE MDCT, NewTom 5G CBCT and Accuitomo CBCT scanners resulted in smaller volumes, viz., 92.1% (13.4 cm<sup>3</sup>), 91.5% (13.3 cm<sup>3</sup>), and 94.6% (13.8 cm<sup>3</sup>), respectively. The most accurate cross-sectional area measurements were acquired using the Siemens MDCT (94.6%; 282.4 mm<sup>2</sup>), Accuitomo CBCT 95.1% (283.8 mm<sup>2</sup>), and Vatech CBCT 95.3% (284.5 mm<sup>2</sup>) scanners. The GE MDCT and NewTom 5G CBCT scanners resulted in smaller areas, viz., 89.3% (266.5 mm<sup>2</sup>) and 89.8% (268.0 mm<sup>2</sup>), respectively.

**Conclusion:** Significant differences were observed in the volume and cross-sectional area measurements of the oropharynx acquired using different MDCT and CBCT scanners. The Siemens MDCT and the Vatech CBCT scanners were more accurate than the GE MDCT, NewTom 5G, and Accuitomo CBCT scanners. In clinical settings, CBCT scanners offer an alternative to MDCT scanners in the assessment of the oropharynx morphology.

## Introduction

Obstructive sleep apnea (OSA) is a sleep-related breathing disorder, often associated with a compromised upper-airway space and an increase in upper-airway collapsibility [1]. The most common complaints of OSA patients are excessive daytime sleepiness, unrefreshing sleep, poor concentration, and fatigue [2]. OSA also has a range of deleterious consequences that include increased cardiovascular morbidity, neurocognitive impairment, and overall mortality [3-6]. An important role in the pathogenesis of OSA is played by anatomical and functional abnormalities of the upper airway [7].

The three-dimensional (3D) morphology of the upper airway is currently assessed using computed tomography (CT) technologies [8]. The two most common CT technologies used to date for the assessment of the upper airway are multi-detector row computed tomography (MDCT) [9] and cone-beam computed tomography (CBCT) [10]. The major advantages of CBCT scanners are their lower radiation dose and costs [11, 12]. As a result, CBCT scanners are being increasingly used for upper-airway imaging in OSA patients [13-15]. CBCT scanners use a single, partial gantry rotation [16], which not only accounts for lower radiation dose, but also produces acceptable diagnostic image quality [17]. However, it remains unclear whether MDCT and CBCT scanners can provide accurate 3D images of the upper airway.

According to a systematic review by Alsufyani et al., only one out of sixteen studies focusing on the use of CBCT to automatically or semi-automatically model the upper airway had a sufficiently sound methodology to test the accuracy of the upper airway dimensions [18]. The main challenge faced in the assessment of the upper airway accuracy using MDCT or CBCT is the lack of a “gold standard” model with known dimensions. Recent studies have used artificial models, hence phantoms of the upper airway, as a gold standard [19-21]. However, commercially available phantoms used in most of the aforementioned studies are commonly manufactured in simple, generic forms and sizes and therefore do not resemble the clinical situation. In the present study, a novel 3D printed anthropomorphic phantom of the upper airway volume (oropharynx) with known dimensions was manufactured that closely resembled a real patient in terms of size, shape, structure, and attenuation profiles.

The aim of this study was to assess the accuracy of two different MDCT scanners and three different CBCT scanners using a novel 3D printed anthropomorphic phantom for the evaluation of the oropharynx morphology.

## Materials and methods

A CBCT dataset of a 27-year-old female that had been previously acquired using a NewTom 5G CBCT scanner (QR systems, Verona, Italy), was used to design and 3D print an anthropomorphic phantom of the airway space (Figure 1 a and b). The aforementioned CBCT dataset was converted into a virtual 3D surface, hence standard tessellation language (STL) model of the upper airway volume that extended from the uvula to the epiglottis: the oropharynx. This STL model served as the gold standard in this study. The gold standard STL model of the oropharynx was subsequently used to manufacture the phantom. All bony structures surrounding the oropharynx were 3D printed using a High Performance Composite powder ZP151 (3D Systems, Rock Hill, USA). This composite material was chosen due to its bone-like density that resembles the attenuation profile of bone [22]. The soft tissue surrounding the oropharynx was fabricated using soft-tissue-equivalent silicon (Dragon Skin 30, Smooth-On, Inc., Macungie, Pennsylvania, USA). During the assembling of the phantom, three metal markers were positioned in a defined plane to acquire a reproducible reference-point system (RPS) for the cross-sectional area measurement of the oropharynx (Figure 1).

As the flowchart (Figure 2) shows, MDCT images of the oropharynx phantom were acquired using two MDCT scanners: GE Discovery CT750 HD 64-slice MDCT (GE Healthcare, Little Chalfont, Buckinghamshire, UK) and Siemens Somatom Sensation 64-slice MDCT (Siemens Medical Solutions, Malvern PA, USA). Furthermore, the following three CBCT scanners were used to acquire CBCT images of the phantom: NewTom 5G CBCT (QR systems, Verona, Italy), 3D Accuitomo 170 CBCT (J Morita, Kyoto, Japan), and Vatech PaX Zenith 3D CBCT (Vatech, Fort Lee, USA). All MDCT and CBCT images were acquired using the vendor-supplied default airway scanning protocol. All imaging parameters of the five CT scanners are presented in table 1.

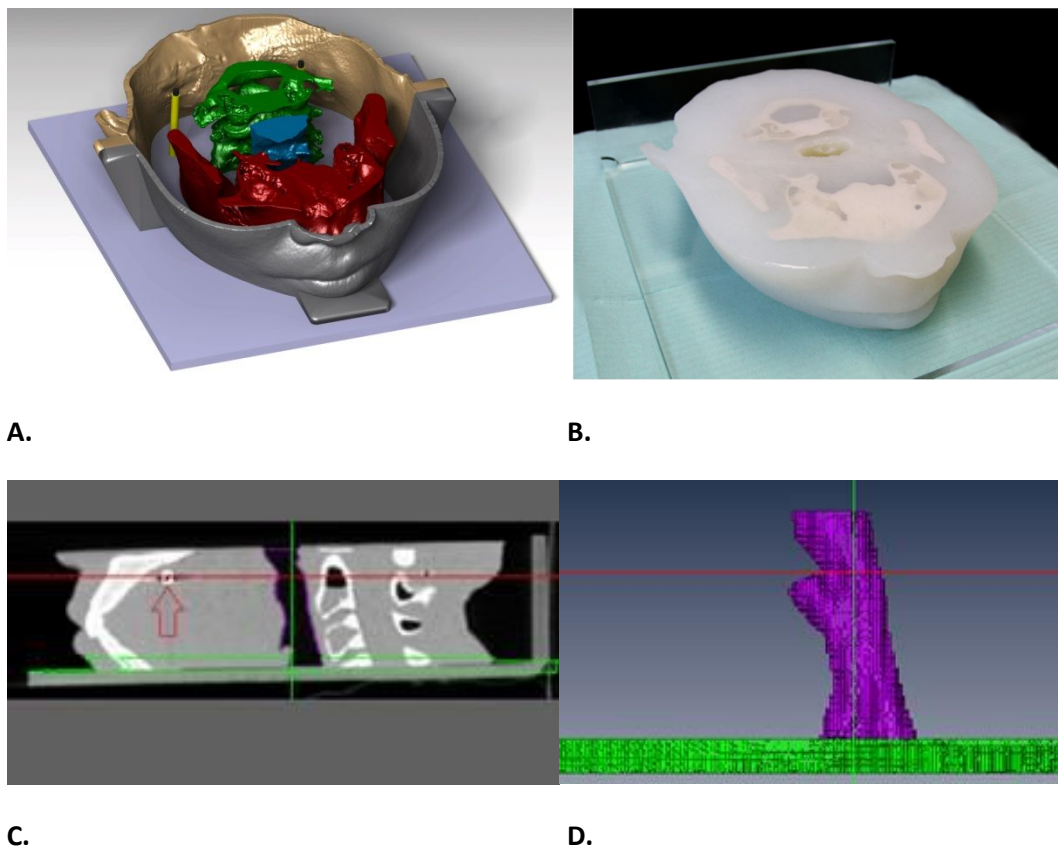


Figure 1A. Design of the oropharynx of the phantom (red = maxilla and mandible; green = cervical vertebrae; yellow = supports of the markers; black = markers at the level of the minimum cross-sectional area of the oropharynx; blue = upper airway; purple = base plane; grey and pale-yellow = mold of the skin). B. The 3D printed phantom. C. Sagittal image of the phantom using GE scanner. Arrow = a marker. D. Segmentation based on GE images (purple = oropharynx; green = base plane of the phantom).

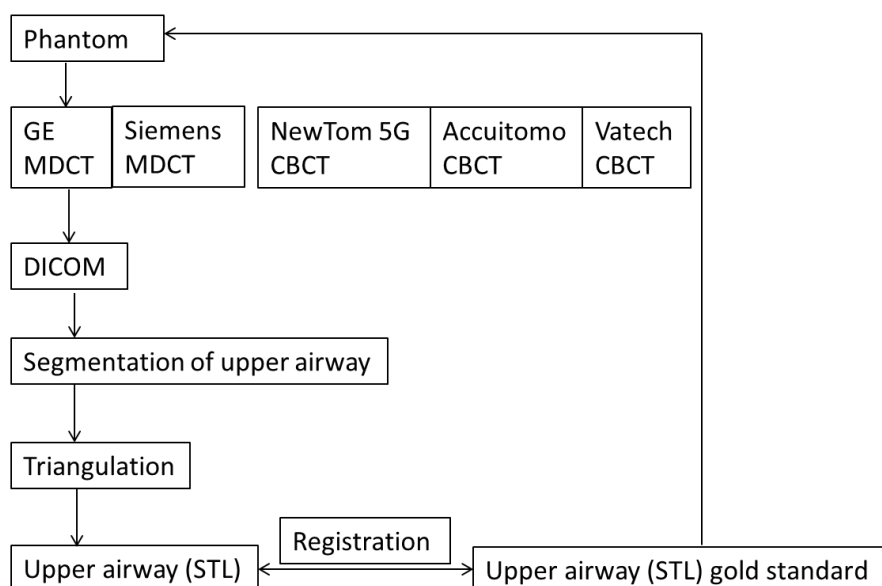


Figure 2. Flowchart of this study.

Table 1. Image acquisition parameters for MDCT and CBCT scans.

	GE	Siemens	NewTom 5G	Accuitomo	Vatech
	MDCT	MDCT	CBCT	CBCT	CBCT
Tube voltage (kV)	120	120	110	90	115
Tube current (mA)	103	57	5.8	5	6
Scan time (s)	0.5	0.5	3.6	17.5	24
Slices thickness (mm)	0.625	0.600	0.300	1	0.200
Number of voxels	512 x 512 x 180	512 x 512 x 151	610 x 610 x 539	684 x 684 x 480	800 x 800 x 632
Reconstruction	Soft	B40f	Standard	N.A.	N.A.
DLP (mGy-cm)	46.49	49	N.A.	N.A.	N.A.
DAP (mGy-cm <sup>2</sup> )	N.A.	N.A.	12.232	N.A.	17.67
CTDIvol (mGy)	N.A.	N.A.	N.A.	8.70	N.A.

CBCT: cone beam computed tomography; CTDI: computed tomography dose index; DAP: dose-area product; DLP: dose-length product; Gy: Gray; MDCT: multi-detector row computed tomography; N.A.: not applicable.

The acquired CT datasets were saved as Digital Imaging and Communications in Medicine (DICOM) files and were imported into Amira® software (v4.1, Visage Imaging Inc., Carlsbad, CA, USA) (Figure 2C). Using thresholding, one maxillofacial radiologist and one orthodontist then segmented all the acquired DICOM datasets of the oropharynx. Both observers were blinded for their own results and those of each other. The segmentation procedure was performed five times for each CT scanner and was subsequently repeated after a ten-day interval. This resulted in a total of 20 threshold values per CT scanner (Table 2). These 20 threshold values per scanner were subsequently used to segment the oropharynx. All segmented oropharynx volumes acquired from the five MDCT and CBCT scanners (Figure 2D) were converted into STL models. These STL models were subsequently imported into GOM Inspect v8® metrology software (GOM, Braunschweig, Germany) for further airway analysis.

The region of interest (ROI) in this study was the volume of the oropharynx between two parallel planes located 1.5 mm and 42 mm above the base plane of the phantom (Figure 3).



In order to obtain comparable oropharynx volume measurements, all STL models derived from the five CT datasets were cropped accordingly. The volume of the oropharynx was subsequently calculated using GOM Inspect software (Figure 4a). Furthermore, the cross-sectional area of the oropharynx at the level of the metal markers in the phantom was calculated (Figure 4b).

To determine the accuracy of the CT-derived STL models, all acquired STL models were superimposed onto the gold standard STL model of the oropharynx using a verified surface registration (local best-fit) algorithm in GOM Inspect software with an accuracy of 0.05 mm [23]. All geometric deviations between the oropharynx STL models and the printed gold standard phantom STL model are depicted in Figure 5.

Finally, statistical analysis was performed, using IBM Statistical Package for Social Sciences for Windows (SPSS® version 21, Chicago, IL, USA). Statistical significance was set at  $\alpha=0.05$ . To determine the intra- and inter-observer reliability of the oropharynx measurements, intraclass correlation coefficients (ICCs) were calculated. Reliability was divided into three categories: poor ( $ICC<0.40$ ); fair to good ( $0.40\leq ICC\leq 0.75$ ); excellent ( $ICC>0.75$ ) [24]. The accuracy of the scanners was calculated as the ratio of the phantom measurements to the gold standard (%). One-way analysis of variance (ANOVA) was used to test the differences in the volume and cross-sectional area measurements between the five different CT scanners. Post-hoc analysis (Tukey's honest significant difference test) was run to establish which CT scanners produced significantly different results.

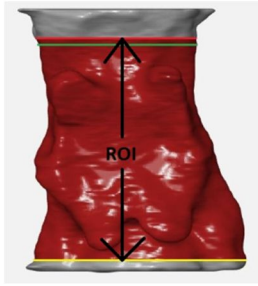
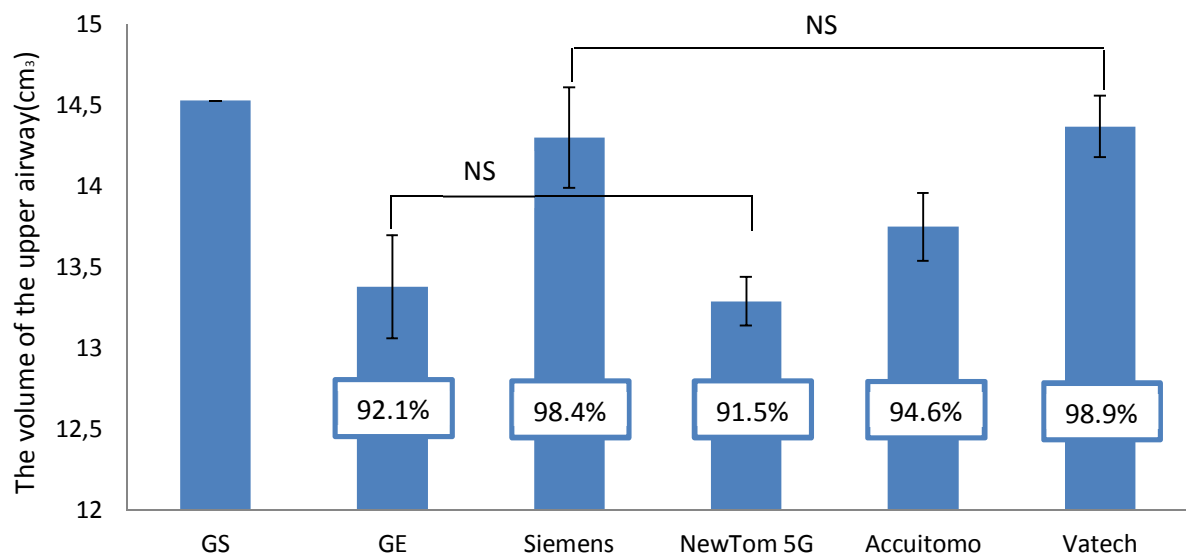
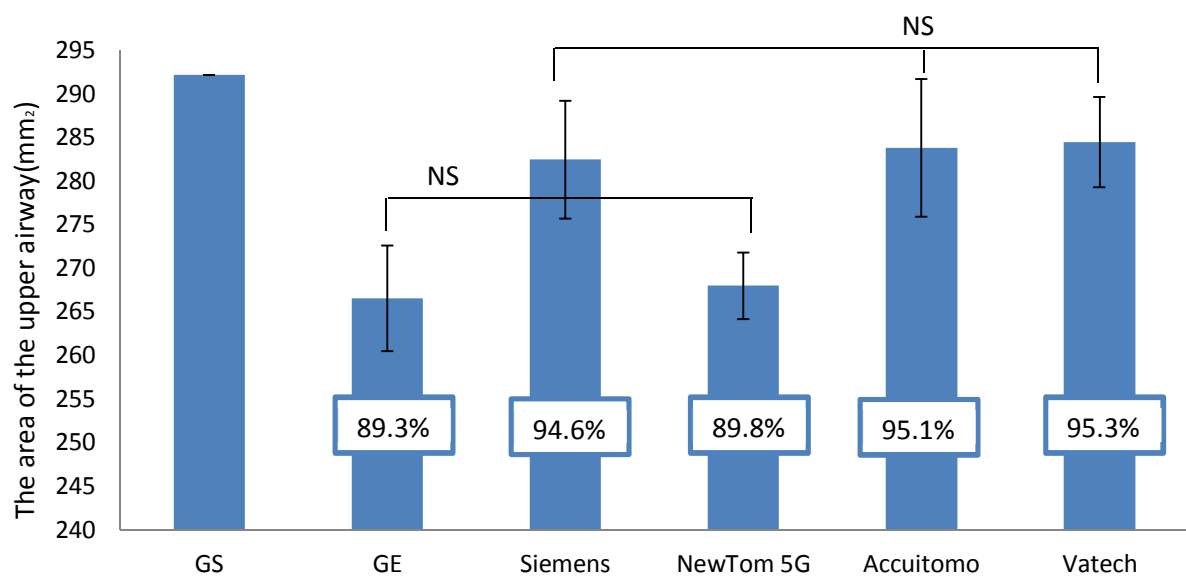


Figure 3. The segmented volume of the oropharynx. (Red line = upper boundary of region of interest (ROI); yellow line = lower boundary of ROI; green line = the location of the markers)



a.



b.

Figure 4a. Mean and standard deviation of the volume of the oropharynx derived from five CT scanners. GS = gold standard; NS = no significant difference. b. Mean and standard deviation of the cross-sectional area of the oropharynx derived from five CT scanners. GS = gold standard; NS = no significant difference. The accuracy (%) was calculated as the ratio between the phantom measurements and the gold standard values.

## Results

All threshold values used for the segmentation of the oropharynx are shown in table 2. Intra- and inter-observer reliability hence ICCs of the threshold values ranged from 0.436 (fair to good) to 0.966 (excellent).

Table 2. Intraobserver and interobserver reliability of the threshold values (Hounsfield Units) chosen for five CT scanners estimated by intraclass correlation coefficients (ICCs), based on 20 measurements in total per scanner.

Scanner	Threshold values (HU)		Threshold values (HU)
	(Intra-observer reliability)		(Inter-observer reliability)
	Observer 1	Observer 2	
	Mean±SD (ICC)	Mean±SD (ICC)	Mean±SD (ICC)
GE (MDCT)	-339±47 (.966)	-389±87 (.864)	-364±73 (.818)
Siemens (MDCT)	-204±54 (.573)	-250±77 (.748)	-231±70 (.558)
NewTom5G (CBCT)	-114±35 (.481)	-102±40 (.720)	-108±37 (.786)
Accuitomo (CBCT)	-289±40 (.661)	-244±62 (.438)	-267±56 (.507)
Vatech (CBCT)	-361±75 (.787)	-330±63 (.436)	-346±70 (.592)

There were significant differences between the volume measurements of the oropharynx STL models acquired using the five different CT scanners ( $F=84.21$ ;  $P=0.00$ ) (Figure 4a). Tukey's test showed that there were no significant differences in volume measurements between the Siemens MDCT and Vatech CBCT scanners, and between the GE MDCT and NewTom 5G CBCT scanners. The Siemens MDCT and Vatech CBCT scanners provided the most accurate volume measurements of the oropharynx (Figure 4a). The NewTom 5G CBCT, Accuitomo CBCT, and the GE MDCT scanners resulted in smaller volume measurements of the oropharynx (Figure 4a, Table 3).

There were also significant differences between the cross-sectional area measurements of the oropharynx STL models acquired using the five different CT scanners ( $F=43.11$ ;  $P=0.00$ ) (Figure 4b). The Siemens MDCT, Vatech CBCT and Accuitomo CBCT scanners provided the most accurate cross-sectional area measurements of the oropharynx (Figure 4b). The GE MDCT and NewTom 5G CBCT scanners resulted in smaller area measurements of the oropharynx (Figure 4b, Table 3).

Table 3. Mean and standard deviation of the volume and the cross-sectional area of the upper airway derived from five CT scanners. GS = gold standard.

Variable	GS	GE MDCT	Siemens MDCT	NewTom 5G CBCT	Accuitomo CBCT	Vatech CBCT
Volume of the upper airway (cm <sup>3</sup> )	14.5	13.4 ± 0.32	14.3 ± 0.31	13.3 ± 0.15	13.8 ± 0.21	14.4 ± 0.19
Area of the upper airway (mm <sup>2</sup> )	295.5	266.5 ± 6.1	282.4 ± 6.8	268.0 ± 3.8	283.8 ± 7.9	284.5 ± 5.2

Figure 5 shows the oropharynx STL models acquired using five different CT scanners. The largest geometric deviations were observed in the vicinity of the uvula and the epiglottis region (Figure 5).

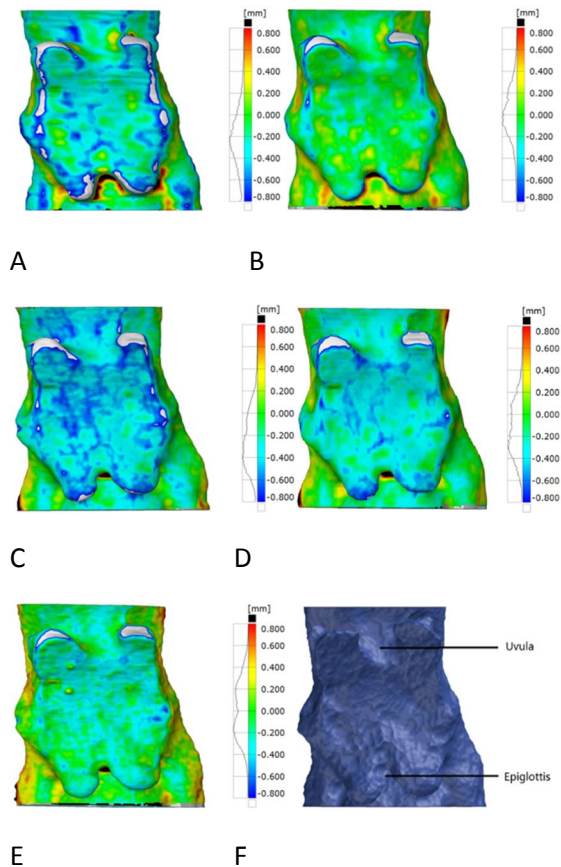


Figure 5. The results of registration between all CT-derived oropharynx STL models (acquired using the mean threshold value) and the gold standard STL model. A = GE; B = Siemens; C = NewTom 5G; D = Accuitomo; E = Vatech; F = Gold standard STL model. Scale: Red = CT-derived STL model is larger than the gold standard; blue = CT-derived STL model is smaller than the gold standard; green = CT-derived STL model is close to the gold standard; black and white = outliers ( $> 0.8$  mm).

## Discussion

Three-dimensional (3D) evaluation of the oropharynx offers new possibilities of assessing anatomical abnormalities in OSA patients. In this study, significant differences ( $P < 0.001$ ) were found between the volume and cross-sectional area measurements of the oropharynx acquired using different MDCT and CBCT scanners (Figure 4, Figure 5).

The most accurate volume measurements of the oropharynx were acquired using the Siemens MDCT (98.4%;  $14.3 \text{ cm}^3$ ) and Vatech CBCT (98.9%;  $14.4 \text{ cm}^3$ ) scanners (Figure 4 a). The GE MDCT, NewTom 5G CBCT and Accuitomo CBCT scanners resulted in smaller volume measurements, viz., 92.1% ( $13.4 \text{ cm}^3$ ), 91.5% ( $13.3 \text{ cm}^3$ ), and 94.6% ( $13.8 \text{ cm}^3$ ), respectively. The most accurate cross-sectional area measurements of the oropharynx were acquired using the Siemens MDCT (94.6%;  $282.4 \text{ mm}^3$ ), Accuitomo CBCT (95.1%;  $283.8 \text{ mm}^3$ ) and Vatech CBCT (95.3%;  $284.5 \text{ mm}^3$ ) scanners (Figure 4 b). The GE MDCT and NewTom 5G CBCT scanners resulted in smaller area measurements, viz., 89.3% ( $266.5 \text{ mm}^3$ ) and 89.8% ( $268.0 \text{ mm}^3$ ), respectively. These results are in good agreement with previous studies that reported an underestimation of the airway area in both MDCT and CBCT images [25, 26]. However, it should be noted that the absolute values of the aforementioned inaccuracies ranged between  $13.3 \text{ cm}^3$  and  $14.4 \text{ cm}^3$  (volume), and between  $266.5 \text{ mm}^2$  and  $284.5 \text{ mm}^2$  (cross-sectional area) (Table 3). Consequently, the authors of this study hypothesize that the reported inaccuracies should not affect the radiological evaluation of OSA patients in clinical settings [27].

Even though the authors of this study used the recommended soft tissue imaging protocols on all CT scanners, the STL models acquired using the GE and NewTom 5G scanners were generally smaller in size than the gold standard STL model (Figure 4). The smaller STL models caused a shift in the histograms towards the negative direction (Figure 5 a, c). This

phenomenon is probably due to the partial volume effect [28], in which voxels in the vicinity of the air-to-soft tissue boundary are commonly allocated to “soft tissue” instead of “air” during the segmentation process.

The higher accuracy of the Vatech STL models could be a result of the smaller spatial resolution used in the default airway scanning protocol (Table 1) [29]. However, a very recent study by Sang et al. (2016) that investigated the influence of voxel size on the accuracy of NewTom 5G and Vatech CBCT reported that increasing the voxel resolution from 0.30 to 0.15 mm does not always result in increased accuracy of 3D tooth reconstructions, while different CBCT modalities (i.e. NewTom 5G vs. Vatech) can significantly affect the accuracy [30].

The largest geometric deviations were found in the uvula and epiglottis area (Figure 5). Interestingly, the acquired oropharynx STL models were generally too large in the epiglottis region and too small in the vicinity of the uvula. One explanation for this phenomenon could be that the epiglottis has a concave-like geometry and the uvula is convex. These findings are in good agreement with a previous study by Barone et al. (2015) who observed discrepancies between the segmentation of concave and convex shapes in teeth [31].

The results of the present study show that CBCT scanners offer an alternative to MDCT scanners in the assessment of the oropharynx. This is in good agreement with a previous study by Suomalainen et al., who reported that CBCT scanners offer images similar to those acquired using low-dose MDCT protocols [32]. Therefore, taking the lower CBCT radiation dose into consideration [12, 33], clinicians should preferably use CBCT modalities for the analysis of the oropharynx. Moreover, all appropriate measures should be undertaken to minimize the dose according to the International Commission on Radiological Protection (ICRP) and the As Low As Reasonably Achievable (ALARA) principles [34].

#### Limitations of the current study

One limitation of this study was that for each of the five CT scanners, only one image dataset was acquired using a single image acquisition protocol. Since there are multiple image acquisition protocols available for each MDCT and CBCT scanner, different protocols should be considered in a future study. Another limitation was that the gold standard values in the

present study were obtained from the original STL model of the oropharynx that was used to 3D print the phantom. 3D printing was performed using a Zprinter 250 inkjet powder printer (3D Systems, Rock Hill, USA), which has a layer thickness of 0.1 mm and an in-plane resolution of approximately 0.05 mm [23]. Therefore, this process may have introduced a manufacturing error, hence measurement uncertainty, of up to 0.2 mm [35]. Nevertheless, this uncertainty can be considered clinically insignificant [36].

## Conclusion

Significant differences were observed in the volume and cross-sectional area measurements of the oropharynx acquired using different MDCT and CBCT scanners. The Siemens MDCT and the Vatech CBCT scanners were more accurate than the GE MDCT, NewTom 5G, and Accuitomo CBCT scanners. In clinical settings, CBCT scanners offer an alternative to MDCT scanners in the assessment of the oropharynx morphology.

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## Chapter 4

### Reliability and accuracy of imaging software for three-dimensional analysis of the upper airway on cone beam CT

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## **Reliability and accuracy of three imaging software packages used for 3D analysis of the upper airway on cone-beam computed tomography images**

### **Abstract**

**Aim:** To assess the reliability and accuracy of three different imaging software packages for three-dimensional analysis of the upper airway using cone-beam computed tomography (CBCT) images.

**Methods:** To assess the reliability of the software packages, fifteen NewTom 5G CBCT datasets were randomly and retrospectively selected. Two observers measured the volume, minimum cross-sectional area, and length of the upper airway using Amira®, 3Diagnosys®, and Ondemand3D® software packages. The intra- and inter-observer reliability of the upper airway measurements were determined using intraclass correlation coefficients (ICC) and Bland & Altman agreement tests.

To assess the accuracy of the software packages, one NewTom 5G CBCT dataset was used to print a 3D anthropomorphic phantom with known dimensions to be used as the “gold standard”. This phantom was subsequently scanned using a NewTom 5G scanner. Based on the CBCT dataset of the phantom, one observer measured the volume, minimum cross-sectional area, and length of the upper airway using Amira®, 3Diagnosys®, and Ondemand3D®, and compared these measurements with the gold standard.

**Results:** The intra- and inter-observer reliability of the measurements of the upper airway using the different software packages were excellent ( $ICC \geq 0.75$ ). There was excellent agreement between all three software packages in volume, minimum cross-sectional area and length measurements. All software packages underestimated the upper airway volume by -8.8% to -12.3%, the minimum cross-sectional area by -6.2% to -14.6%, and the length by -1.6% to -2.9%.

**Conclusion:** All three software packages offered reliable volume, minimum cross-sectional area and length measurements of the upper airway. The length measurements of the upper airway were the most accurate results in all software packages. All software packages underestimated the upper airway dimensions of the anthropomorphic phantom.

## Introduction

The upper airway is an important and complex anatomical structure in respiratory medicine. The anatomical and functional abnormalities of the upper airway play an important role in the pathogenesis of many breathing disorders such as obstructive sleep apnea (OSA) [1, 2].

Recently, cone-beam computed tomography (CBCT) has been used to analyze the upper airway three-dimensionally (3D) [3]. In this context, it is important to emphasize that the ever-increasing use of medical computed tomography (CT) technologies since the 1980s has raised concerns about possible cancer risks [4]. The radiation dose incurred by CBCT scanners is lower than that from medical CT scanners, which makes CBCT easier to justify as part of the diagnostic procedure [5].

After image acquisition, CBCT datasets are usually saved as Digital Imaging and Communications in Medicine (DICOM) files and imported into dedicated software packages for upper airway analysis. A wide variety of engineering, medical, and dental software packages are currently available on the market [6, 7]. To the best of our knowledge, the reliability and the accuracy of most software packages for upper airway analysis have not yet been tested [3].

One previous study concluded that several software packages showed high reliability in the volume measurement of the upper airway, but without mentioning their reliability in area and linear measurements of the upper airway [7]. Moreover, the study did not assess the accuracy of the upper airway measurements. Three previous studies have, however, used artificial phantom models of the upper airway as a gold standard to assess the accuracy of software packages [6, 8, 9]. In this context, it should be noted that such phantom models were mostly manufactured using generic forms, which do not correctly mimic the complex anatomy of the upper airway. Recent developments in the field of 3D printing offer new opportunities for manufacturing life-like anthropomorphic phantoms [10]. In the present study, an anthropomorphic phantom was manufactured based on the anatomical characteristics of a human. This is, to the best of our knowledge, the first time a humanoid phantom has been used to assess the accuracy of different imaging software packages for upper airway analysis.

The aim of this study was to assess the reliability and accuracy of three different software packages for linear, area, and volume measurements of the upper airway using CBCT images.

## Materials and methods

### Part I: Reliability of software packages

The participants were referred to the Department of Oral and Maxillofacial Radiology at the Academic Centre for Dentistry Amsterdam (ACTA), The Netherlands between April 1st, 2013 and July 1st, 2014 for the examination of their temporomandibular joints (approved by Medical Ethics Committee of the VU University, Amsterdam, protocol number: NL18726.029.07).

Fifteen NewTom 5G (QR systems, Verona, Italy) CBCT datasets of these participants (mean age  $\pm$  SD =  $39.6 \pm 12.6$  years; 67% female, 23% male) were randomly and retrospectively selected from the image archives of the department of Oral and Maxillofacial Radiology at the Academic Centre for Dentistry Amsterdam (ACTA), The Netherlands [2].

Two observers (a radiologist and an orthodontist) measured the volume, the minimum cross-sectional area ( $CSA_{min}$ ), and the length of the upper airway using Amira® engineering software (v4.1, Visage Imaging Inc., Carlsbad, CA, USA), 3Diagnosys® medical software (v5.3.1, 3diemme, Cantu, Italy), and Ondemand3D® dental software (CyberMed, Seoul, Korea) [6, 11, 12]. After 10 days, the measurements were repeated. During the second measurement session, all CBCT datasets were analyzed in random order to allow for a blinded assessment, and the observers did not have access to their previous measurements.

In all three software packages, the upper airway was segmented from the hard palate plane to the base of the epiglottis and saved as a standard tessellation language (STL) model. The volume, the  $CSA_{min}$ , and the length of the upper airway were calculated from these STL models. In Amira®,  $CSA_{min}$  was calculated automatically. The corresponding CBCT image slice was subsequently used in 3Diagnosys® and Ondemand3D® to calculate  $CSA_{min}$ .

## Part II: Accuracy of software packages

One existing CBCT dataset of a patient (27-year-old female) was used to fabricate an anthropomorphic phantom of the upper airway volume with known dimensions. The dataset was converted into an STL model of the upper airway, which served as the “gold standard” in this study. The gold standard STL model of the upper airway was subsequently used to manufacture the anthropomorphic phantom according to the steps described in Figure 1. The material used to mimic the bony tissue surrounding the upper airway was ZP151 High Performance Composite powder (3D Systems, Rock Hill, USA). The material used to mimic the soft tissue surrounding the upper airway was Liquid silicon (Dragon Skin 30, Smooth-On, Inc., Macungie, Pennsylvania, USA). Three metal markers (diameter\*height = 3 mm \* 3 mm) were placed in the phantom corresponding to the axial plane in which the  $CSA_{min}$  of the upper airway was located. The volume, the  $CSA_{min}$  in the plane indicated by the markers, and the length were measured on the STL model of the phantom (Figure 2) using Geomagic 3D scanning, design and reverse engineering software (studio® 2012, Morrisville, NC, USA). These measurements were considered as the gold standard values.

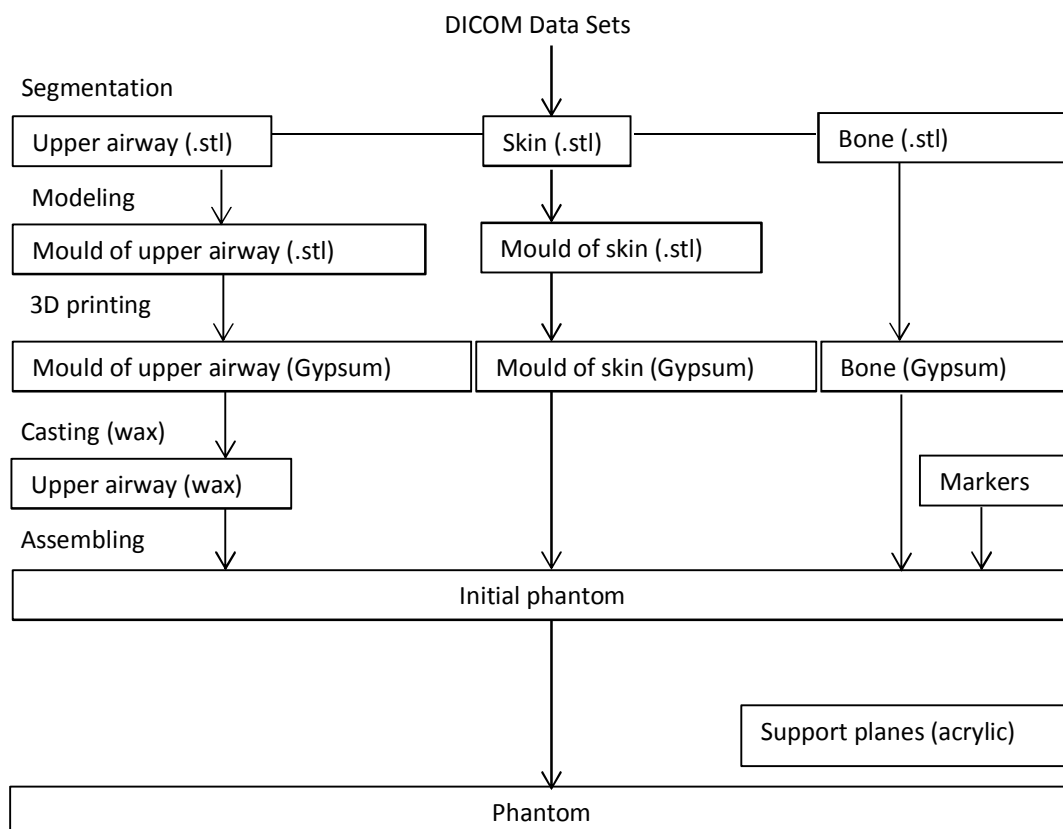


Figure 1. Flowchart for manufacturing the phantom.

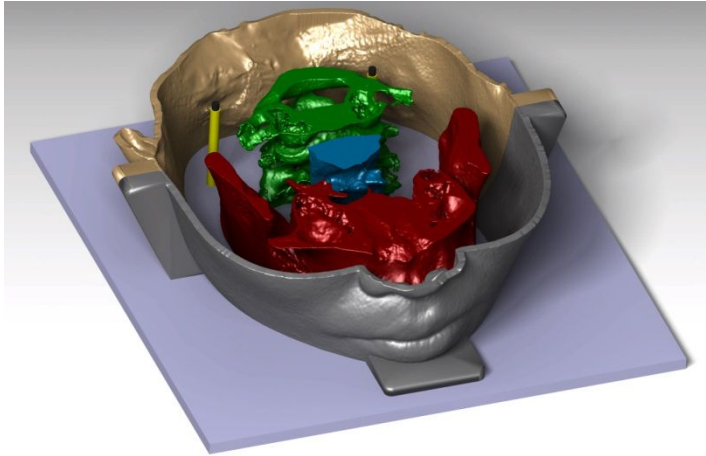
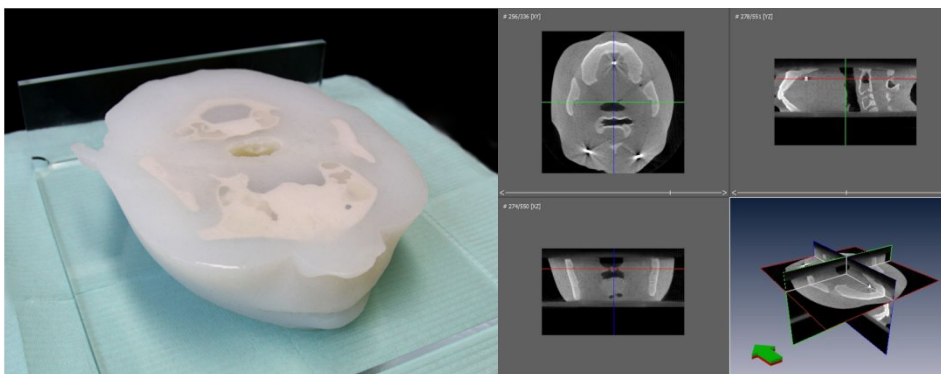


Figure 2. Representation of the STL file of the phantom. (Red = maxilla and mandible; green = cervical vertebrae; yellow = supports of the markers; black = markers at the level of the minimum cross-sectional area of the upper airway; blue = upper airway; purple = base plane; grey and pale-yellow = mold of the skin.)

The anthropomorphic phantom (Figure 3a) was scanned using a NewTom 5G CBCT scanner (QR systems, Verona, Italy). The exposure settings were 110 kV, 4 mA, 18 cm \* 16 cm field of view, 0.3 mm voxel size, and 3.6 second exposure time (pulsed radiation). The resulting CBCT images of the phantom were saved as DICOM files, and imported into Amira®, 3Diagnosys®, and Ondemand3D® to measure the volume,  $CSA_{min}$ , and length of the upper airway (Figure 3b). To minimize the random error, these measurements were performed 20 times over 20 days (once per day) by one observer (an orthodontist).



a.

b.



Figure 3. The 3D-printed phantom (a) and its cone beam CT (CBCT) images (b). The soft and hard tissues as well as the airway space can be clearly distinguished.

### Statistical methods

All measurements were imported into Microsoft Excel® (2007; Microsoft Corporation, Redmond, USA) and statistically evaluated using the IBM Statistical Package for Social Sciences for Windows (SPSS® version 21, Chicago, IL, USA). Statistical significance was set at  $\alpha=0.05$ .

Intraclass correlation coefficients (ICC) were calculated to evaluate the intra- and inter-observer reliability of the measurements. Reliability was divided into three categories: poor ( $ICC < 0.40$ ); fair to good ( $0.40 \leq ICC \leq 0.75$ ); and excellent ( $ICC > 0.75$ ) [13]. Furthermore, Bland & Altman agreement tests with confidence intervals set at 95% were used to assess the agreement between the three software packages [14, 15].

To evaluate the accuracy of the software packages, the one-sample T-Test was used to test the difference between the gold standard values and the measurements of the upper airway. The measurement error (%) was calculated as the difference between the measurements performed on the CBCT-derived models of the upper airway and the gold standard values. One-way ANOVA was used to test the difference in the measurements of the upper airway on the CBCT images of the phantom using the three different software packages. The independent variable was the software package; the dependent variables were the volume,  $CSA_{min}$ , and length of the upper airway.

### Results

The intra- and inter-observer reliability of the measurements of the upper airway using all three software packages were excellent ( $ICC \geq 0.75$ ) as shown in table 1. Furthermore, high reliability was observed for all three software packages, with narrow confidence intervals, thereby demonstrating excellent agreement for all upper airway measurements (Figure 4).

Table 1 Intraclass correlation coefficient (ICC) for the measurements of the upper airway.

Software package	Amira		3Diagnosisys			OnDemand3D			
	Intra	Inter	Intra	Inter	Inter	Intra	Inter	Inter	Inter
Volume of the upper airway (cm <sup>3</sup> )	0.98	0.99	0.97	0.98	0.97	0.97	0.99	0.82	0.89
Minimum cross sectional area (CSA <sub>min</sub> )(mm <sup>2</sup> )	1.00	1.00	0.99	0.99	0.99	0.99	0.97	0.99	0.97
Length of the upper airway (mm)	1.00	0.78	0.85	0.99	0.99	0.99	0.97	0.98	0.90

Intra: intra-observer reliability; Inter: inter-observer reliability.

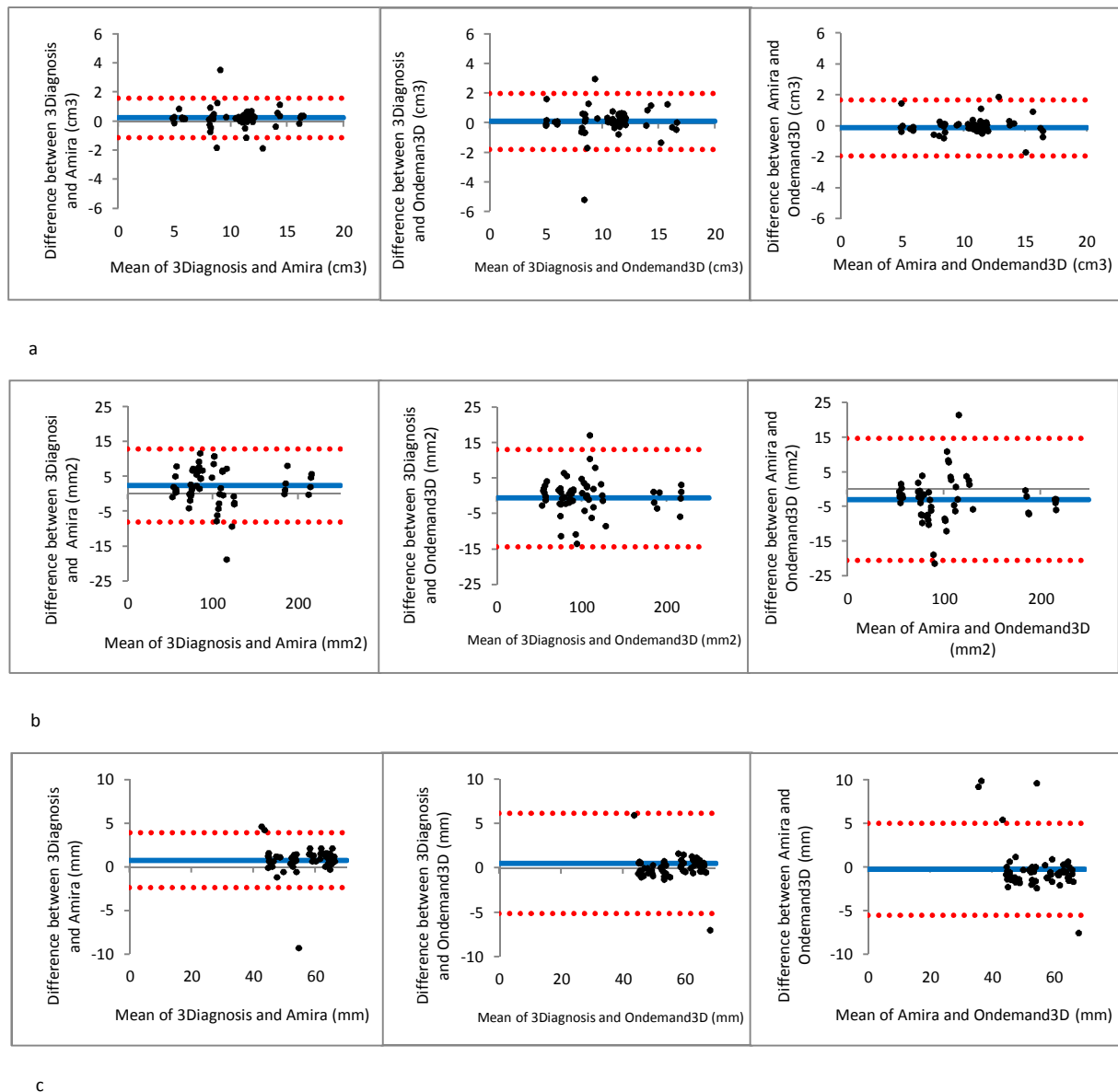


Figure 4. Bland-Altman plots. a. Agreement between the software packages with respect to the volume measurement; b. Agreement between the software packages with respect to the minimum

cross-sectional area measurement; c. Agreement between the software packages with respect to the length measurement. Dotted line: upper and lower bounds of the 95% confidence interval; solid line: mean difference.

The 3D printed anthropomorphic phantom and the CBCT images of this phantom are shown in Figure 3. There were significant differences between the gold standard values and the measurements of the upper airway using the three dedicated software packages (one sample T-Test,  $p < 0.05$ ; Table 2). The measurement errors (%) of the three software packages are listed in table 2. All software packages demonstrated errors in the volume (-10.8%), the  $CSA_{min}$  (-10.3%), and the length (-2.1%) measurements (Table 2). All measurements of the upper airway were smaller than the gold standard. There were significant differences in the measurements between the different software packages (One-way ANOVA,  $p < 0.05$ ; Figures 5-7)

Table 2 The measurements of the upper airway based on the phantom and the CBCT images of the phantom.

Measurement	Phantom	CBCT of the phantom			Measurement error (ME) (%)			
		(Mean $\pm$ Standard Deviation)			[Mean(2)-(1)]/(1)			
	(1)	(2)						
		Amira	3Diagnosys	Ondemand3D	Amira	3Diagnosys	Ondemand3D	Average
Volume of the upper airway (cm <sup>3</sup> )	17.58*	15.59 $\pm$ 0.20	15.42 $\pm$ 0.33	16.04 $\pm$ 0.35	-11.3	-12.3	-8.8	-10.8
Minimum cross sectional area ( $CSA_{min}$ ) (mm <sup>2</sup> )	314.14*	282.10 $\pm$ 11.97	294.61 $\pm$ 8.20	268.31 $\pm$ 10.95	-10.2	-6.2	-14.6	-10.3
Length of upper airway (mm)	48.88*	48.08 $\pm$ 0.28	47.99 $\pm$ 0.45	47.46 $\pm$ 0.29	-1.6	-1.8	-2.9	-2.1

\* indicates there was significant difference between the gold standard values and the measurements done by each of the three software packages, using one-sample T-Test. ME: Measurement error is the difference between the measurements done based on the CBCT images of the phantom and the gold standard values.

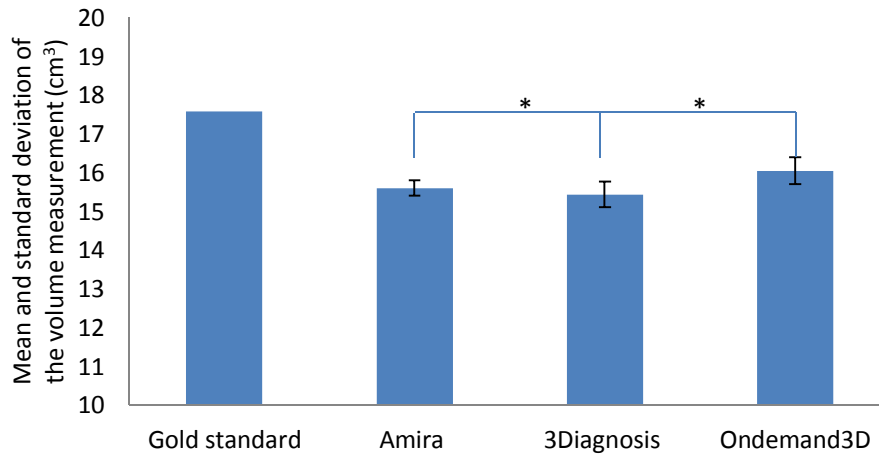


Figure 5. Mean and standard deviation of the volume ( $\text{cm}^3$ ) measurement. \* indicates a significant difference between Ondemand3D and Amira and between 3Diagnosis and Ondemand3D,  $p < 0.05$ .

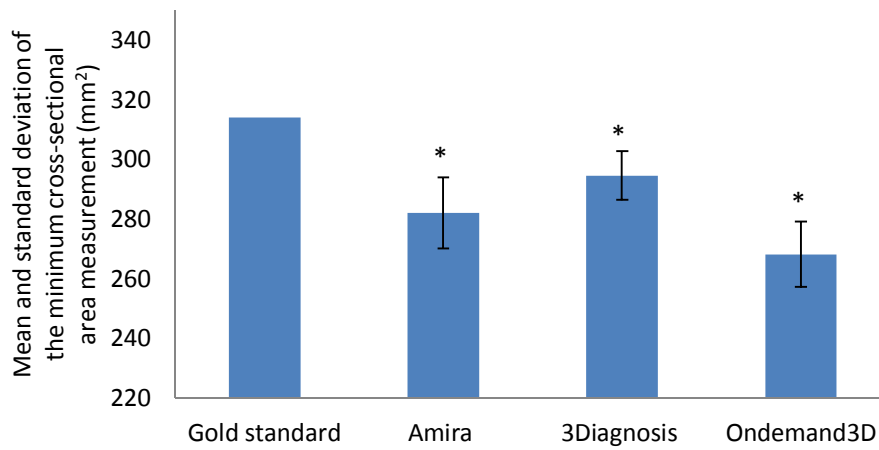


Figure 6. Mean and standard deviation of the minimum cross-sectional area ( $\text{mm}^2$ ) measurement. \* indicates a significant difference between all software packages,  $p < 0.05$ .

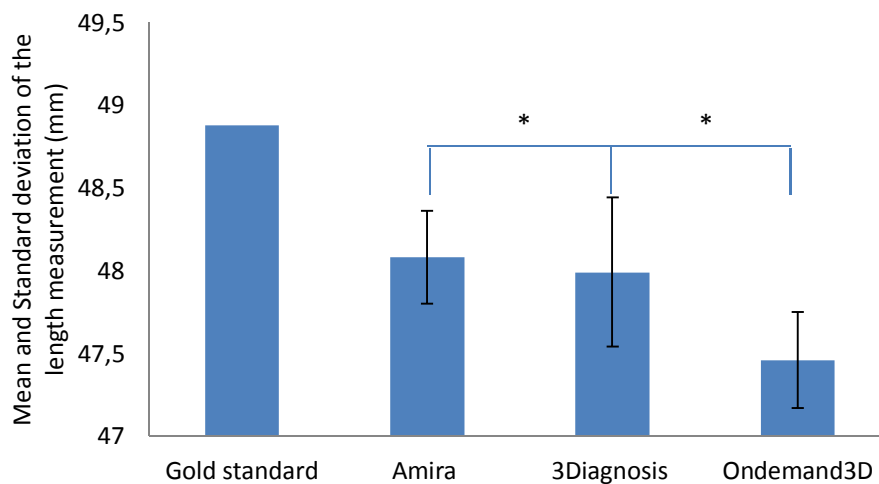


Figure 7. Mean and standard deviation of the length (mm) measurement. \* indicates a significant difference between Ondemand3D and Amira and between 3Diagnosys and Ondemand3D,  $p < 0.05$ .

## Discussion

In this study, the reliability and accuracy of three different commercially available software packages (Amira®, 3Diagnosys®, and Ondemand3D®) used for the 3D analysis of the upper airway were assessed.

The reliability of the upper airway volume measurements was excellent for all three software packages (Table 1), which is in good agreement with previous studies [6, 8, 16]. Furthermore, Burkhard et al. conducted a study to investigate the morphological changes in oropharyngeal structures in mandibular prognathic patients before and after orthognathic surgery [17] and concluded that the OsiriX®, Mimics® and BrainLab® software packages were reliable in assessing the posterior airway space. However, one previous study by Mattos et al. [18] reported that CSA<sub>min</sub> measurements of the upper airway acquired using Dolphin® software were unreliable, which is in contrast with the results of the present study. This difference in results may be due to the ambiguous definition of the CSA<sub>min</sub> of the upper airway in the Dolphin® software package [18].

The accuracy of the upper airway measurements varied between the software packages (Figures 5 to 7). All three software packages generally underestimated the upper airway volume by -8.8% to -12.3%, the CSA<sub>min</sub> by -6.2% to -14.6%, and the length by -1.6% to -2.9% (Table 2). These results are in good agreement with a previous study by El and Palomo et al., [7] who reported that Ondemand3D® software sometimes fails to depict certain parts of the upper airway, which subsequently leads to an underestimation of the airway volume [7]. This phenomenon could originate from the CBCT image acquisition process and/or the subsequent image segmentation by means of thresholding. During CBCT image acquisition, anatomical structures are discriminated based on their radiographic density. However, voxels residing on tissue boundaries can contain more than one tissue type. This phenomenon is known as the partial volume effect (PVE). The result of the PVE is that voxels are erroneously allocated to “soft tissue” instead of “air” and hence “upper airway” during the image segmentation process [19, 20].

One way of circumventing these accuracy issues is to calibrate the software packages using a phantom with known dimensions. Most previous studies have used either an acrylic airway model attached to a human dry skull [8] or an acrylic block to mimic the upper airway [6, 9]. Such phantoms are, however, commonly manufactured in simple, generic forms and sizes, and therefore do not resemble the attenuation and scattering profiles of human bones, soft tissues, and upper airway structures. The phantom used in the present study was composed of 3D printed hard tissue-equivalent gypsum combined with soft tissue-equivalent silicon [21] and fiducial markers (Figure 3). These components offered the unique possibility of assessing the reliability and accuracy of upper airway measurements in real life- like conditions. However, one general limitation of using phantoms in validation studies is their static nature that consequently does not portray involuntary head motion [22] and physiological movements of the upper airway during breathing [23].

One limitation of the present study was that only one CBCT scanner and only three imaging software packages were included. To date, there are a plethora of different software packages on the market for 3D analysis of the upper airway (at least 18 in 2011) [3]. Future research should focus on evaluating multiple software packages and different imaging modalities in dynamic settings. Another limitation was that the gold standard measurements of the upper airway were obtained from an STL file of a phantom. Therefore, a measurement uncertainty of up to 0.2 mm may have been introduced during the 3D printing procedure of manufacturing the phantom [24]. Nevertheless, this uncertainty can be considered clinically insignificant [25].

## **Conclusion**

All three software packages assessed in this study offered reliable measurements of the volume, minimum cross-sectional area, and length of the upper airway. The length measurements of the upper airway were the most accurate in all software packages. All software packages underestimated the upper airway dimensions. The 3D printed anthropomorphic phantom that was used in this study offered a feasible method to validate software packages used for 3D analysis of the upper airway on CBCT images.

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## Chapter 5

### Three-dimensional imaging of the upper airway anatomy in obstructive sleep apnea: a systematic review

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## **Three-dimensional imaging of the upper airway anatomy in obstructive sleep apnea: a systematic review**

### **Abstract**

**Aim:** The pathogenesis of upper airway collapse in obstructive sleep apnea (OSA) patients is not fully understood. The aim of this study was to systematically review the literature to assess the most relevant anatomical characteristics of the upper airway related to the pathogenesis of OSA by analyzing the three-dimensional upper airway anatomy.

**Methods:** A PICO (population/patient, intervention, comparison, outcome) search strategy, focusing on upper airway anatomy of OSA patients, was conducted in the following databases: Medline (Pubmed), Excerpta medica database (EMBASE), Web of science, and Cochrane library. The studies in which three-dimensional images were made from the participants who were awake and in supine position during quiet breathing were selected in this systematic review.

**Results:** Of 758 unique retrieved studies, only 8 studies fulfilled the criteria for this systematic review. The minimum cross-sectional area of the upper airway of OSA patients, which is influenced by many factors, such as hard and soft tissues surrounding the upper airway, was significantly smaller than that of non-OSA patients.

**Conclusion:** Within the limitation of the selected studies, this systematic review suggested that the most relevant anatomical characteristic of the upper airway related to the pathogenesis of OSA is a small minimum cross-sectional area.

## **Introduction**

Obstructive sleep apnea (OSA) is a sleep-related breathing disorder, often associated with a compromised upper airway space and an increase in upper airway collapsibility [1]. Excessive daytime sleepiness, snoring, and reduction in cognitive functions are among the common symptoms of OSA [2]. The consequences of OSA are increased cardiovascular morbidity, neurocognitive impairment, and overall mortality [3-5]. OSA is a major public health problem affecting a significant portion of the population, and it is estimated that, in the general population, approximately 80 to 90% of patients meeting the criteria of at least moderate OSA remain undiagnosed [6]. Although it is assumed that both anatomical and neuromuscular factors are of significance in the pathogenesis of upper airway obstruction in OSA, the pathogenesis of this disorder is not fully understood [1].

Previous studies using different imaging techniques suggested that an abnormal anatomy of the upper airway is a key factor in the development of OSA [7-9]. Compared with non-OSA patients, OSA patients have in general a small upper airway [10], an oval airway shape [11], and a longer upper airway [12]. However, no consensus has been reached regarding the question which anatomical variables of the upper airway are the most relevant ones in the pathogenesis of OSA. Therefore, the aim of this systematic review is to assess the most important anatomical characteristics of the upper airway related to the pathogenesis of OSA by analyzing the three-dimensional (3D) upper airway anatomy.

## **Materials and methods**

### *Database search*

This systematic review was conducted according to the preferred reporting items for systematic review and meta-analyses (PRISMA) [13]. The search strategy, inclusion and exclusion criteria, data collection, and assessment methodology were carried out according to the protocol described in the following sections.

### *Search strategy*

A PICO-based (population/patient, intervention, comparison, outcome) search strategy was conducted using the following electronic databases: Medline (PubMed), Excerpta medica

database (EMBASE), Web of science, and Cochrane library (Table 1). The searches were performed on July 22<sup>nd</sup> 2014, and updated until July 14<sup>th</sup> 2015. The main search items were “obstructive sleep apnea”, “computed tomography”, “magnetic resonance imaging”, “cone beam computed tomography”, and “upper airway”. Free-text terms and keywords were used for searching in EMBASE, Web of Science, and Cochrane library. For PubMed, apart from free-text terms and keywords, medical subject headings (MeSH) were also used (Table 2). Boolean operators (or, and) were applied to combine searches. No language restrictions were used.

Table 1 Systematic search strategy following the PICO system

Search strategy	Search items
P: Population/Patient	#1: obstructive sleep apnea #2: computed tomography
I: Intervention	#3: magnetic resonance imaging #4: cone beam computed tomography
C: Comparison	Controls
O: Outcome	#5: upper airway
Search combination	#1 and (#2 or #3 or #4) and #5
Electronic database	Medline (PubMed), Excerpta medica Database (EMBASE), Web of Science, Cochrane Library

#### *Data collection and inclusion/exclusion criteria*

Eligible studies were selected according to the inclusion and exclusion criteria through two phases. During the first phase, the title and abstract of the studies were examined by the first reviewer (HC). Inclusion criteria were: (1) adults diagnosed with OSA based on polysomnography (PSG, apnea hypopnea index (AHI), or respiratory disturbance index (RDI)); and (2) upper airway dimensions or proportions analysis (linear, area, volume, or shape) based on computed tomography (CT), magnetic resonance imaging (MRI), or cone beam computed tomography (CBCT) taken while awake. Exclusion criteria were: (1) editorials; (2) reviews; (3) case reports; (4) no control group; (5) animal experiment; and (6) publications not retrievable, neither on paper nor online.

During the second phase, the full texts of all potentially eligible studies identified at the first phase were examined independently by two reviewers (HC and GA). According to PRISMA

2009 flow diagram [14], during full-text assessment, irrelevant studies were excluded for the following reasons: (1) studies without comparison of upper airway anatomy between OSA patients and normal subjects; (2) studies on upper airway anatomy analysis without linear, area, volume, or shape measurements; (3) studies on upper airway anatomy analysis at certain levels instead of covering the full region from the hard palate to the base of epiglottis; (4) 3D images taken during maximum inspiration/expiration phases; and (5) OSA patients with comorbidities (such as stroke). Information was extracted from the finally selected studies by one reviewer (HC) and confirmed by the other reviewer (GA). During review process, discrepancies between the first two reviewers were solved by discussion with the other reviewers (FL and PvdS) to reach a consensus. A manual search of potentially missing studies was completed by screening the references of the studies identified at the second phase.

#### *Quality assessment*

Currently, there is no single universal tool to assess the risk of bias for different studies [15]. In order to assess the risk of bias of the selected studies, a custom assessment tool of study quality and risk of bias was formulated by following the suggestions from the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) checklist and the recommendations by Viswanathan *et al.* [15, 16]. This assessment tool consists of 16 items with a maximum score of 16. Quality scores were divided into five categories: poor (score $\leq$ 8), fair (score=9-10), good (score=11-12), very good (score=13-14), and excellent (score=15-16) [17].

#### *Data synthesis*

Due to the heterogeneity of the participants, the software, and the upper airway boundary definition among the finally selected studies, a meta-analysis could not be carried out.

Table 2 Electronic database search terminology

Item	Medline (PubMed)		Excerpta medica database (EMBASE)		Web of science		Cochrane library	
	Search terminology	Results	Search terminology	Results	Search terminology	Results	Search terminology	Results
1	'obstructive sleep apnea'/[ALL Fields] or 'sleep apnea, obstructive' [MeSH Terms]	22,022	'obstructive sleep apnea'/exp or 'obstructive sleep apnea'	48,979	topic: obstructive sleep apnea	43,985	obstructive sleep apnea	2,295
2	'computed tomography' [ALL Fields] or "tomography, x-ray computed"[MeSH Terms]	430,500	'computed tomography' exp/ or 'computed tomography'	683,022	topic: computed tomography	612,368	computed tomography	9,343
3	'magnetic resonance imaging'/[ALL Fields or magnetic resonance imaging"[MeSH Terms]	391,080	'magnetic resonance imaging'/exp or 'magnetic resonance imaging'	619,777	topic: magnetic resonance imaging	583,832	magnetic resonance imaging	10,565
4	'cone beam computed tomography'/exp or 'cone beam computed tomography'	6,607	'cone beam computed tomography'/exp or 'cone beam computed tomography'	7,468	topic: cone beam computed tomography	11,640	cone beam computed tomography	151
5	'upper airway'/exp or 'upper airway'	14,388	'upper airway'/exp or 'upper airway'	18,053	topic: upper airway	31,553	upper airway	1,626
Total	#1 and (#2 or #3 or #4) and #5	351	#1 and (#2 or #3 or #4) and #5	604	#1 and (#2 or #3 or #4) and #5	498	#1 and (#2 or #3 or #4) and #5	6



Table 3 Quality assessment of the eight selected studies\*

	A. Selection assessment						B. Measurement assessment							C. Interpretation assessment			
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	
First author [ref.]	Prospective study	N>30	OSA group (PSG)	Matched control group	Inclusion/exclusion criteria	Observer blinded	VP	OP	Software	Linear	Area	Shape	Volume	Statistical tests	ICC	Complete reporting the results	Total
Abramson [24]	0	1	0	0	0	0	1	1	1	1	1	1	1	0	0	0	8
Ciscar [20]	1	0	1	1	1	0	1	0	0	1	1	0	0	1	0	1	9
Galvin [23]	1	1	1	1	0	0	1	1	0	0	1	0	0	0	0	1	8
Hora [8]	1	1	1	1	1	0	1	1	1	1	1	0	0	1	0	1	12
Ogawa [21]	0	0	1	0	0	0	1	1	1	1	1	1	1	1	0	1	10
Peh [22]	1	1	1	1	0	0	1	1	0	1	1	0	0	1	0	1	10
Schwab [18]	1	1	1	0	1	0	1	0	1	1	1	0	0	1	0	1	10
Shigeta [19]	1	1	1	0	0	0	1	1	1	1	0	0	0	1	1	1	10
Total	6	6	7	4	3	0	8	6	5	7	7	2	2	6	1	7	

\* Scored as 1 (completely fulfills the criterion) or 0 (does not completely fulfill the criterion). ICC: inter-examiner correlation coefficient; N: sample size; OP: oropharynx; OSA: obstructive sleep apnea; PSG: polysomnography; VP: velopharynx.

## Results

### *Search results*

The search results are shown in Figure 1. In the first phase, 1461 potentially relevant studies were obtained following the PICO search strategy. After removing the 703 duplicates, 758 studies were left for the first phase screening. Based on the first inclusion and exclusion criteria, 736 studies were removed and only 22 studies moved into the second phase. 20 studies were in English and two studies in Chinese, which were reviewed by the first author of this current study. After the second phase of selection, eight studies were considered to be suitable for this systematic review.

### *Quality assessment of studies*

The quality assessment of the selected eight studies is summarized in Table 3. According to quality scores of the selected studies, the quality of one study was good [8], that of five studies was fair [18-22], and the quality of two studies was poor [23, 24]. Regarding the study design analysis, none of the eight studies reported a power calculation and the blinding of observers. There were four studies recruiting matched control groups [8, 20, 22, 23]. In terms of data measurements, all studies included at least one measurement of the upper airway dimension (linear, area, volume, or shape). For data analysis, only one study tested the reliability of the measurements and reported the intra-class correlation coefficient (ICC), which ranged from 0.997 to 0.999 [19].

### *Study design*

Characteristics of the selected eight studies are summarized in Table 4. There were two retrospective studies and six prospective studies. The participants in these studies covered the entire spectrum of OSA, ranging from mild to moderate and severe. All OSA patients underwent PSG, with AHI or RDI as the diagnostic outcome measurement, but the cut-off point for the diagnosis of OSA was different between these studies (Table 4). Some studies used  $AHI > 5$  [19, 23] or  $AHI > 10$  [8, 20] for the diagnosis of OSA. Some studies also used AHI, but did not mention their cut-off point [21, 22]. Besides, the other studies used  $RDI > 15$  for the diagnosis of OSA [18, 24]. The OSA patients and control groups were matched by body mass index (BMI) in two studies [20, 22] and by gender and age in two studies [8, 22]. Both

men and women were included in all, except one study, in which only men were included [8].

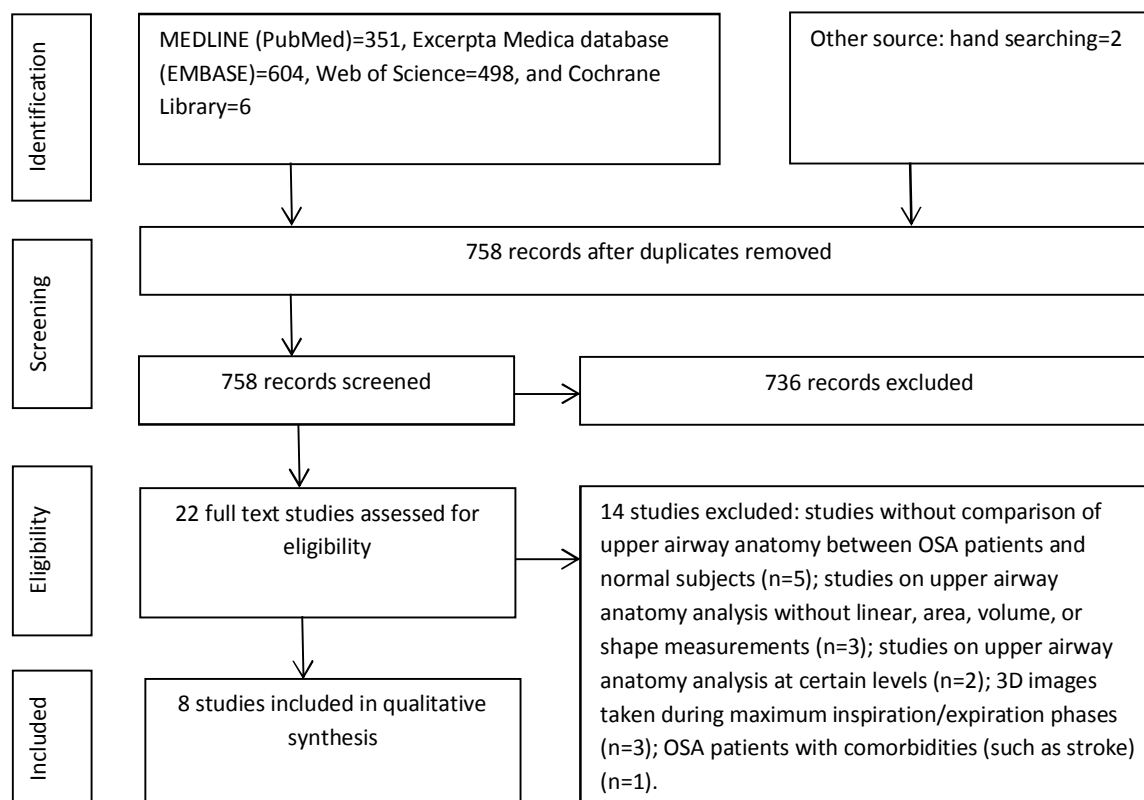


Figure 1. Flow diagram for study selection. OSA: obstructive sleep apnea.

### *Study measurements*

All studies except two [22, 23] mentioned that software was used for the upper airway segmentation. 3D images taken in all studies covered the region between the hard palate and the base of epiglottis, but the definition of the inferior boundary of the upper airway varied among studies. For example, one study choose the base of the epiglottis [24], while others choose the top of epiglottis [19] or the second cervical vertebrae [21] as the inferior boundary of the upper airway.

Table 4 Characteristics of the eight selected studies\*

First author [ref.]		Abramson [24]	Ciscar [20]	Galvin [23]	Hora [8]	Ogawa [21]	Peh [22]	Schwab [18]	Shigeta [19]
Study design	Study type	Retrospective	Prospective	Prospective	Prospective	Retrospective	Prospective	Prospective	Prospective
	Severity of OSA				AHI:			RDI:	AHI:
	Cut-off of OSA	RDI: 55,0±23,9 RDI=15	AHI: 29,8±3,8 AHI=10	AHI: 20-102 AHI=5	44,2±20,2 AHI=10	AHI: 23,4±9,59 NR	AHI: 41,3±21,8 NR	51,6±30,3 RDI=15	24,7±16,55 AHI=5
	Sample size	15 OSA; 17 non-OSA 10M/5F; 11M/6F	17 OSA; 8 non-OSA 14M/3F; 6M/2F	11 OSA; 24 non-OSA 8M/3F; 19M/5F	37 OSA; 14 non-OSA	10 OSA; 10 non-OSA 2F/8M; 4F/6M	25 OSA; 25 non-OSA NR; 23M/2F	26 OSA; 21 non-OSA 24M/2F; 14M/7F	25 OSA; 20 non-OSA 19M/6F; 12M/8F
	Gender				Males				
	Race	NR	NR	NR	NR	NR	Chinese	NR	Japanese
	Age(year)	36.4 ± 14.2; 33.7 ± 14.8	46.4 ± 9; 39 ± 8;	53,4±17,4; 43±10,7	47,9±9,6; 50,0±10,2 45,4±3,2;	52.9 ± 14.7; 45.4±19.5	44.8±8.3; 44.1 ± 11.1	43,2±11,8; 34,3±7,7 44,5±3,8;	56,0±12,38; 6,7±15,36
	NC(cm)	NR	NR 29.8 ± 3.8;	NR	43.2±2.5* 35.5±4.7;	NR 29.5 ± 9.05;	NR 26.7±4;	36,6±3,5 32,5±5,3;	NR 24,5±2,94;
	BMI	NR	27.8 ± 4	NR	31.5±2.7* Age and gender	23.1±3.05* NR	25.9±3.4 Age, gender, BMI	23,1±3,4* NR	22,0±3,94* NR
	Matched	NR	BMI	Weight					
Study measurements		CT	MRI	CT	MRI	CBCT	CT	MRI	CT
	Imaging technique								
	Position	Supine	Supine	Supine	Supine	Supine	Supine	Supine	Supine
	Software	3-D Slicer	Sun-Sparcs 20	NR	Philips Easy Version	Amira	NR	VIDA	Amira 3.1
	AP (mm)	10.1 ± 5,6; 10.9 ± 4.1	10.6 ± 5,5; 16.4 ± 2.3*	NR	AP of retroglossal: 6.2 ± 6.0; 5.2±2.9	4.6 ± 1.2; 7.8 ± 3.31*	AP of oropharynx: 5.8±3.5; 8±2.8*;	4,7±2,5; 5,8±2,4;	NR
	Lat (mm)	22.6±7,8; 22.3±7,7	6.4±2,6; 13.9±2,6*	NR	Lat of retroglossal: 9.3±4,1; 13.7±6,1*	11.6 ± 4,5; 16.2 ± 6,8	NR	6,7±4,5; 12,9±4,0*	NR
	Length (mm)	76.7 ± 11,1; 66,3±10,1*	NR	NR	NR	NR	NR	NR	45,1±6,61; 47,5±8,26
	CSA <sub>min</sub> (mm <sup>2</sup> )	61.5 ± 44,7; 73.9 ± 39,2	35,3±23,5; 103,2±10*	40,4±44,5; 77,8±88,6*	Area of retroglossal: 69,5±115,7; 72,2±71,0	45,8 ± 17,5; 146,9±111,7*	Area of velopharynx: 78,2±50,1; 173±97,6*	29,3±24,1; 64,4±39,9*	NR
	Volume (cm <sup>3</sup> )	12.5 ± 6,9; 12,3±4,6	NR	NR	NR	4,9 ± 1,8; 6,0 ± 1,8	NR	NR	NR
	Shape	0.38 ± 0,9; 0,42 ± 1,4	0,76; 0,52	NR	NR	0,39 ± 0,26; 0,48 ± 0,49	NR	NR	NR
	Factor related to upper airway	NR	NS	NR	NR	BMI	NR	Thickness of the lateral pharyngeal muscular walls	NR
	Predictor of OSA	Airway length; Airway shape.	NR	Oropharyngeal compliance; Nasal airway size.	Lateral dimension at retroglossal level	NR	NR	NR	The proportion between soft palate length and upper airway length ICC: 0.998
Data analysis	Reliability	NR	NR	NR	NR	NR	NR	NR	
Summary (results and conclusion)		The airway length was significantly increased in OSA patients.	Velopharynx is smaller in OSA patients.	OSA patients are characterized by a small, collapsible oropharyngeal and nasopharyngeal airway.	The transversal diameter of the airways at the retroglossal level was found to be an independent predictor of the presence and severity of OSA.	The OSA group presented a concave or elliptic shaped airway and the non-OSA group presented a concave, round, or square shaped airway.	CSA of velopharynx and hypopharynx differed significantly.	Minimum airway area was significantly smaller in apneic compared with normal subjects and occurred in retro-palatal region.	No difference between groups was found in upper airway length.

\* AHI: apnea hypopnea Index, apnea defined as cessation of airflow for > 10 s and hypopnea defined as a 50% reduction in airflow for 10 s associated with a >4% fall in oxygen saturation and/or an arousal; AP: the anterior-posterior dimension of the minimum cross-sectional area; BMI: body mass index; CBCT: cone beam computed tomography; CSA<sub>min</sub>: minimum cross-sectional area; CT: computed tomography; F: female; ICC: inter-examiner correlation coefficient; Lat: the lateral dimension of the minimum cross-sectional area; M: male; NC: neck circumference; NR: not reported; NS: not significant; MRI: magnetic resonance imaging; OSA: obstructive sleep apnea; RDI: respiratory disturbance index, defined as the mean number of apneas, hypopneas, and respiratory effort-related arousals (RERAs) per hour of sleep.

### *Upper airway anatomy analysis*

Table 5 shows the measurements used in the upper airway analysis by the eight selected studies. Most authors have chosen the anterior-posterior (AP) and lateral dimension of the minimum cross-sectional area ( $CSA_{min}$ ) and  $CSA_{min}$  itself as the primary outcomes. In the four studies about the AP dimension measurement [18, 20, 21, 24], there were two studies that found a significant difference in the AP dimension between OSA patients and non-OSA patients [20, 21], while two studies did not find this difference [18, 24]. Compared with non-OSA patients, OSA patients had a smaller  $CSA_{min}$  of their upper airway [18, 20, 21, 23]. Two studies that recruited matched groups found that OSA patients had a significant smaller  $CSA_{min}$  at oropharynx level than non-OSA patients (Figure 2a) [20, 23]. Three studies except one that recruited unmatched groups also found this difference in  $CSA_{min}$  between OSA patients and non-OSA patients (Figure 2b) [18, 21, 24]. To specify the matching factor BMI, two studies recruited groups matched for BMI [20, 22], four studies recruited groups unmatched for BMI [8, 18, 19, 21], and another two studies did not mention whether their groups were matched for BMI or not [23, 24]. In total, there are six studies that calculated BMI of the participants [8, 18-22] and three of them did the measurement of  $CSA_{min}$  [18, 20, 21]. All of these three studies found that the OSA patients had a smaller  $CSA_{min}$  than non-OSA patients, whether the groups were matched for BMI or not (Figure 3) [18, 20, 21]. None of the eight studies found significant differences in the volume of the upper airway. In the three studies that involved upper airway shape measurement, there was no significant difference in the shape of upper airway between OSA patients and non-OSA patients [20, 21, 24]. In the selected studies, different factors were found to cause upper airway narrowing in OSA patients, e.g., elevated BMI and thick pharyngeal muscular walls [18, 21].

Table 5 Results analysis based on the eight selected studies\*

Variable	N=number of studies measuring the following variables	N=significant difference found between OSA and non-OSA	N=significant difference not found between OSA and non-OSA
AP	4	2	2
Lat	4	2	2
Length	2	1	1
$CSA_{min}$	5	4	1
Volume	2	0	2
Shape	3	0	3

\* AP: the anterior-posterior dimension of the minimum cross-sectional area;  $CSA_{min}$ : minimum cross-sectional area; Lat: the lateral dimension of the minimum cross-sectional area.

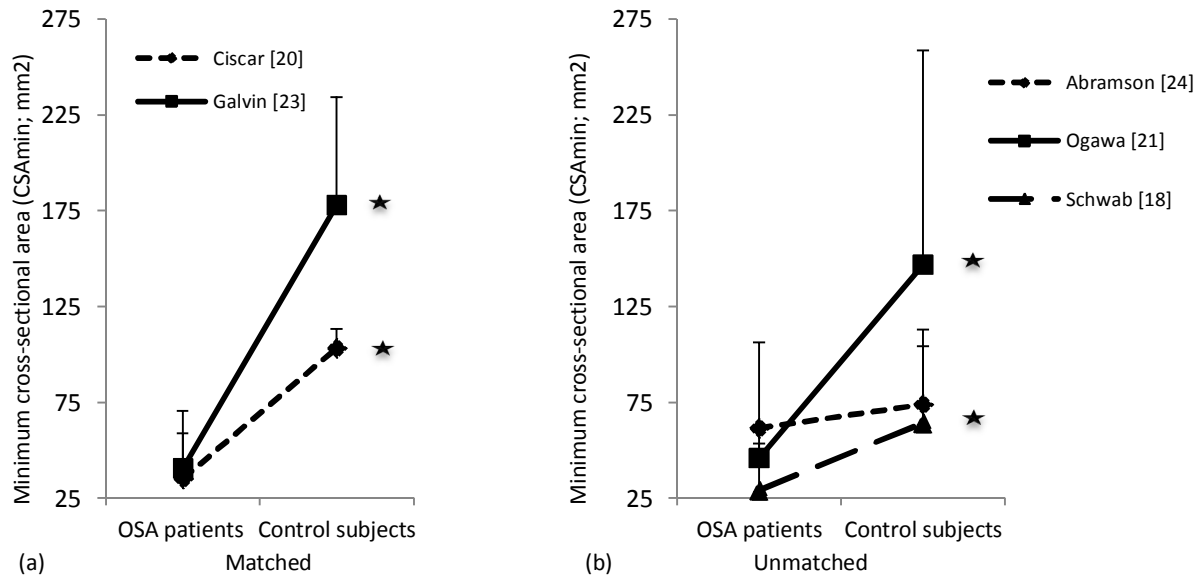


Figure 2. Mean and standard deviation of minimum cross-sectional area (CSAmin) at oropharyngeal level between obstructive sleep apnea patients and control subjects in matched (a) and unmatched (b) groups (matched for gender, age, weight, and/or BMI; only studies presenting the CSAmin are included; \*  $P < 0.05$ ).

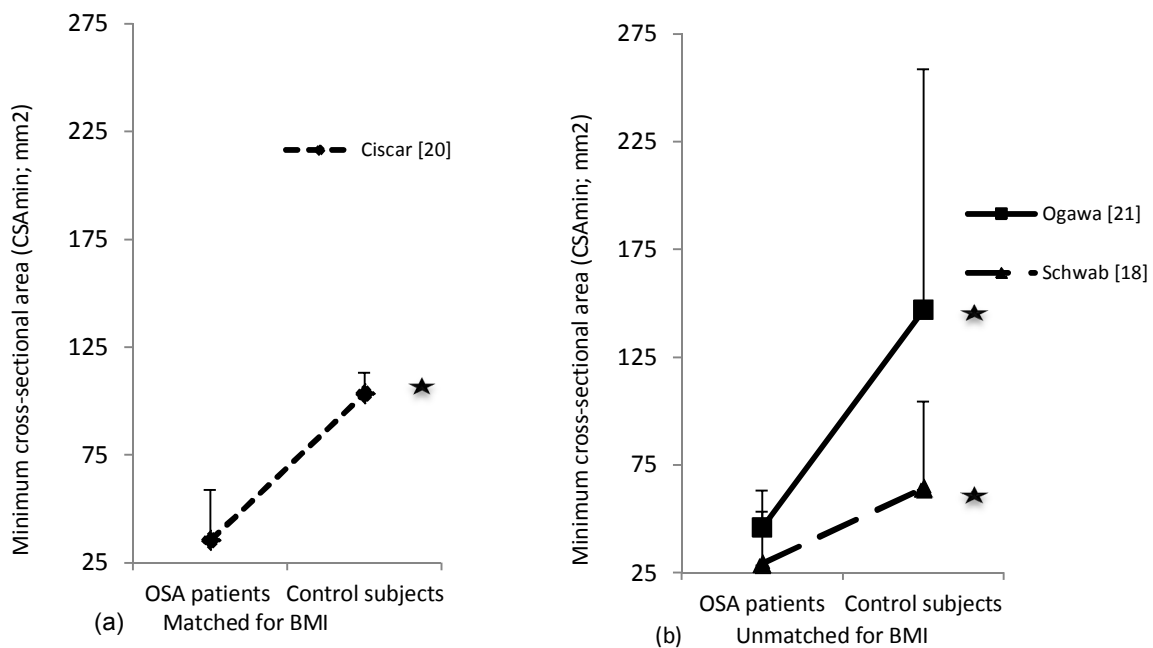


Figure 3. Mean and standard deviation of minimum cross-sectional area (CSAmin) at oropharyngeal level between obstructive sleep apnea patients and control subjects in matched (a) and unmatched (b) groups (matched only for BMI; only studies presenting the CSAmin are included; \*  $P < 0.05$ ).

## Discussion

The objective of this study was to systematically review the literature to assess the most important anatomical characteristics of the upper airway related to the pathogenesis of OSA by analyzing the 3D upper airway anatomy. From 758 unique titles, a total number of eight studies was included and the quality of these studies was evaluated in detail. This systematic review demonstrated that  $CSA_{min}$  is the most relevant variable to explain the role of the upper airway anatomy in the pathogenesis of OSA.

### *Limitations of this study*

There are several potential limitations in the database search process. Except for hand-searching, only four databases were chosen for this systematic review. However, as there were 703 duplicate citations, this review most likely covers all of the studies on this topic. Another limitation could be the terms used for search strategy. Both keywords and Mesh terms were used in these four electronic databases, which could increase the number of the studies and decrease the sensitivity of the results. To eliminate this limitation, all of the searched studies were reviewed following strict inclusion and exclusion criteria to guarantee the accuracy of the results.

### *The quality assessment of the studies*

Based on the quality assessment, there are several limitations in the methodology of the eight selected studies, such as recruitment of unmatched participants, not blinded measurements, and lack of reliability assessment (Table 3). Besides, in terms of the measurement assessment, the selected studies chose different anatomical measurements of the upper airway, which impeded the comparison between studies (Table 3). These limitations of the selected studies can contribute to the heterogeneity in the results of different studies.

Only three studies recruited participants that were matched for age, gender, and/or BMI [8, 20, 22]. The interaction between these factors (age, gender and/or BMI) with upper airway anatomy determines the risk of OSA [25]. The prevalence of OSA increases with age, with a peak between the ages of 55 to 64 years [26]. In adults, OSA is 2-3 times more prevalent in men compared with women [27]. Elevated BMI that could result in upper airway narrowing

is the most important risk factor for OSA [28, 29]. In Figure 3a, one study that recruited the groups matched for BMI found that the OSA patients had a smaller  $CSA_{min}$  than their controls, which suggested that BMI may not influence the difference in the upper airway size between the OSA patients and their controls [20]. Due to limited studies, it is difficult to draw strong conclusion about the influence of BMI on the upper airway size. Considering the above confounding factors, we recommend to recruit OSA and control groups matched for age, gender and BMI for future studies related to the role of the upper airway anatomy in the pathogenesis of OSA.

#### *Patients' condition during imaging procedure*

The anatomy of the upper airway is different between the supine and upright positions due to gravity [30]. Furthermore, the anatomy of the upper airway is also different between the awake and sleep state [31]. Therefore, the measurements done on the images taken in the awake state may not reflect the real anatomy of the upper airway in the sleep state. As OSA only occurs during sleep, it is better to examine the anatomy of the upper airway when the patients are asleep. However, it is hardly impossible to take images during natural sleep, and thus it is only scarcely performed [32-33]. In this context, drug-induced sleep could be an option, but drugs can have inhibitory effects on airway muscle tone and ventilator drive, thereby potentially confounding the imaging results [34]. In the eight selected studies, all the images were taken in the supine position during the awake state, which facilitates the comparison between the studies.

The wall of the upper airway moves during the breathing cycle resulting in changes in the anatomy of the upper airway during max inspiration/expiration phases [35]. The minimum cross-sectional area of the upper airway is smaller during max inspiration/expiration phases than during quiet breathing [36]. It is at this moment unclear if the collapse of the upper airway is more likely to occur at the end of the inspiration [37] or at the end of the expiration [38]. Therefore, we included only the studies performing 3D images during quiet breathing in order to ascertain the consistence of the methods of the selected studies in our systematic review.

#### *The underlying mechanism of upper airway dimensional changes in OSA patients*



All of the five studies that involved CSA<sub>min</sub> measurement [18, 20, 21, 23, 24], except one [24], found that OSA patients had a significantly smaller CSA<sub>min</sub> than non-OSA patients. However, the question remains what the underlying mechanism is related to these upper airway dimensional changes in OSA patients. Schwab *et al.* suggested that examination of the soft tissue structures surrounding the upper airway can lead to an understanding of these airway changes, and concluded that the lateral pharyngeal walls, in addition to the soft palate and tongue, should be considered as important structures in determining airway caliber [18]. However, it is still unclear how various soft tissue structures interact mechanically to control upper airway dimensions, and which changes in soft tissue structures lead to a compromised upper airway size. Furthermore, obesity is the most common predisposing factor for OSA [39]. Previous studies showed that obese OSA patients had a narrowed upper airway even during wakefulness [40, 41]. The mechanism by which obesity leads to a narrowed upper airway in OSA patients is, however, unknown [28, 29]. Developing such knowledge is essential to fully understand the relative role of obesity in the dimensional changes of the upper airway in the OSA patients.

The anatomical abnormality of hard tissue structures is also related to the presence of OSA. Shelton *et al.* [42] brought forward the “mandible enclosure” hypothesis and concluded that the severity of OSA is related to the size of the region enclosed by the mandible, viz., the smaller the area of the mandibular enclosure, the more severe the OSA symptoms are. It was suggested that maxillary and mandibular malformations are likely to have direct etiological roles in OSA by reducing the upper airway size [43, 44]. However, further investigation is still needed to understand how hard tissue structures surrounding the upper airway control the upper airway dimensions.

Also a combination of the soft tissue enlargement and the hard tissue reduction could lead to increased risk for OSA [43, 45]. Recently a combined variable, that is the ratio of soft tissue to craniofacial space (STCF) was brought forward and investigated [45]. In adolescents, the value STCF of OSA patients was higher than that of non-OSA patients, suggesting that increasing soft tissues within the craniofacial space increases the risk for OSA [45]. However, it still needs to be tested whether this variable is also higher in adult OSA patients. In this way, the role of STCF in the pathogenesis of the OSA could be further illustrated.

Furthermore, upper airway collapse in OSA patients could be caused not only by structural abnormalities, but also by neuromuscular abnormalities, such as muscle dysfunction [46]. The dysfunction of dilating muscles of the upper airway could predispose to OSA [46]. Adequate contraction of the genioglossus could keep the upper airway open during sleep, while fatigue, neural injury, and myopathy might cause the genioglossus to malfunction in OSA patients [47, 48]. Besides, some other factors may also account for the pathogenesis of OSA. For example, lung volume could be a causative factor [49-51]. A relatively small change in lung volume has an important effect on the upper airway size in OSA patients [52, 53]. When lung volume decreases, the cross-sectional area of the upper airway decreases, which causes a substantial increase in sleep disordered breathing in OSA patients [49].

Moreover, some neuroventilatory factors, such as unstable ventilatory control (high loop gain) [54-56], and a low respiratory arousal threshold [49, 57, 58] may also play an important role in the presence of OSA. It has been demonstrated that the loop gain is high in severe OSA patients compared to mild OSA patients [59]. Also, a lower arousal threshold is likely to be an important contributor to the pathogenesis of OSA in approximately one third of the patients [55, 57, 60, 61]. However, to our best knowledge, there is no literature about how the loop gain and the arousal threshold influence the upper airway size. There is at this moment no evidence to show that our main result of this systematic review, which is that there is a significant difference in the upper airway size (eg.,  $CSA_{min}$ ) between OSA and non-OSA patients, could be explained by either the loop gain or by the arousal threshold. Based on current literature, it is hypothesized that the etiology of the OSA is multifactorial and varies considerably between individuals [55]. Therefore, one important objective of future research should be the clarification of the relative contributions and the interaction of the above factors to the development of recurrent sleep-related collapse of the upper airway in OSA patients [62-64]. This kind of research will help us understand the pathogenesis of OSA which could result in the development of new effective treatment strategies for OSA patients.

#### *Presence of OSA based on the images*

Based on different imaging techniques, four studies found several predicting factors for the presence of OSA [8, 19, 23, 24]. Abramson et al., concluded that the presence of OSA was associated with an increase in airway length and a more circular airway shape [24]. Besides,

there are also other factors, which could be used to predict the presence of upper airway obstructions in OSA patients, such as oropharyngeal compliance, nasal airway size, and the proportion between soft palate length and upper airway length [19, 23]. In the eight selected studies, there was only one study using a cut-off point to “screen” OSA patients, which concluded that a lateral dimension of the upper airway at retroglossal level of more than 12mm was especially useful to rule out severe OSA patients (AHI>30) [8]. All these studies can help us further unraveling the pathogenesis of OSA.

## Conclusion

Within the limitation of the selected studies, this systematic review suggested that the most relevant anatomical characteristic of the upper airway related to the pathogenesis of OSA is a small minimum cross-sectional area.

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## **Chapter 6**

### **Aerodynamic characteristics of the upper airway: obstructive sleep apnea patients versus control subjects**

**Chen H**, Li Y, Reiber Johan H.C., de Lange J, Tu X, van der Stelt PF, Lobbezoo F, Aarab G. Aerodynamic characteristics of the upper airway: obstructive sleep apnea patients versus control subjects. (Submitted)





## **Aerodynamic characteristics of the upper airway: obstructive sleep apnea patients versus control subjects**

### **Abstract**

**Aim:** To determine the most relevant aerodynamic characteristic of the upper airway related to the collapse of the upper airway in obstructive sleep apnea (OSA) patients; and to determine the correlation between the most relevant aerodynamic characteristic(s) of the upper airway and anatomical characteristics of the upper airway in OSA patients.

**Methods:** 31 mild to moderate OSA patients (mean $\pm$ SD age = 43.5 $\pm$ 9.7 yrs) and 13 control subjects (mean $\pm$ SD age = 48.5 $\pm$ 16.2 yrs) were included in this prospective study. The diagnosis of OSA patients was based on an overnight polysomnographic recording. To exclude the presence of OSA in the control subjects, they filled out a validated questionnaire to determine the risk of OSA. NewTom5G cone beam computed tomography (CBCT) scans were obtained from both OSA patients and control subjects. Computational models of the upper airway were reconstructed based on CBCT images. The aerodynamic characteristics of the upper airway were calculated based on these computational models. Pearson correlation analysis was used to analyze the correlation between the most relevant aerodynamic characteristic(s) and anatomical characteristics of the upper airway in OSA patients.

**Results:** Compared with controls, the airway resistance during expiration ( $R_{ex}$ ) of the OSA patients was significantly higher ( $P=0.04$ ). There was a significant negative correlation between  $R_{ex}$  and the minimum cross-sectional area ( $CS_{Amin}$ ) of the upper airway ( $r=-0.41$ ,  $P=0.02$ ), and between  $R_{ex}$  and the volume of the upper airway ( $r=-0.48$ ,  $P=0.01$ ) in OSA patients.

**Conclusion:** Within the limitations of this study, we concluded that the most relevant aerodynamic characteristic of the upper airway in the collapse of the upper airway in OSA patients is  $R_{ex}$ . Therefore, the repetitive collapse of the upper airway in OSA patients may be explained by a high  $R_{ex}$ , which is related to the  $CS_{Amin}$  of the upper airway and to the volume of the upper airway.

## Introduction

Obstructive sleep apnea (OSA) is a sleep-related breathing disorder, characterized by recurrent obstructions of the airflow in the upper airway [1, 2], often associated with compromised upper airway space and an increase in upper airway collapsibility [3]. The most common complaints of OSA patients are excessive daytime sleepiness, unrefreshing sleep, poor concentration, and fatigue [4]. The real pathogenesis of OSA is still unknown [5]. However, both anatomical and functional abnormalities of the upper airway may play an important role in the repetitive collapse of the upper airway [6].

Various imaging techniques have been used for upper airway analysis, such as multi-detector row computed tomography (MDCT) [7] and magnetic resonance image (MRI) [8]. In recent decades, the use of cone beam computed tomography (CBCT) in dentistry has increased considerably. Due to its high spatial resolution, adequate contrast between the soft tissue and empty space, and the relatively low radiation dose compared to MDCT, CBCT can be used to analyze the upper airway anatomy three dimensionally [9]. Computational fluid dynamics (CFD) has been introduced for simulating airflow in OSA research using three-dimensional (3D) datasets from CBCT [10-12]. Comparison of the aerodynamic characteristics of the airflow within the upper airway using CBCT, between OSA patients and control subjects, can add insight into the recurrent obstructions of the airflow in the upper airway of OSA patients from the perspective of aerodynamics. So far, only one study compared the aerodynamic characteristics of OSA patients and control subjects, however with a relatively small sample size ( $n=8$ ) [12]. Based on that study, it is unclear which aerodynamic characteristic of the upper airway is the most relevant one in the collapse of the upper airway. In this study, we will compare the aerodynamic characteristics of the upper airway in OSA patients and controls within a relatively large sample size based on CBCT images.

The primary aim of this study was to determine the most relevant aerodynamic characteristic of the upper airway related to the collapse of the upper airway in OSA patients. The secondary aim was to assess the correlation between the most relevant aerodynamic characteristic(s) of the upper airway and the anatomical characteristics of the upper airway in OSA patients.

## Methods

### *Recruitment process*

OSA patients were recruited from a prospective study designed to compare two different mandibular advancement device (MAD) therapies in mild and moderate OSA patients (ClinicalTrials.gov.identifier: NCT02724865). The inclusion criteria were: 1. 18 years and older; 2. Ability to speak, read, and write Dutch; 3. Ability to follow-up; 4. Ability to use a computer with internet connection for online questionnaires; 5. Diagnosis with symptomatic mild or moderate OSA ( $5 \leq \text{apnea-hypopnea index (AHI)} < 30$ ); and 6. Expected to maintain current lifestyle (sports, medicine, diet, etc.).

The exclusion criteria were: 1. Untreated periodontal problems, dental pain, and a lack of retention possibilities for a MAD; 2. Medication used/related to sleeping disorders; 3. Evidence of respiratory/sleep disorders other than OSA (eg. central sleep apnea syndrome); 4. Systemic disorders (based on medical history and examination; e.g. rheumatoid arthritis); 5. Temporomandibular disorders (based on the function examination of the masticatory system); 6. Medical history of known causes of tiredness by day, or severe sleep disruption (Insomnia, PLMS, Narcolepsy); 7. Known medical history of mental retardation, memory disorders, or psychiatric disorders. 8. Reversible morphological upper airway abnormalities (e.g. enlarged tonsils); 9. Inability to provide informed consent; 10. simultaneous use of other modalities to treat OSA; and 11. Previous treatment with a MAD.

Control subjects were prospectively recruited from among those who were referred for various diagnostic reasons to the department of Oral and Maxillofacial Radiology of the Academic Centre for Dentistry Amsterdam (ACTA), The Netherlands. The inclusion criteria were age  $> 18$  years and CBCT images covering the entire upper airway from the level of the hard palate to the base of the epiglottis. The exclusion criteria were edentulousness, presence of a palatal cleft, presence of a craniofacial syndrome, and upper airway surgery in the past.

This study was approved by the Medical Ethics Committee of Academic Medical Center Amsterdam, protocol number: NL44085.018.13. Written informed consent was obtained from all participants.

### *Polysomnography (PSG)*

For the diagnosis of OSA, all patients included in this study underwent an overnight PSG recording (SOMNOscreen™ Plus PSG, Randersacker, Germany) at Onze Lieve Vrouwe

Gasthuis West (OLVG) in Amsterdam. PSG included the following variables: electroencephalogram, electro-oculogram, leg and chin electromyograms, electrocardiogram, pulse oximetry, body position, neck microphone, nasal cannula pressure transducer, and inductive plethysmography by means of thoracic and abdominal bands. The PSG recordings were scored manually in a standard fashion.<sup>13</sup> Apnea was defined as cessation of airflow  $\geq 90\%$  for at least 10 seconds. Hypopnea was defined as a decrease in airflow of more than 30% for at least 10 seconds, and an oxygen desaturation greater than 3% [13]. The mean apnea-hypopnea index (AHI) of the OSA group, defined as the number of apneas and hypopneas per hour of sleep, is shown in table 1.

#### *Questionnaire*

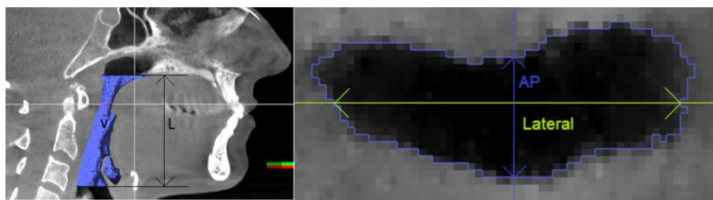
To evaluate their risk (%) of having OSA, each control subject was asked to complete a validated questionnaire on sleep apnea [14]. This questionnaire was specifically developed to calculate the risk (%) of having OSA. It consists of 3 sections with a total of 23 questions on personal characteristics, sleep behavior, and health condition. On the basis of their answers to the questionnaire, only the controls with a low risk (%) of having OSA were included in this study.

#### *Cone beam computed tomography (CBCT)*

The CBCT data sets of the OSA patients and control subjects were obtained using a NewTom 5G CBCT system (QR systems, Verona, Italy), according to the standard imaging protocol of the department of Oral and Maxillofacial Radiology of ACTA. During the imaging procedure, the patients were positioned in a supine position with the Frankfort horizontal (FH) plane perpendicular to the floor [15]. They were instructed to maintain light contact between the molars in natural occlusion, to keep quiet breathing, and to avoid swallowing and other movements during the scanning period. The exposure settings were 110 kV, 4 mA, 0.3 mm voxel size, 3.6 seconds exposure time (pulsed radiation), and 18-36 seconds scanning time, depending on the size of the patient [15]. The CBCT scans were imported into NNT software to obtain a standard head orientation. The re-orientation was performed by using the palatal plane as a reference (anterior nasal spine (ANS)-posterior nasal spine (PNS)) parallel to the global horizontal plane in the sagittal view and perpendicular to the global horizontal plane in the axial view) [16]. For further analysis, the images were saved as digital imaging and communications in medicine (DICOM) files.

### *Anatomical modeling of the upper airway*

Using Amira® (v4.1, Visage Imaging Inc., Carlsbad, CA, USA), the automatic process of the upper airway segmentation was performed following the same protocol as in a previous study [15]. First, a voxel set was built to include all of the information of the upper airway; second, a new mask was built with its thresholds ranging from -1000 to -400; and third, the superior boundary (i.e., the plane across the PNS parallel to the FH plane) and the inferior boundary (i.e., the plane across the base of the epiglottis parallel to the FH plane) of the upper airway were selected in the corresponding axial planes and put into the voxel set. Finally, all of the slices between the upper and lower boundaries were selected and put into the voxel set. The minimum cross-sectional area ( $CSA_{min}$ ), the anterior-posterior dimension of  $CSA_{min}$ , the lateral dimension of  $CSA_{min}$ , the volume of the upper airway, and the length of the upper airway were calculated based on the segmented upper airway (Figure 1) [15]. By surface triangulation, all the segmented upper airway models were subsequently converted into 3D standard tessellation language (STL) models.



A.

B.

Figure 1A. The segmented upper airway. V, volume of the upper airway; L, length of the upper airway. B. The minimum cross-sectional area ( $CSA_{min}$ ) on the axial slice of the cone beam computed tomography (CBCT) image. AP, anteroposterior dimension of  $CSA_{min}$ ; Lateral, lateral dimension of  $CSA_{min}$ .

### *Aerodynamic modeling of the upper airway*

The segmented STL models of the upper airway were exported into ANSYS ICEM CFD 17.0 (ANSYS, Inc., Canonsburg, Pennsylvania) to generate tetrahedral volume meshes. Depending on the complexity of the upper airway model, a typical grid consisted of about 1,000,000 tetrahedral cells. ANSYS Fluent (ANSYS, Inc.) was used to conduct flow simulation within the upper airway. The steady-state Reynolds Averaged Navier-Stokes (RANS) formulation with the  $\kappa$ - $\omega$  shear stress transport (SST) turbulence model was used to model aerodynamic characteristics within the upper airway [17]. The air within the upper airway was considered

adiabatic [18]. Least squares cell-based gradient was used for spatial discretization [19-20]. Second-order discretization schemes were used for the pressure and momentum equations. The coupling between the velocity and pressure fields was realized using the SIMPLE algorithm [12, 18, 21]. The density of the air within the upper airway is set as  $1.225 \text{ kg/m}^3$  and the viscosity of the air is set as  $1.79\text{E-}05 \text{ kg/m/s}$ . One boundary was set at the hard palate plane, and another boundary was set at the base of the epiglottis. The boundary condition consisted of axial velocity at the inlet plane, and no-slip boundary conditions for the upper airway wall. An inlet volume flow rate of  $166 \text{ ml/s}$  ( $10 \text{ L/min}$ ) was used in the flow simulation [22, 23].

The aerodynamic characteristics, viz., velocity, wall shear stress, and wall static pressure, were calculated in each upper airway model of OSA patients and controls during both inspiration and expiration. The inspiration phase was simulated by setting the inlet plane at the hard palate level and the outlet plane at the base of epiglottis. Vice versa, the expiration phase was simulated by setting the inlet plane at the base of epiglottis, and the outlet plane at the hard palate level.

Based on CFD calculations, the airway resistance (R) was determined using the following formulation:

$$R = \Delta P / Q,$$

where  $\Delta P$  is the total pressure drop between the inlet and outlet boundaries of the upper airway, and Q is the volume flow rate within the upper airway.

### *Statistical analysis*

Whether the data are normally distributed was tested by the Shapiro-Wilk W Test. The Mann-Whitney-U test (for non-normally distributed variables) or Chi-squared test (for categorical variables) and the independent t-test (for normally distributed variables) were used to compare the differences in the demographic characteristics between the OSA patients and their controls. Patient characteristics that were significantly different between the two groups were used as covariate(s) in the following between-group analysis. One-way multivariate analysis of covariance (MANCOVA) was used to compare the differences in aerodynamic and anatomical characteristics between the OSA patients and their controls. In the OSA group, Pearson correlation analysis was used to analyze whether significant

aerodynamic characteristic(s) are correlated with the anatomical characteristics of the upper airway. A significance level was set at  $p < 0.05$ .

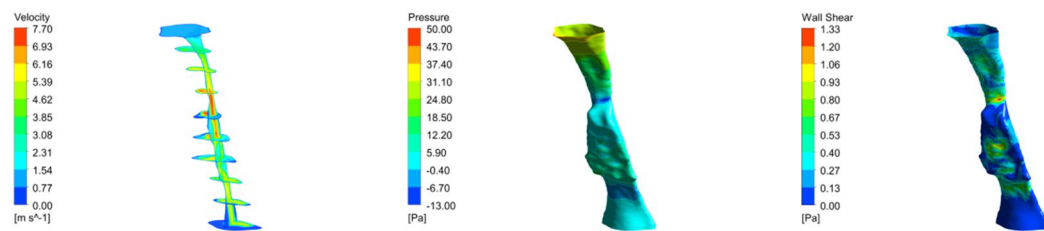
## Results

Contours of the velocity (m/s), wall shear stress (Pa), and wall static pressure (Pa) for an OSA patient and a control subject during inspiration are shown in Figure 2. Contours of the velocity (m/s), wall shear stress (Pa), and wall static pressure (Pa) for an OSA patient and a control subject during expiration are shown in Figure 3.

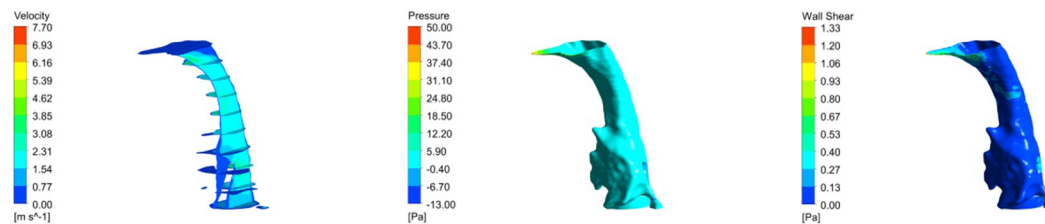
The demographic characteristics of the OSA patients and the control subjects are shown in Table 1. 31 OSA patients and 17 control subjects were recruited in the study, but four control subjects were excluded due to their high risk of having OSA. There was no significant difference in age between OSA patients and control subjects ( $P=0.21$ ). The OSA patients tended to have a higher body mass index (BMI) than their controls ( $P=0.06$ ). There was a significant difference in the gender distribution between OSA patients and control subjects ( $\chi^2=5.1$ ,  $P=0.02$ ): there were fewer females in the OSA group (32%) than in the control group (69%). Therefore, BMI and gender were entered as covariates in the below-described analyses of covariance.

The aerodynamic characteristics within the upper airway of OSA patients and control subjects are shown in Table 2. There was a significant difference in the airway resistance during expiration ( $R_{ex}$ ) between OSA patients and control subjects ( $F=2.90$ ,  $P=0.04$ ). Compared to control subjects, the  $R_{ex}$  of OSA patients was significantly higher. The other aerodynamic characteristics in OSA patients were not significantly different from those in control subjects ( $P=0.08-0.77$ ).



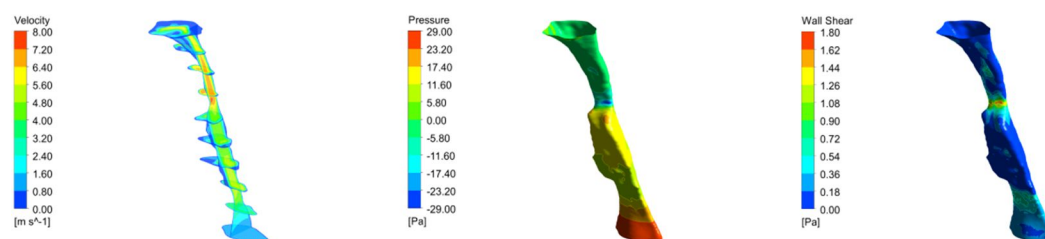


a.

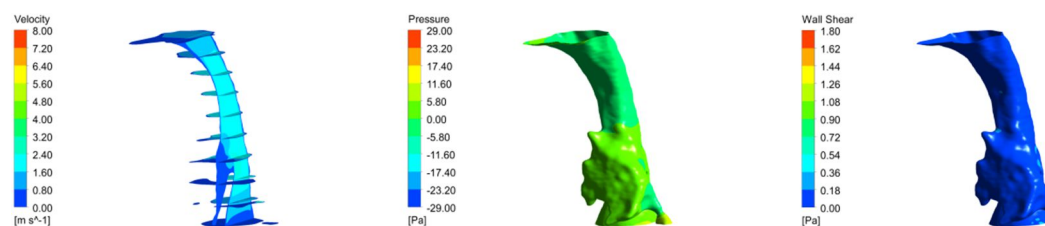


b.

Figure 2. Contours of the velocity (m/s), wall shear stress (Pa), and wall static pressure (Pa) of a typical OSA patient (a) and control subject (b) during inspiration. Scale: Red = higher value of the aerodynamic characteristics of the upper airway; blue = lower value of the aerodynamic characteristics of the upper airway.



a.



b.

Figure 3. Contours of the velocity (m/s), wall shear stress (Pa), and wall static pressure (Pa) of a typical OSA patient (a) and control subject (b) during expiration. Scale: Red = higher value of the aerodynamic characteristics of the upper airway; blue = lower value of the aerodynamic characteristics of the upper airway.

Table 1 Baseline demographic characteristics of obstructive sleep apnea (OSA) patients and control subjects

	OSA (31)	Control (13)	T/X <sup>2</sup>	P
	Mean±SD	Mean±SD		
Age (year)	43.5±9.7	48.5±16.2	-1.28(T)	0.21
Gender	32% (F)	69% (F)	5.1(X <sup>2</sup> )	0.02 *
BMI (kg/m <sup>2</sup> )	26.4±3.0	24.7±2.1	1.93(T)	0.06 <sup>a</sup>
AHI (time/hour)	15.0±6.8	N.A.		
Risk (%)	N.A.	11.7±8.6		

SD: standard deviation; BMI: body mass index; AHI: apnea-hypopnea index; N.A.: Not applicable. Risk (%): risk (%) of having OSA, obtained by completing Philips questionnaire. \* P<0.05; <sup>a</sup> tendency to significance.

Table 2 Results of computational fluid dynamics analysis of obstructive sleep apnea (OSA) patients and control subjects during respiration, with gender and body mass index as covariates

	OSA	Control	F	P
Subject	Mean±SD/ Median (Interquartile range)	Mean±SD/Median (Interquartile range)		
Maximum velocity during inspiration (m/s)	7.1±5.3	5.1±1.4	1.24	0.31
Maximum wall shear stress during inspiration (Pa)	2.4±2.3	2.4±1.4	0.37	0.77
Minimum wall static pressure during inspiration (Pa)	-5.0(-17.2, -3.4)	-5.7(-7.4, -1.9)	1.21	0.31
Airway resistance during inspiration (R <sub>in</sub> ) (Pa/L/min)	1.2(0.9, 2.5)	0.96(0.69, 1.1)	1.95	0.13
Maximum velocity during expiration (m/s)	7.7±5.9	4.9±2.7	2.27	0.09
Maximum wall shear stress during expiration (Pa)	1.26(0.7, 3.3)	0.83(0.6, 1.71)	2.25	0.09
Minimum wall static pressure during expiration (Pa)	-21.2±34.3	-8.0±11.3	2.37	0.08
Airway resistance during expiration (R <sub>ex</sub> ) (Pa/L/min)	1.5(0.7, 2.8)	0.73(0.42, 1)	2.90	0.04

\* P<0.05.

The anatomical measurements of the upper airway of OSA patients and control subjects are shown in Table 3. There were significant differences in the minimum cross-sectional area ( $CSA_{min}$ ) and the length of the upper airway between OSA patients and control subjects. The  $CSA_{min}$  of the upper airway of OSA patients, 65.5 (SD 30.7)  $mm^2$ , was significantly smaller than that of control subjects, 97.2 (SD 56.5)  $mm^2$  ( $F=4.26$ ,  $P=0.01$ ). The length of the upper airway of OSA patients, 65.2 (SD 8.1) mm, was significantly longer than that of control subjects, 56.1 (SD 8.1) mm ( $F=19.19$ ,  $P=0.00$ ).

Table 3 The mean ( $\pm$ SD) of the upper airway morphology of obstructive sleep apnea (OSA) patients and control subjects, with gender and body mass index as covariates

Variable	OSA	Control	F	P
Minimum cross-sectional area ( $CSA_{min}$ ) ( $mm^2$ )	65.5 $\pm$ 30.7	97.2 $\pm$ 56.5	4.26	0.01 *
Anterior-posterior dimension of the $CSA_{min}$ (mm)	5.1 $\pm$ 2.2	6.6 $\pm$ 2.1	1.39	0.26
Lateral dimension of the $CSA_{min}$ (mm)	13.4 $\pm$ 4.4	15.3 $\pm$ 4.7	4.13	0.01 *
Volume of the upper airway ( $cm^3$ )	11.2 $\pm$ 3.7	10.8 $\pm$ 4.1	2.10	0.12
Length of the upper airway (mm)	65.2 $\pm$ 8.1	56.1 $\pm$ 8.1	19.2	<0.001 *

\*  $P<0.05$ .

The correlation between  $R_{ex}$  and anatomical characteristics of the upper airway in OSA patients is shown in Table 4. There were significant negative correlations between  $R_{ex}$  and the  $CSA_{min}$  of the upper airway ( $r=-0.41$ ,  $P=0.02$ ) and between  $R_{ex}$  and the volume of the upper airway ( $r=-0.48$ ,  $P=0.01$ ).

Table 4 Correlation between airway resistance during expiration ( $R_{ex}$ ) and upper airway characteristics in OSA patients

	r	P
Minimum cross-sectional area ( $CSA_{min}$ ) ( $mm^2$ )	-0.41	0.02 *
Anterior-posterior dimension of the $CSA_{min}$ (mm)	-0.25	0.18
Lateral dimension of the $CSA_{min}$ (mm)	-0.24	0.19
Volume of the upper airway ( $cm^3$ )	-0.48	0.01 *
Length of the upper airway (mm)	-0.23	0.21

\*  $P < 0.05$ .

## Discussion

The aerodynamic characteristics within the upper airway of OSA patients and control subjects were compared based on their CBCT images. The most relevant aerodynamic characteristic of the upper airway was the airway resistance during expiration ( $R_{ex}$ ). Subsequently, the  $R_{ex}$  was correlated with anatomical characteristics of the upper airway in OSA patients. The  $R_{ex}$  was related to the  $CSA_{min}$  of the upper airway and to the volume of the upper airway.

### Limitations

One limitation is that we have no PSG recordings of the control subjects, because there was no medical need for these recordings. All control subjects, however, have completed a validated questionnaire to certify their low risk of having OSA [14]. Besides, severe OSA patients ( $AHI > 30$ ) were not included in this study. It is hypothesized that the  $R_{ex}$  of severe OSA patients will be much higher than the  $R_{ex}$  of controls due to their smaller  $CSA_{min}$  [24]. This hypothesis needs to be investigated in a future study.

### Confounders

There are many risk factors of OSA, such as higher age, elevated BMI, and male gender [25]. The prevalence of OSA increases with age, with a peak between the ages of 55 to 64 years [26]. It is suggested that BMI is the most important risk factor for OSA [27]. In this study, there was no significant difference in age between OSA patients and control subjects. In

addition, BMI of OSA patients tended to be higher than that of control subjects. In this study, 32% of the OSA patients were female, which is in accordance with the prevalence of OSA in the population [28]. In the control group, however, 69% of the patients were female. For that reason, in this study, the possible confounding effects of BMI and gender were taken into consideration in the statistical analyses.

#### *Aerodynamic characteristics of the upper airway*

In this study, we simulated the aerodynamic characteristics of OSA patients and control subjects. We found that the airway resistance of OSA patients is higher than that of control subjects during expiration, which suggests that  $R_{ex}$  may be the most relevant aerodynamic characteristic of the upper airway in the repetitive collapse of the upper airway in OSA patients. A previous study by Powell et al. also found that the airway resistance of the OSA patients is higher than that of controls subjects [12]. However, only four controls and four OSA patients were included in their study, and they did not perform between-group statistical analysis, because this was not the aim of their study [12]. Further, there is no consensus in literature if the collapse of the upper airway is more likely to occur during inspiration [29, 30] or at the end of the expiration [31-34]. Based on the present study, we concluded that the collapse of the upper airway in OSA patients probably occurs during expiration.

#### *Correlation between aerodynamic characteristics and anatomical characteristics of the upper airway in OSA patients*

In the current study, we found that OSA patients have a smaller  $CSA_{min}$  than control subjects, which is consistent with the conclusion of a systematic review wherein the most relevant anatomical characteristic of the upper airway related to the pathogenesis of OSA was a small  $CSA_{min}$  [24]. Further, we found a negative correlation between the  $CSA_{min}$  and volume of the upper airway on the one hand and the  $R_{ex}$  of the upper airway on the other hand. To the best of our knowledge, no studies have been performed on the correlation between the anatomical characteristics and aerodynamic characteristics of the upper airway in the OSA patients. However, one study reported that the change in the anatomical characteristics of the upper airway after treatment is related to the change in the airway resistance in OSA patients [12]. Powell et al. found that the airway resistance was significantly decreased after upper airway surgery, which was in agreement with an increase of the upper airway volume

by  $120 \pm 70\%$  [12]. Therefore, it is hypothesized that in OSA patients, the smaller  $CSA_{min}$  and volume of the upper airway will result in a higher  $R_{ex}$  of the upper airway and therefore to a higher risk of collapse during sleep.

#### *Clinical relevance*

Previous studies have concluded that various OSA therapies (viz., MAD, and upper airway surgery) change the airflow characteristics within the upper airway of the OSA patients [10-12, 35-42]. In responders, the airway resistance reduced significantly as a result of treatment, which shows that the repetitive collapse of the upper airway may indeed be explained by the high  $R$  of the upper airway [10-12, 36, 41, 42]. However, there is still a lack of knowledge on the comparison of the aerodynamic characteristics of the upper airway between responders and non-responders at baseline, which can help to recognize the non-responders before starting a treatment. These kinds of studies may improve our selection of OSA patients for a certain OSA treatment.

#### **Conclusion**

The airway resistance during expiration ( $R_{ex}$ ) is the most relevant characteristic of the airflow in the upper airway related to the upper airway collapse in OSA patients. Therefore, the repetitive collapse of the upper airway may be explained by the high  $R_{ex}$ , which is related to the  $CSA_{min}$  of the upper airway and the volume of the upper airway.

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## **Chapter 7**

### **Differences in three-dimensional craniofacial anatomy between responders and non-responders to mandibular advancement device therapy in obstructive sleep apnea patients**

**Chen H, Aarab G, de Lange J, van der Stelt PF, Lobbezoo F, Darendeliler MA, Dalci O.** Differences in three-dimensional craniofacial anatomy between responders and non-responders to mandibular advancement device therapy in obstructive sleep apnea patients. **(Submitted)**



## **Differences in three-dimensional craniofacial anatomy between responders and non-responders to mandibular advancement device therapy in obstructive sleep apnea patients**

### **Abstract**

**Aim:** To assess the differences in craniofacial anatomical structures between responders and non-responders to mandibular advancement device (MAD) therapy in obstructive sleep apnea (OSA) patients.

**Methods:** 105 OSA patients were retrospectively recruited to investigate whether any differences exist in the anatomical structures of the upper airway, mandible, maxilla, soft palate and tongue at baseline between responders and non-responders to MAD based on NewTom3G imaging. Data from 64 eligible patients were included in the study. All patients were provided with an adjustable acrylic MAD that was activated at 75% of the patients' maximum protrusion. Patients were instructed to titrate the splint until the maximum comfortable limit was reached. Follow up polysomnography (PSG) tests were done to assess OSA status with the MAD in situ. The patients were considered a responder if they achieved an apnea-hypopnea index (AHI)<10/hour with MAD, and a non-responder with an AHI≥ 10/hour. Several airway and craniofacial measurements were undertaken to compare responders vs non responders to MAD.

**Results:** There were 42 responders and 22 non-responders to MAD. There were no significant differences in the anatomy of the upper airway between responders and non-responders ( $P=0.17-0.97$ ). The length of the maxilla of the responders,  $52\pm 3.9$  mm, was significantly shorter than that of non-responders,  $54.8\pm 4.4$  mm ( $T=-2.65$ ;  $P=0.01$ ). The maxillomandibular enclose size of the responders,  $4675.4\pm 533.2$  mm<sup>2</sup>, was significantly smaller than that of the non-responders,  $4993.8\pm 588.6$  mm<sup>2</sup> ( $T=-2.19$ ;  $P=0.03$ ). The tongue area on the mid-sagittal plane of the responders,  $3263.9\pm 384.3$  mm<sup>2</sup>, was significantly smaller than that of non-responders,  $3484.9\pm 442.1$  mm<sup>2</sup> ( $T=-2.08$ ;  $P=0.04$ ). After controlling for the effect of BMI, however, there was no longer a significant difference in the tongue area between responders and non-responders ( $F=2.39$ ;  $P=0.13$ ).

**Conclusion:** OSA patients with a shorter maxillary length, a smaller maxillomandibular

enclose size, and a small tongue area may respond better to MAD treatment than patients with a longer maxillary length, a larger maxillomandibular enclosure size, and a large tongue area. However, after controlling the effect of BMI, there no longer was a significant difference in the tongue area between responders and non-responders.

## Introduction

Obstructive sleep apnea (OSA) is a sleep-related breathing disorder, often associated with a compromised upper airway space and an increase in upper airway collapsibility [1]. Mandibular advancement splints (MAD) are indicated for patients with mild to moderate OSA and in patients with severe OSA that refuse or are unable to tolerate continuous positive airway pressure (CPAP) therapy [2-5]. Although OSA patients prefer MAD over CPAP, the reported success rates with MAD have a large distribution, ranging from 30% to 81%. [6]. Therefore there is a need for ongoing research to find predictors of treatment response to MAD therapy in order to reduce waste of resources [3].

The anatomical and functional abnormalities of the upper airway play an important role in OSA [7]. Some studies found that the upper airway anatomy of non-responders to MAD was different from that of responders [8-16], while others found no difference [17, 18]. In addition, the upper airway is surrounded by hard tissues such as the maxilla and mandible, and soft tissues such as the soft palate and tongue. It is suggested that there are many skeletal factors related to the treatment outcome of MAD, such as the position of the maxilla and the mandible relative to the base of the skull [8]. Cephalometric studies have reported that craniofacial measurements, such as a longer maxilla, smaller overjet, shorter soft palate, mandibular plane-to-hyoid distance, facial height, and reduced retropalatal airway space, are associated with MAD treatment success [19-21]. However, there are also some inconsistencies amongst studies. Some studies found that responders had a retrognathic mandible [8, 16, 22], while others did not confirm this [14]. These contradictory results may be due to the multifactorial nature of OSA pathogenesis as well as the use of different anatomical variables, imaging techniques, treatment device designs, and small sample sizes.

Therefore, it is difficult to draw a solid conclusion on whether or not there are differences in the anatomical structures between responders and non-responders at baseline. It was suggested that the anatomical imbalance between the soft and hard tissues play an important role in the treatment outcome of MAD [23, 24]. Also in the last decade, cone beam computed tomography (CBCT) has come into use more widely in dentistry. CBCT has a high spatial resolution and a low radiation dose as compared to medical CT [25]. It is possible

to perform a three-dimensional (3D) analysis of the anatomical structures, including the upper airway, the hard tissue, and the soft tissue surrounding the upper airway of responders and non-responders using CBCT. Studies investigating craniofacial anatomy of responders versus non-responders to MAD treatment using CBCT are limited [26-28]. Therefore, the aim of this study was to assess the differences in craniofacial anatomical structures and the anatomical balance of the dimensions of the soft and hard tissues between responders and non-responders to MAD treatment within a large sample based on CBCT images.

## **Material and methods**

### *Patient selection*

This retrospective cohort study includes data obtained from 105 patients undergoing MAD therapy for the management of their OSA [19, 21]. Ethics approval was obtained from the Ethics Review Committee of the Sydney Local Health Network and written informed consent was obtained from all subjects. The patients included in this study were selected based on the following inclusion criteria: at least two symptoms of OSA (snoring, witnessed apneas, fragmented sleep, daytime sleepiness) and evidence of OSA during polysomnography (PSG) at baseline with an apnea-hypopnea index (AHI)  $\geq 10$ /hour of sleep, sound dentition with no active periodontal or restorative problems and no temporomandibular joint disorders.

A total of 105 patients were recruited for this study. Forty-one patients were excluded from the study because of dental pathology that could interfere with MAD treatment, refusal to participate in the study, or incomplete data (Figure 1). The second PSG with the MAD in situ was to assess treatment response, responders were defined by a treatment AHI < 10/hour, and non-responders as patients with a treatment AHI  $\geq 10$ /hour [20].

### *Mandibular advancement device (MAD)*

The MAD was a custom made two piece adjustable splint (SomnoMed® Ltd, Sydney, Australia). The maximum mandibular advancement was determined with a George Gauge (Great Lakes Orthodontics, Tonawanda, NY). The splints were constructed with 75% of the maximum mandibular protrusion for each subject. During 6 weeks, a daily titration of 0.2 mm bilaterally was performed, until the maximum comfortable level of the mandibular

advancement was reached. After this titration period, a second PSG was obtained with the MAD in situ to assess treatment response.

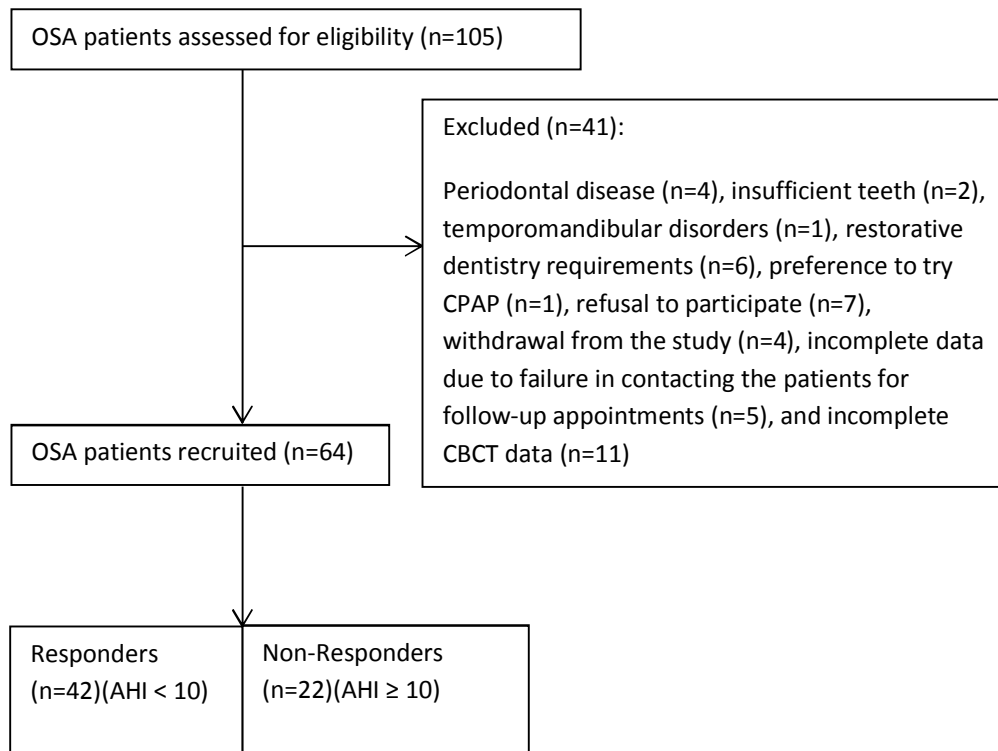


Figure 1. Flow-chart of the OSA patients. OSA: obstructive sleep apnea; CPAP: continuous positive airway pressure; CBCT: cone beam computed tomography.

### *CBCT images*

At baseline, all subjects underwent a NewTom 3G CBCT scan (QR systems, Verona, Italy) during quiet breathing, with exposure settings 110 kV, 18\*16-in field of view, and 5.4 seconds exposure time (pulsed radiation). During the imaging procedure the patients were positioned in the supine position with the Frankfort horizontal (FH) plane perpendicular to the floor. They were instructed to maintain maximum intercuspation and to avoid swallowing and other movements. All images were reconstructed to DICOM (Digital Imaging and Communications in Medicine) files prior to the analyzing phase in software.

### *The measurement of the upper airway*

The segmentation of the upper airway, using Amira software (v4.1, Visage Imaging Inc., Carlsbad, CA, USA), was performed as follows: first, a voxel set was built to include all of the information of the upper airway volume; second, the superior boundary (plane across the posterior nasal spine parallel to the Frankfort horizontal (FH) plane) and inferior boundary



(plane across the base of the epiglottis parallel to the FH plane) of the upper airway were selected in the corresponding axial planes and put into the material category; third, after the threshold values were determined for each patient to cover the entire region of the upper airway, all slices between the above boundaries were semi-automatically selected using the “magic tool” integrated in the software; and finally, all the information of the upper airway was put into the material category. In this way, the upper airway from the hard palate to the base of the epiglottis was segmented (Figure 2). The software then calculated the cross-sectional area (CSA) of every axial slice automatically. Based on these results, the CSA at the upper and lower boundaries ( $CSA_{upper}$  and  $CSA_{lower}$ ), and the minimum CSA ( $CSA_{min}$ ) were identified. On the specific slice where the  $CSA_{min}$  was located, the anterior-posterior dimension and lateral dimension of  $CSA_{min}$  were measured by the observer, using the linear measuring tool integrated in the software. The length of the upper airway was defined as the distance between the plane across the posterior nasal spine parallel to the FH plane and the plane across the base of the epiglottis parallel to the FH plane. The average CSA ( $CSA_{avg}$ ) and shape of the upper airway were calculated using the following formula:

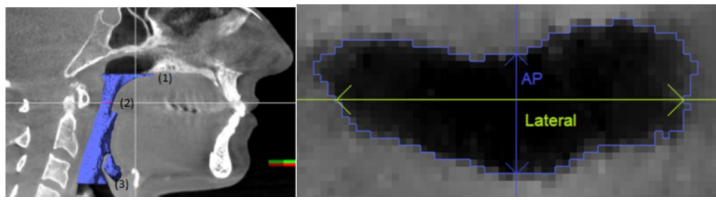
$$CSA_{avg} = (CSA_{min} + CSA_{upper} + CSA_{lower}) / 3$$

$$Shape^* = CSA_{min} / CSA_{avg}$$

*\* If the value tends to be 1, it means the shape of the upper airway tends to be cylindrical. If the value tends to be 0, it means the shape of the upper airway tends to be funnel-shaped.*

#### *The measurement of the mandible, maxilla, soft palate and tongue*

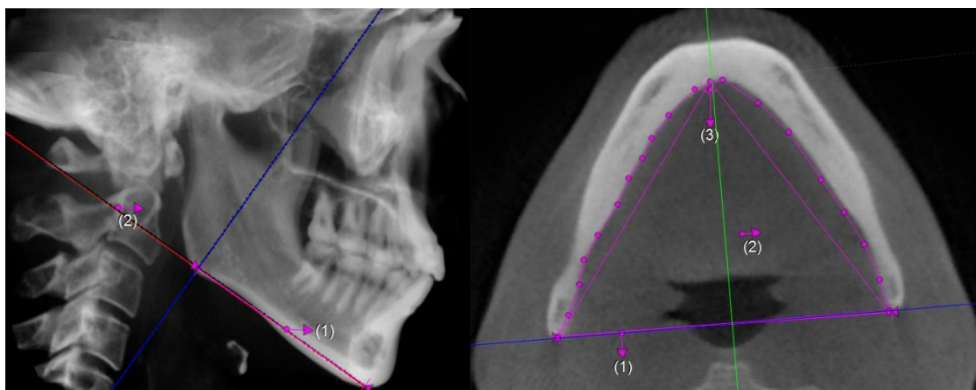
The measurements of the mandible, maxilla, soft palate and tongue were performed using 3Diagnosys® software (v5.3.1, 3diemme, Cantu, Italy). This software allows to adjust the orientation of the X/Y/Z axis according to anatomical landmarks. The orientation of the 3D image was adjusted, so that the right and left ramus and corpus mandibulae were superimposed. In order to do the measurement of the mandible, the axial, coronal, and sagittal planes were adjusted according to the rotation of the X/Y/Z planes. Subsequently, the axial plane going through the menton and gonion points was selected and defined as the mandibular plane (Figure 3).



a.

b.

Figure. 2a. The segmented upper airway. (1) The upper boundary of the upper airway; (2) The minimum cross-sectional area (CSAmin) on the axial slice of the CBCT image; and (3) The lower boundary of the upper airway. b. AP: anterior-posterior dimension of CSAmin; Lateral: lateral dimension of CSAmin.



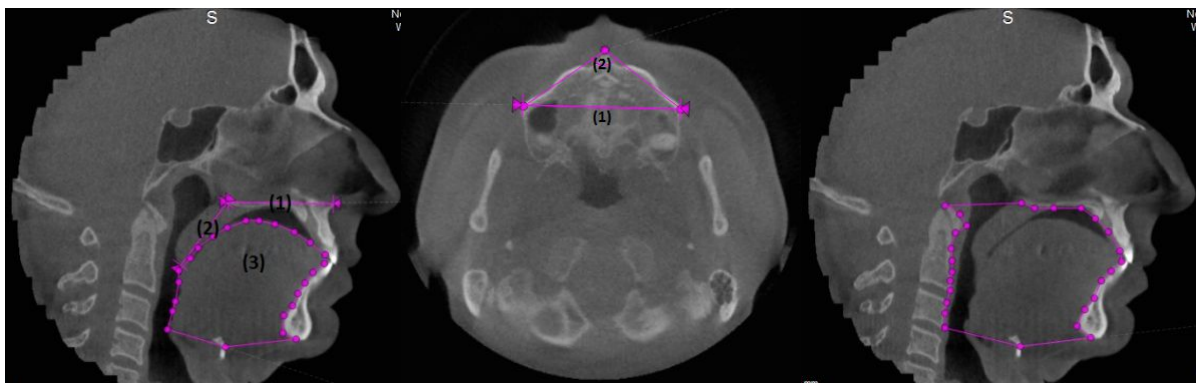
a

b

Figure 3a. Lateral view, with (1) The external length of the mandible; and (2) The projection of the mandibular plane on the lateral view of the skull. b. The mandibular plane according to the orientation of the line of Figure 3a. (1) The mandibular internal width; (2) The area of the mandible; and (3) The mandibular divergence.

On the lateral view of the skull, the external length of the mandible, which is defined as the distance between menton and gonion, was measured. The mandibular internal width, divergence, and area were measured on the axial slice at the level of the mandibular plane (Figure 3). By measuring the distance from the internal left gonion (ILG) to the internal right gonion (IRG), the mandibular internal width was determined. The angle between IRG, the spina mentalis (SM), and ILG determined the mandibular divergence. The area enclosed by the mandibular body on this axial slice was also measured (Figure 3).

The mid-sagittal plane was determined by the nasion, the anterior nasal spine (ANS), and the posterior nasal spine (PNS) (Figure 4a). On this mid-sagittal plane, the length of the maxilla, the tongue area, and the length of the soft palate were measured. The length of the maxilla was defined by the distance from the ANS to PNS. The tongue area was determined by the area enclosed by the hyoid bone, the mandible, the front teeth, the maxilla, and the anterior boundary of the upper airway. The length of the soft palate was the distance from PNS to the tip of the soft palate. On the plane across the ANS-PNS perpendicular to the mid-sagittal plane, the width of the maxilla and the maxillary divergence were measured (Figure 4b).



a.

b.

c.

Figure 4. The measurement of the maxilla and the tongue. A. (1) The length of the maxilla; (2) The length of the soft palate; and (3) The area of the tongue. B. (1) The width of the maxilla; and (2) The maxillary divergence. C. The maxillomandibular enclosure size.

*The measurement of the maxillomandibular enclosure size and the anatomical balance (ratio)*

On the mid-sagittal plane, the maxillomandibular enclosure size was determined by the area enclosed by the hyoid bone, the mandible, the front teeth, the maxilla, and the anterior boundary of the 2<sup>nd</sup> and 3<sup>rd</sup> cervical vertebra (Figure 4c). The anatomical balance (ratio) was calculated using the following formula:

$$\text{Ratio} = \frac{\text{Area of the tongue}}{\text{Maxillomandibular enclosure size}}$$

At the time of data analysis the examiner was blinded to the treatment outcome of the patients. To determine the reliability of the measurements, 30% of all CBCT scans were re-measured after one week.

### *Statistical analysis*

All measurements were statistically evaluated using the IBM Statistical Package for Social Sciences for Windows (SPSS® version 21, Chicago, IL, USA). All descriptive statistics are presented as means and standard deviations. An intraclass correlation coefficient (ICC) was used for determining the intra-observer reliability of the outcome variables that were measured twice with a one-week interval. To determine the significant differences between the responders and non-responders in the outcome variables, the Mann-Whitney-U test (for non-normally distributed variables) or Chi-squared test (for categorical variables) independent t-test (for normally distributed variables) were used, with a significance level set at  $p < 0.05$ . When there was a significant difference in the anatomical characteristics between responders and non-responders, analysis of covariance (ANCOVA) was used to exclude the effect of confounding factors.

### **Results**

The characteristics of the responders and non-responders at baseline are shown in Table 1. 42 responders and 22 non-responders were included in this study. There were significant differences in the BMI and AHI values between responders and non-responders. Responders had on average a BMI of  $27.6 \pm 3.8 \text{ kg/m}^2$  and an AHI of  $23.0 \pm 11.9$  events/hour of sleep, while non-responders had on average a BMI of  $30.8 \pm 5.9 \text{ kg/m}^2$  and an AHI of  $36.3 \pm 20.1$  events/hour of sleep. Both BMI and AHI were significantly smaller at baseline in the responders than in the non-responders (respectively,  $P = 0.011$  and  $P = 0.001$ ).

The outcomes of the measurements of the anatomical structures and the anatomical balance of the responders and of the non-responders are shown in Table 2. There were no significant differences in the anatomy of the upper airway between responders and non-responders ( $P = 0.17-0.97$ ). There is no significant difference in the anatomical balance (ratio) between responders and non-responders ( $P = 0.95$ ). The length of the maxilla of the

responders,  $52.0 \pm 3.9$  mm, was significantly shorter than that of non-responders,  $54.8 \pm 4.4$  mm ( $T = -2.65$ ;  $P = 0.01$ ). The maxillomandibular enclosure size of the responders,  $4675.4 \pm 533.2$  mm<sup>2</sup>, was significantly smaller than that of the non-responders,  $4993.8 \pm 588.6$  mm<sup>2</sup> ( $T = -2.19$ ;  $P = 0.03$ ). The tongue area of the responders,  $3263.9 \pm 384.3$  mm<sup>2</sup>, was significantly smaller than that of the non-responders,  $3484.9 \pm 442.1$  mm<sup>2</sup> ( $T = -2.08$ ;  $P = 0.04$ ). However, this significant difference in the tongue area between responders and non-responders disappeared after controlling for the effect of BMI ( $F = 2.39$ ;  $P = 0.13$ ).

The intra-observer reliability in the primary and secondary outcome variables measurements was excellent, with ICC's ranging from 0.878 to 1.000.

Table 1. Characteristics of the responders and non-responders at baseline

Variable	Responders (n=42) mean $\pm$ SD	Non-responders (n=22) mean $\pm$ SD	T/Z/X <sup>2</sup>	P
Age	58.64 $\pm$ 10.14	55.73 $\pm$ 10.66	1.07	.287
BMI	27.62 $\pm$ 3.83	30.79 $\pm$ 5.85	-2.19	.028*
Female (%)	17/42 (40.48)	6/22 (27.27)	1.09	.296
AHI baseline	23.05 $\pm$ 11.85	36.31 $\pm$ 20.07	-2.84	.004*
AHI with MAD in situ	5.00 $\pm$ 2.76	18.74 $\pm$ 10.06	-6.28	.000*

\* Statistically significant at the 0,05 probability level.

To determine the significant differences between the responders and non-responders in the anthropological characteristics, the independent t-test (for age) or Chi-squared test (for gender) Mann-Whitney-U test (for BMI/AHI baseline/AHI with MAD in situ) were used.

Table 2. The mean ( $\pm$ SD) of the primary and secondary outcome variables of the responders and non-responders

Variable	Responders (n=42)	Non-responders (n=22)	T	P
Primary outcome variables:				
The minimum cross-sectional area of upper airway ( $CSA_{min}$ ) ( $mm^2$ )	53.2 $\pm$ 37.8	57.8 $\pm$ 32.6	-0.49	0.62
Mandibular external length (mm)	72.9 $\pm$ 5.3	74.8 $\pm$ 5.8	-1.30	0.20
ANS-PNS (maxillary length) (mm)	52.0 $\pm$ 3.9	54.8 $\pm$ 4.4	-2.65	0.01*
The area of the tongue ( $mm^2$ )	3263.9 $\pm$ 384.3	3484.9 $\pm$ 442.1	-2.08	0.04*
Maxillomandibular enclosure size ( $mm^2$ )	4675.4 $\pm$ 533.2	4993.8 $\pm$ 588.6	-2.19	0.03*
Secondary outcome variables:				
The volume of upper airway ( $cm^3$ )	9.8 $\pm$ 4.2	9.5 $\pm$ 3.1	0.32	0.75
The average cross-sectional area of upper airway ( $CSA_{avg}$ ) ( $mm^2$ )	201.2 $\pm$ 58.0	183.0 $\pm$ 52.5	1.23	0.22
The shape of upper airway ( $CSA_{min}/CSA_{avg}$ )	0.26 $\pm$ 0.13	0.30 $\pm$ 0.12	-1.40	0.17
The anterior-posterior dimension of $CSA_{min}$ (mm)	5.0 $\pm$ 2.4	5.1 $\pm$ 1.8	-0.22	0.83
The lateral dimension of $CSA_{min}$ (mm)	12.3 $\pm$ 5.8	12.3 $\pm$ 4.5	-0.03	0.97
Upper airway length (mm)	46.9 $\pm$ 8.1	48.8 $\pm$ 6.7	-0.96	0.34
Maxillary divergence ( $^\circ$ )	100.8 $\pm$ 9.3	97.9 $\pm$ 7.3	1.29	0.20
The width of the maxilla (mm)	68.6 $\pm$ 6.7	68.9 $\pm$ 5.8	-1.61	0.87
Mandibular internal width (mm)	93.3 $\pm$ 6.5	94.8 $\pm$ 4.9	-0.96	0.34
Mandibular divergence ( $^\circ$ )	73.3 $\pm$ 4.8	73.8 $\pm$ 5.7	-0.37	0.71
Mandibular area ( $mm^2$ )	3615 $\pm$ 437	3731 $\pm$ 396	-1.04	0.30
Soft palate length (mm)	40.7 $\pm$ 4.9	40.0 $\pm$ 9.7	0.41	0.69
Anatomical balance (ratio)	0.7 $\pm$ 0.05	0.7 $\pm$ 0.05	0.06	0.95

\* Statistically significant at the 0.05 probability level

## Discussion

In this study, CBCT scans were obtained at baseline from responders and non-responders to MAD treatment. The anatomical structures of the upper airway, mandible, maxilla, and tongue at baseline were compared between responders and non-responders. For the anatomical structures, we found a significant difference in the length of the maxilla, the maxillomandibular enclosure size, and the tongue area between responders and non-responders. However, after controlling the effect of BMI, there no longer was a significant difference in the tongue area between responders and non-responders.

Previously, it has been reported that non-responders to MAD treatment have a higher BMI than responders [22, 29]. This is in agreement with the findings in the present study. BMI may play a useful clinical role in the prediction of the treatment outcome [23, 30, 31]. Isono et al have investigated effects of mandibular advancement in anesthetized patients and reported that mandibular advancement enlarged the upper airway and decreased collapsibility in non-obese individuals, but not in obese subjects [32]. It was suggested that the palatoglossal arch may not be integrated enough to stiffen the velopharyngeal wall and to increase the velopharyngeal cross-sectional area in obese persons [32]. Furthermore, excess tissue surrounding the upper airway may not be displaced effectively to increase the upper airway size in obese subjects [17].

The severity of baseline AHI on the response to MAD treatment has been investigated by several studies [12, 15, 16, 31]. Some showed that baseline AHI is a minor, albeit significant, contributor to the prediction model [12, 31], while others did not confirm that baseline AHI contributed [15, 16]. Therefore, future research needs to investigate whether the AHI at baseline can be used in combination with other parameters as a strong predictor for the treatment outcome of the MAD.

Based on a previous systematic review, which suggested that a small minimum cross-sectional area is the most relevant anatomical characteristic of the upper airway related to the pathogenesis of OSA [33], it was hypothesized that this anatomical structure also plays an important role in the treatment outcome of OSA. Contrary to this however, in our study there was no significant difference in the minimum cross-sectional area ( $CSA_{min}$ ) of the upper airway or in the anterior-posterior and lateral dimensions of the  $CSA_{min}$  of the upper airway between responders and non-responders. Some studies reported similar findings [17, 34]. Otsuka et al. found that the cross-sectional area of the upper airway was

significantly larger in non-responders than in responders based on 2D lateral cephalometric images [10]. Also, a study by Schwab et al. using magnetic resonance imaging (MRI), found that the minimum anterior-posterior distance in the retropalatal region was significantly longer in responders than in non-responders [11]. The difference between Otsuka et al.'s, Schwab et al.'s findings and our results may be due to the different imaging technique used. Schwab et al.'s study also had a very low number of non-responders (n=4) [11]. In addition, positioning of the patients as well as the breathing phases during the imaging procedure can also influence the results [33]. The anatomy of the upper airway is different between the supine and upright positions due to gravity. The wall of the upper airway moves during the breathing cycle resulting in changes in the anatomy of the upper airway during maximum inspiration/expiration phases [30]. An advantage of our study is that the NewTom CBCTs were taken while the patient was in supine position. However this still cannot replicate the real condition of the upper airway morphology while sleeping. For future studies, the above-mentioned factors should be considered to facilitate comparison between the studies.

Previous studies based on cephalometric radiographs have assessed whether craniofacial measurements are associated with MAD treatment outcome [12, 18, 35-40]. Some studies suggested that cephalometric analyses did not reveal any significant differences between responders and non-responders [18, 35, 36]. However, other studies showed that cephalometric measurements, e.g. retropalatal airway space and the angle between the anterior cranial base and the mandibular plane (SN-MP) can be independent predictors of the treatment outcome [12, 18, 37-40]. In our study, after extracting mid-sagittal plane from CBCT images, we only found that the length of the maxilla of the responders was shorter than that of the non-responders. It was previously reported that maxillary morphology differed in patients with OSA compared to controls, with OSA patients showing a shorter and more narrow maxilla [41-43], more obtuse palatal angle and shorter PNS-posterior pharyngeal distance [44]. It was shown that the relative size of the oral enclosure was relatively smaller to the tongue area in OSA patients that respond to MAD. However, in this study, the ratio is calculated only on the mid-sagittal plane, which may provide a limited perspective on a 3-D problem; this may be the reason for not finding a difference in the anatomical balance between responders and non-responders as in previous studies [23, 24]. Sutherland et al. suggested that increasing the maxillomandibular enclosure size, using



mandibular advancement, could help improve the anatomical imbalance between the soft and hard tissues in OSA patients [23]. Furthermore Isono et al. reported that excessive soft tissue for a given maxillomandibular enclosure size (upper airway anatomical imbalance) can increase tissue pressure surrounding the pharyngeal airway, thereby narrowing the airway [24]. Therefore, the interaction between the tissues surrounding the upper airway such as the hard palate, soft palate, tongue, and adjacent muscles as well as their bony enclosure can play an important role in predicting success to MAD treatment.

The mechanism of action of the MAD on the upper airway patency is still speculative [32], although it primarily acts by advancing the mandible anteriorly during sleep [45]. In this study, we cannot distinguish the responders and non-responders based on their anatomical characteristics of the mandible, but we found that the non-responders had a larger tongue area. As the tongue directly connects to the mandible, forward displacement of the mandible moves the base of the tongue anteriorly and increases the upper airway dimension [46]. For the OSA patients with a smaller tongue area, it is supposed to be easier to change the tongue position and enlarge the upper airway size, and therefore, obtain better treatment outcome. Even though in our study the subjects had their CBCT scans done in supine position, this does not reflect the conditions of sleep and this is a shortcoming of our study.

## **Conclusion**

OSA patients with a short maxillary length, a smaller maxillomandibular enclosure size, and a small tongue area may respond better to MAD treatment than patients with a longer maxillary length, a larger maxillomandibular enclosure size, and a large tongue area. However, after controlling the effect of BMI, there no longer was a significant difference in the tongue area between responders and non-responders.

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**Appendix 1** Primary and secondary outcome variables

Variables	Definitions
<i>Primary outcome variables</i>	
Minimum cross-sectional area of upper airway ( $CSA_{min}$ ) ( $mm^2$ )	Minimum cross-sectional area of the segmented upper airway on the axial plane
Mandibular external length (mm)	Distance between the menton and gonion
ANS-PNS (maxillary length) (mm)	Distance from the anterior nasal spine (ANS) to the posterior nasal spine (PNS)
Area of the tongue ( $mm^2$ )	Area enclosed by the mid-posterior point of the hyoid bone, the menton, the frontal teeth, ANS-PNS, the tip of the soft palate, the anterior-inferior point of the 3 <sup>rd</sup> cervical vertebra.
Maxillomandibular enclosure size	Area enclosed by hyoid bone, the mandible, the front teeth, the maxilla, and the anterior boundary of the 2 <sup>nd</sup> and 3 <sup>rd</sup> cervical vertebra
<i>Secondary outcome variables</i>	
Volume of upper airway ( $cm^3$ )	Volume of the upper airway between the level of the hard palate and the level of base of epiglottis
Average cross-sectional area of upper airway ( $CSA_{avg}$ ) ( $mm^2$ )	$CSA_{avg} = (CSA_{min} + CSA_{upper} + CSA_{lower}) / 3$
Shape of upper airway ( $CSA_{min} / CSA_{avg}$ )	Shape = $CSA_{min} / CSA_{avg}$
Anterior-posterior dimension of $CSA_{APmin}$ (mm)	Anterior-posterior dimension of the minimum cross-sectional area of upper airway
Lateral dimension of $CSA_{LATmin}$ (mm)	Lateral dimension of the minimum cross-sectional area of upper airway
Upper airway length (mm)	Length of the upper airway between the level of the hard palate and the level of base of epiglottis
Width of the maxilla (mm)	Distance between the most distal point of the maxilla at both sides
Maxillary divergence (°)	Angle between ANS, the most distal point of the maxilla at both sides
Mandibular internal width (mm)	Distance between the internal left gonion (ILG) and the internal right gonion (IRG)
Mandibular divergence (°)	Angle between IRG, the spina mentalis (SM) and ILG

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Mandibular area (mm <sup>2</sup> )	Area enclosed by the mandible body on this axial slice
Soft palate length (mm)	Distance from PNS to the tip of the soft palate
Ratio	Area of the tongue/Maxillomandibular enclose size

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## **Chapter 8**

### **The effects of maxillomandibular advancement surgery and mandibular advancement device therapy on the aerodynamic characteristics of the upper airway of obstructive sleep apnea patients: a systematic review**

**Chen, H**, Aarab G, de Lange J, Lobbezoo F, van der Stelt PF. The effects of maxillomandibular advancement surgery and mandibular advancement device therapy on the aerodynamic characteristics of the upper airway of obstructive sleep apnea patients: a systematic review. (Under review)





## **The effects of maxillomandibular advancement surgery and mandibular advancement device therapy on the aerodynamic characteristics of the upper airway of obstructive sleep apnea patients: a systematic review**

### **Abstract**

**Aim:** The primary aim of this study was to systematically review the literature to determine the effects of various non-continuous positive airway pressure (non-CPAP) therapies on the aerodynamic characteristics of the airflow in the upper airway of OSA patients. The secondary aim of this study was to determine the difference in aerodynamic characteristics of the upper airway between responders and non-responders to these therapies at baseline.

**Methods:** A PICO (population/patient, intervention, comparison, outcome) search strategy, focusing on the effects of various non-CPAP therapies (viz., upper airway surgery and mandibular advancement device (MAD)) on the aerodynamic characteristics of the upper airway of OSA patients, was conducted in the following databases: Medline (Pubmed), Excerpta medica database (EMBASE), and Web of Science. The aerodynamic characteristics of the upper airway were evaluated by computational fluid dynamic (CFD) analysis.

**Results:** Of 51 retrieved unique studies, nine studies fulfilled the criteria for this systematic review. Seven studies were on maxillomandibular advancement (MMA) surgery, and two studies were on MAD therapy. The aerodynamic characteristics (viz., velocity, wall shear stress, wall static pressure, airway resistance, pressure drop, and pressure effort) of the upper airway improved in OSA patients who underwent MMA surgery. All the patients in the studies on MMA surgery were responders. In the responders to MAD therapy, the velocity, wall static pressure, and airway resistance of the upper airway decreased. In non-responders to MAD therapy, the wall static pressure and airway resistance of the upper airway increased. In both therapies, the decrease in velocity, wall shear stress, airway resistance, and pressure drop were significantly correlated with the improvement in polysomnographic parameters. **Conclusion:** This systematic review suggests that MMA surgery and MAD treatment may improve several aerodynamic characteristics of the upper airway in OSA patients by CFD analysis. However, due to several limitations of the selected studies, there is not enough evidence yet to support CFD analysis as a useful tool to predict the treatment outcome in OSA patients before starting these therapies.

## Introduction

Obstructive sleep apnea (OSA) is a sleep-related breathing disorder, often associated with oxygen desaturations and arousals from sleep [1, 2]. The most common complaints of OSA patients are snoring, excessive daytime sleepiness, unrefreshing sleep, poor concentration, and fatigue [3]. OSA has a range of deleterious consequences that include increased cardiovascular morbidity, neurocognitive impairment, and increased overall mortality [4-7].

The most common non-continuous positive airway pressure (non-CPAP) therapies for OSA are upper airway surgery [8] and mandibular advancement device (MAD) [9]. Upper airway surgery, such as maxillomandibular advancement (MMA) surgery, tongue base surgery, uvulopalatopharyngoplasty (UPPP) et al., aims at enlarging the volume of the upper airway and thereby preventing its obstruction [10]. MAD, which has been recommended for mild and moderate OSA patients, protrudes the mandible and improves the patency of the upper airway by enlarging the upper airway and/or by reducing its collapsibility [11]. However, the response to upper airway surgery is variable [12]. Also, reported success percentage of MAD therapy in OSA patients ranges from 30% to 81% [9]. Therefore, non-response on these therapies is common, which raises the question if we can recognize the non-responders for these therapies beforehand to avoid ineffective treatment of this group of OSA patients [13].

Recently, the use of computational fluid dynamics (CFD) has come more into focus, because it allows quantification of the aerodynamic characteristics of the airflow in the upper airway, such as, velocity, wall shear stress, wall static pressure, airway resistance, pressure drop, and pressure effort [14-17]. Because OSA is characterized by obstruction of the airflow, assessment of the aerodynamic characteristics of the airflow within the upper airway using CFD could provide more insight into the airflow of the OSA patients, and into how various non-CPAP therapies affect their airflow [16, 18-21]. There is no definite answer, however, to the question how non-CPAP therapies differ with regard to their effects on the aerodynamic characteristics of the upper airway. This kind of research can help us understand the working mechanism of these non-CPAP therapies and may help to determine the optimal treatment strategy for a specific OSA patient. Therefore, the primary aim of this study was to systematically review the literature to determine the effects of various non-CPAP therapies on the aerodynamic characteristics of the airflow in the upper airway of OSA patients. The

secondary aim of this study was to determine the difference in aerodynamic characteristics of the upper airway between responders and non-responders to these therapies at baseline.

## **Material and methods**

### **Database search**

This systematic review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [22]. The search strategy, inclusion and exclusion criteria, data collection, and assessment methodology were carried out according to the protocol described in the following sections.

### **Search strategy**

A PICO-based (Population/Patient, Intervention, Comparison, Outcome) search strategy was conducted using the following electronic databases: Medline (PubMed), Excerpta Medica database (EMBASE), and Web of Science (Table 1). The searches were performed on Nov 22<sup>nd</sup> 2016, and updated until May 28<sup>th</sup> 2017. The main search items were “obstructive sleep apnea”, “treatment/therapy”, and “computational fluid dynamics”. Free-text terms and keywords were used for searching in EMBASE and Web of Science. For PubMed, apart from free-text terms and keywords, medical subject headings (MeSH) were also used (Table 2). Boolean operators (AND/OR) were applied to combine searches. No language restrictions were used.

### **Data collection and inclusion/exclusion criteria**

Eligible studies were selected in two phases. During the first phase, the title and abstract of the studies were reviewed by the first reviewer (HC). Inclusion criteria were: (1) adults diagnosed with OSA by polysomnography (PSG) recordings; (2) treatment outcome assessed by a second PSG recording; and (3) CFD was applied. Exclusion criteria were: (1) no treatment modalities mentioned or CPAP therapy; and (2) editorials or reviews.

During the second phase, the full texts of all potentially eligible studies identified during the first phase were reviewed independently by two reviewers (HC, PvdS). According to the

PRISMA 2009 flow diagram [14], during the full-text assessment, irrelevant studies were excluded based on the same inclusion and exclusion criteria as mentioned above.

Information was extracted from the finally selected studies by one reviewer (HC) and confirmed by the other reviewer (PvdS). A manual search of potentially missing studies was completed by screening the references of the studies identified in the second phase.

Table 1 Systematic search strategy following the PICO system

Search strategy	Search items
P: Population/Patient	#1: obstructive sleep apnea at baseline
I: Intervention	#2: non-continuous positive airway pressure (CPAP)
C: Comparison	#3: obstructive sleep apnea with treatment
O: Outcome	#4: airflow characteristics by computational fluid dynamics analysis
Search combination	#1 and #2 and #4
Electronic database	Medline (PubMed), Excerpta Medica Database (EMBASE), Web of Science

Table 2 Electronic database search terminology

Search Item	Medline (PubMed)	Results	Excerpta medica database (EMBASE)		Web of science	
	Search terminology		Search terminology	Results	Search terminology	Results
#1	"obstructive sleep apnoea"[All Fields] OR "sleep apnea, obstructive"[MeSH Terms] OR ("sleep"[All Fields] AND "apnea"[All Fields] AND "obstructive"[All Fields]) OR "obstructive sleep apnea"[All Fields] OR ("obstructive"[All Fields] AND "sleep"[All Fields] AND "apnea"[All Fields])	25,619	Obstructive sleep apnea	31,437	topic: obstructive sleep apnea	39,112
#2	"treatment"	9,482,655	Treatment or therapy	9,504,245	topic: treatment or therapy	12,038,597
#4	computational[All Fields] AND ("hydrodynamics"[MeSH Terms] OR "hydrodynamics"[All Fields] OR ("fluid"[All Fields] AND "dynamics"[All Fields]) OR "fluid dynamics"[All Fields])	4,738	Computational fluid dynamics	7,718	topic: computational fluid dynamics	133,884
Total	#1 and #2 and #4	24	#1 and #2 and #4	29	#1 and #2 and #4	46

## Quality assessment

Currently, there is no single universal tool available to assess the quality of different studies [23]. Due to small sample size of the selected studies (N=2-20), we followed the Case Report (CARE) checklist to assess the study quality [24]. This tool uses a checklist of 13 specific questions, to be answered with 'yes' or 'no'. The questions answered with 'yes' are given one point, so the possible maximum score for each study is 13. Quality scores were divided into four categories, viz., poor (score  $\leq 7$ ), fair (score = 8-9), good (score = 10-11), and very good (score = 12-13) [25, 26].

## Data synthesis

Due to the small sample sizes as well as to the heterogeneity of the participants, treatment modalities, and imaging modalities, a meta-analysis could not be carried out. Therefore, only a qualitative assessment of the outcomes of the included studies was performed.

## Results

### Search results

The search results are shown in Figure 1. In the first phase, 100 potentially relevant studies were obtained following the PICO search strategy. After removing the 49 duplicates, 51 unique studies were left for the first phase screening. Based on the inclusion and exclusion criteria, 38 studies were removed and 13 studies moved into the second phase. After the second phase, nine studies were considered to be suitable for this systematic review (Figure 1).

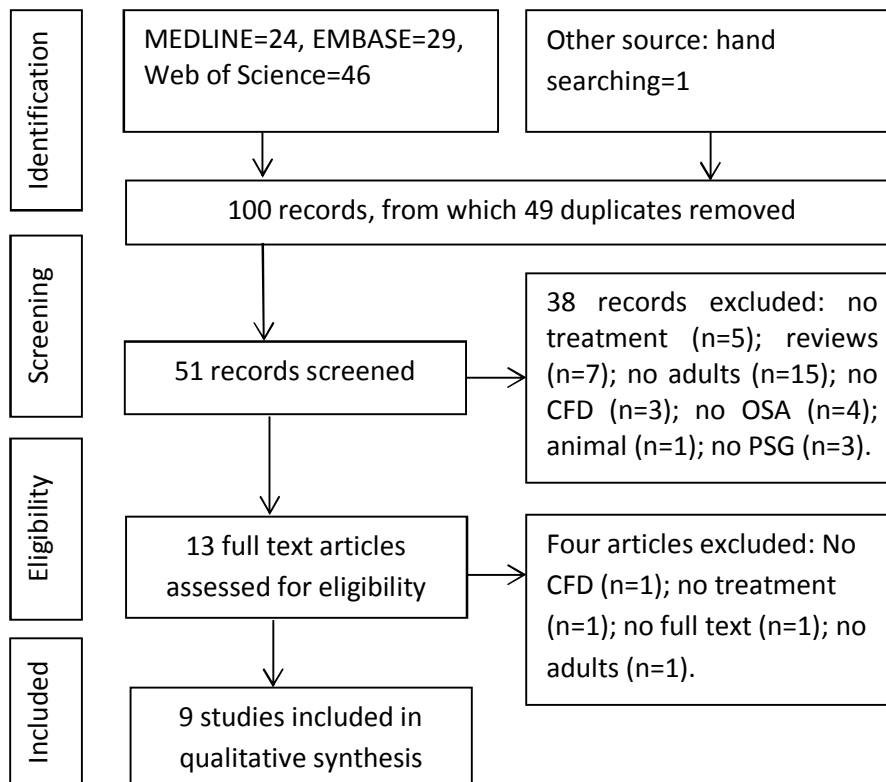


Figure 1: Flow diagram with search strategy and number of articles. OSA: obstructive sleep apnea; CFD: computational fluid dynamics; PSG: polysomnography.

### Quality assessment

The quality assessment of the nine selected studies is summarized in Table 3. According to the CARE tool, the quality of two studies was good [16, 18], that of five studies was fair [19, 27-30], and that of two studies was poor [31, 32]. The two studies with good quality were on MAD therapy [16, 18]. The seven studies with fair or poor quality were on MMA surgery [19, 27-32]. Three studies did not mention the time interval of the follow-up [29, 31, 32]. Informed consent was obtained from the patients in only three studies [16, 18, 29]. Only two studies on MMA [28, 30] and one study on MAD [16] used statistical methods to analyze the CFD results.

Table 3 Quality assessment of the nine selected studies

First author [ref.]	Yu [19]	Ito [32]	Powell [29]	Sittitavorn wong [30]	Cheng [31]	Kim [27]	Liu [28]	De Backer [16]	Zhao [18]	Total
1. Title	0	1	0	0	0	0	0	0	0	1
2. Key Words	1	1	1	0	1	0	1	1	1	7
3. Abstract	1	1	1	1	1	1	1	1	1	9
4. Introduction	1	0	1	1	0	1	1	1	1	7
5. Patient Information	1	1	1	1	1	1	1	1	1	9
6. Clinical Findings	0	0	0	0	0	0	0	0	0	0
7. Timeline	1	0	0	1	0	1	1	1	1	6
8. Diagnostic Assessment	1	1	1	1	1	1	1	1	1	9
9. Therapeutic Intervention	1	1	1	1	1	1	1	1	1	9
10. Follow-up and Outcomes	1	1	1	1	1	1	1	1	1	9
11. Discussion	1	0	1	1	1	1	1	1	1	8
12. Patient Perspective	0	0	0	0	0	0	0	0	0	0
13. Informed Consent	0	0	1	0	0	0	0	1	1	3
Total	9	7	9	8	7	8	9	10	10	

\* Scored as 1 (completely fulfills the criterion) or 0 (does not completely fulfill the criterion).

### Study design

Characteristics of the nine selected studies are summarized in Table 4. All studies had a retrospective design and a small sample size (N= 2-20). In the selected studies, the diagnosis of the OSA patients was based on overnight PSG and the treatment response was evaluated by a second PSG. Two studies reported that the body mass index (BMI) of the OSA patients had decreased after treatment [19, 29]. Two studies provided information about race [27, 32].

There were two studies using MADs to treat OSA patients [16, 18]. In Zhao et al.'s study, all patients used a commercially available, customized two-piece MAD. The second MRI was taken in patients with their MAD in situ at the maximal comfortable position [18]. In De Backer et al.'s study, all patients used a custom-made monobloc MAD without mentioning the position of the MAD in situ during the imaging procedure [16]. In both studies, the OSA patients were categorized as responders or non-responders to MADs [16, 18].



In the seven studies that treated the OSA patients by upper airway surgery, the surgery option was either MMA surgery [19, 28-32] or modified MMA with anterior segmental setback osteotomy (MMA-ASSO) [27]. All OSA patients in these studies were responders to MMA surgery. Only two studies mentioned the MMA surgery protocol in detail. [27, 31]

#### Study measurements

For upper airway imaging, seven studies used computed tomography (CT) [16, 19, 27, 28, 30-32], one study used magnetic resonance imaging (MRI) [18], and one study used cone beam computed tomography (CBCT) [29]. The CBCT scanning was done with the patient in supine position [29], which is similar to the studies using CT and MRI scan.

Based on the CT, MRI, or CBCT images, four different software programs for segmentation of the upper airway and three different software programs for CFD analysis were used in the nine selected studies (Table 4). During CFD analysis, the number of cells generated in the computational models of the upper airway ranged from 158,000 to 1.3 million [18, 32]. Different flow rates at the inlet plane of the upper airway, ranging from 166ml/s to 700ml/s, were used to model the aerodynamic characteristics within the computational models of the upper airway [18, 31]

Table 4 Characteristics of the nine selected studies

	First author [ref.]	Yu [19]	Ito [32]	Powell [29]	Sittitavornwong [30]	Cheng [31]	Kim [27]	Liu [28]	De Backer [16]	Zhao [18]
Study design	Study type	Retrospective	Retrospective	Retrospective	Retrospective	Retrospective	Retrospective	Retrospective	Retrospective	Retrospective
	Severity of OSA	Severe	N.A	Moderate to severe	Moderate to severe	Mild to severe (RDI>40)	Severe	Moderate to severe	Snorer to severe	Moderate to severe
	Responder or non-responder	Responders	Responders	Responders	Responders	Responders	Responders	Responders	7Responders/3 non-responders	4 Responder/ 3 non-responder
	Sample size	2	8	2	8	10	2	20	10	7
	Sex	M	4M; 4F	M	4M; 4F	N.A	M	17M; 3F	8M; 2F	N.A
	Race	N.A	White	N.A	N.A	N.A	Asian	N.A	N.A	N.A
	Age (year)	43; 30	58.5±9.2	49.25±8.38	N.A	N.A	27	44±12	51.3±5.94	45.8±14.4
	AHI at baseline	75; 83	32.6±13.7	36.85±12.18	32.61±13.72	RDI 46.5±31.9;	43.2; 22.9	53.6±26.6	17.2±10.3	24.4±9.45
	AHI after treatment	30.4; 23.5	6.3±4.3	7±4.69	6.31±4.25	RDI 7.8±7.5	15.2; 6	9.5±7.4	16.9±8.4	14.3±12.66
Study measurement	BMI	31.5-27.6; 26.3-23.2	N.A	17.15±4.07	N.A	30.3±4.2	25;22.9	27±4.6	27.9±3.9	29.31±4.72
	Treatment modality	MMA	MMA	MMA	MMA	MMA	MMA; MMA-ASSO	MMA	MAD	MAD
	Imaging technique	CT	CT	CBCT	CT	CT	CT	CT	CT	MRI
	Position	Supine	Supine	Supine	Supine	Supine	Supine	Supine	Supine	Supine
	Respiration period	N.A	N.A	End of expiration	End of expiration	N.A	End of expiration	N.A	N.A	Normal nasal breathing
	Software for segmentation	Amira	Insight segmentation and registration toolkit	Mimics	Insight segmentation and registration toolkit	Insight segmentation and registration toolkit	Mimics	Intage Volume Editor	Mimics	Amira
	Software for CFD	Ansys	Mixed-Element Grid Generator in 3D (MEGG3D)	Ansys	Mixed-Element Grid Generator in 3D (MEGG3D)	Mixed-Element Grid Generator in 3D (MEGG3D)	Ansys	Phoenix, CHAM -Japan	Ansys	Ansys
	Boundary condition inlet flow rate	133 ml/s	Nominal flow rate	500ml/s	700 ml/s	700 ml/s	572ml/s	300ml/s	Mass flow rate measured by the pneumotach	166ml/s
	Number of cells	N.A	158.000-173.000	N.A	N.A	N.A	N.A	N.A	600.000-800.000	1.3 million
	Velocity (m/s)	Decrease	N.A	Decrease	N.A	N.A	Decrease	Decrease	N.A	Decrease in responders
	Wall shear stress(Pa)	N.A	N.A	Decrease	Decrease	Decrease	N.A	N.A	N.A	N.A
	Wall static pressure (Pa)	Decrease	N.A	Decrease	N.A	N.A	Decrease	Decrease	N.A	Decreased in the responders; Increased in

	Airway resistance	Decrease	N.A	Decrease	N.A	N.A	N.A	N.A	Decreased in the responders; Increased in non-responders	non-responders N.A
	Pressure drop (Pa) Pressure effort	Decrease N.A	N.A Less pressure effort after MMA	N.A N.A	Decrease Less pressure effort after MMA	N.A Less pressure effort after MMA, except Case 25.	Decrease N.A	N.A N.A	N.A N.A	N.A N.A
	Correlation between changes in aerodynamic and PSG parameters	N.A	N.A	Decrease in wall shear stress correlated with a decrease in AHI.	N.A	N.A	N.A	Decrease in velocity correlated significantly with a decrease in AHI.	Decrease in airway resistance correlated significantly with a decrease in AHI.	Decrease in pressure drop correlated with a decrease in AHI.
Data analysis	Validation	N.A	N.A	N.A	N.A	N.A	N.A	N.A	N.A	Yes.
	Statistic method	N.A	N.A	N.A	Spearman rank correlation; Paired t test	N.A	N.A	Mann-Whitney-Wilcoxon test; Student test; McNemer test; Pearson correlation	Spearman correlation; Mann-Whitney U test	N.A
Summary (results and conclusion)		This study demonstrates the possibility of computational fluid dynamics in providing information for understanding the pathogenesis of OSA and the effects of its treatment.	Our steady-state, turbulent inspiratory flow simulation results for two cases clearly showed that the postoperative upper airways required less pressure efforts because of the enlarged pharyngeal airway space due to the MMA surgery.	This feasibility study supports the concept that flow modeling methods for upper airway airflow in SDB may be used in understanding the complicated pathophysiology of SDB.	Decreasing the pressure effort will decrease the breathing workload. This improves the condition of OSA.	The numerical results demonstrate that the computational framework developed in this study is capable of qualitatively predicting both the effect of airway obstruction on the breathing effort and the surgical effect on improving pressure efforts.	Modified MMA-ASSO method might be an effective treatment option for OSAS patients with improvement of airway problems and esthetic facial profile.	AHI improvement after MMA is best correlated with decreased retropalatal airflow velocity modeled by CFD.	The results of this pilot study suggest that the outcome of MAD treatment can be predicted using the described UA model.	Changes in upper airway geometry alone did not significantly correlate with treatment response. We provide further support of CFD as a potential tool for prediction of treatment outcome with MAD in OSA patients.

\* AHI: apnea hypopnea Index; BMI: body mass index; CBCT: cone beam computed tomography; CFD: computational fluid dynamics; CT: computed tomography; F: female; M: male; MAD: mandibular advancement device; MMA: maxillomandibular advancement; N.A: not available; MRI: magnetic resonance imaging; OSA: obstructive sleep apnea; RDI: respiratory disturbance index.

#### Aerodynamic characteristics of the upper airway based on CFD analysis

The selected nine studies assessed different aerodynamic characteristics of the upper airway before and after MMA, and without and with MAD in situ (Table 4). In general, MMA studies measured more aerodynamic characteristics of the upper airway (1-4) than the MAD studies (1-2).

In the seven studies that treated the OSA patients by MMA, four studies reported a decrease in the velocity after MMA [19, 27-29]. Three studies reported that wall shear stress decreased [29-31], four studies reported that wall static pressure decreased [19, 27-29], and two studies concluded that the airway resistance reduced after MMA [19, 29]. Three studies reported that pressure drop decreased [19, 27, 30]. Besides, OSA patients needed less pressure effort to breath after MMA except for one case, perhaps due to technical failure during CT imaging [30-32].

Importantly, in these studies on MMA, only two studies used statistical methods to analyze CFD results [28, 30]. One study found that after MMA, the wall shear stress and pressure drop decreased, and the patients needed significantly less pressure effort to breath [30]. The other study found that the velocity and wall static pressure decreased significantly after MMA [28].

In responders to MAD, the airway resistance and the wall static pressure of the upper airway decreased, while in non-responders to MAD, these values increased [16, 18]. The velocity of the upper airway decreased in responders. No information on the velocity was provided for the non-responders [18]. Notably, only one study on MAD used statistical methods to analyze CFD results [16]. This study found that the airway resistance decreasing significantly in responders and increased significantly in non-responders [16].

There was a correlation between the change in the aerodynamic characteristics and the change in PSG parameters (e.g., AHI) [16, 18, 28, 29]. Zhao et al. suggested that a decrease in

the pressure drop with MADs in situ had a correlation with a decrease of AHI [18]. Using MMA, Powell et al. found that the decrease in the wall shear stress correlated with the decrease in AHI [29]. Remarkably, by using statistical methods, De Backer et al. concluded that a decrease in airway resistance correlates significantly with a decrease in AHI with MAD in situ [16]. Also using statistical methods, Liu et al. suggested that the decrease in velocity correlates significantly with the decrease in AHI after MMA [28].

## **Discussion**

The primary aim of this study was to systematically review the literature to assess the effects of non-CPAP therapies on the aerodynamic characteristics of the upper airway. The secondary aim of this study was to determine the difference in aerodynamic characteristics in the upper airway between responders and non-responders to the non-CPAP therapies at baseline. From 51 unique publications, nine studies could be included according to the PRISMA flow diagram, and the quality of these studies was evaluated using the CARE tool.

### *Validation of CFD analysis*

Using CFD analysis, we can simulate the airflow in the upper airway, which can further improve our understanding of upper airway collapse in OSA. Like every new technique, before being applied in the clinical setting, the method should be validated. Only in one of the selected studies, the values of the velocity and wall static pressure by CFD analysis was validated using a physical 3D-airway model in vitro [18]. This study provided support for CFD as a potential tool to estimate the role of aerodynamic characteristics of the upper airway in the pathogenesis and treatment of OSA [18]. However, the upper airway model used in this validation experiment is made of transparent acrylic, which is different from the real upper airway. For future studies, it is suggested to set up upper airway models using specific materials that could mimic more closely the behavior of the upper airway.

### *Quality assessment*

Based on the quality assessment of the selected studies, there were several limitations in the study designs, such as being a retrospective study [16, 18, 19, 27-32], having a small sample size (N=2-20) [16, 18, 19, 27-32], or neglecting confounding factors (age, gender, and

race) [16, 18, 28, 30-32]. Besides, in the study assessment, only two studies on MMA and one study on MAD used statistical methods to analyze the CFD results [16, 28, 30]. Therefore, the evidence on the value is of CFD in the analyses of aerodynamics in the upper airway of OSA patients is very limited. Another limitation is that not all the studies measured the same set of variables. It is still unclear which aerodynamic characteristic(s) of the airflow is/are the most relevant one(s) in relation to the treatment outcome. Therefore, in future studies on CFD analysis, a comprehensive set of variables (viz., velocity, wall shear stress, wall static pressure, airway resistance, pressure drop, and pressure effort) should be included to find the most relevant variable related to the treatment outcome.

### *Imaging procedure and CFD analysis*

Different imaging techniques, such as CT, MRI, and CBCT, were used in the selected studies. Previous studies showed that all these imaging techniques can be used for the analysis of the upper airway in OSA patients [33]. The OSA patients were all in the supine position during the imaging procedure, which may be similar to the natural sleeping position. The anatomical structure of the upper airway during sleep, however, is different from awake, because of the suppression of upper airway muscle activity [34]. In the selected studies, the patients underwent the imaging procedure before and after therapy both while awake. We nevertheless hypothesize that the difference between the before and after therapy conditions is influenced in a comparable way during sleep and while awake, which would minimize the effect of sleep on the comparison of CFD analysis before and after therapies in the selected studies.

For CFD analysis, different flow rates were chosen to simulate the velocity at the inlet plane of the upper airway. In some studies, the flow rate was obtained from a Fleisch pneumotachograph [16], or based on the weight of the patient and on a tidal volume of 7 ml/kg for one breathing cycle (12 cycles/min) [32]. In other studies, the flow rate was set at a certain value without an explanation [18, 19, 27-31]. As the flow rate fluctuated during the breathing cycle, it is suggested to use its average value during one breathing cycle to simulate the aerodynamic characteristics within the upper airway [32]. These different flow rates set at the inlet influence the outcome of the calculations of the aerodynamic characteristics in OSA patients, which impedes comparison of these calculations between

studies. According to these calculations, however, we can still assess whether the aerodynamic characteristics in the upper airway improve or aggravate with treatment [35].

*The working mechanism of MMA surgery and MAD therapies from the perspective of aerodynamics*

MMA surgery is especially performed in severe OSA, but it is invasive and non-reversible [36]. Among numerous surgical options, MMA is accepted as one of the most successful treatment modalities, with 60% to 100% success rates [27, 37, 38]. In the included seven studies on MMA surgery, the OSA patients were all responders to surgery. The values of different aerodynamic characteristics (viz., velocity, wall shear stress, wall static pressure, airway resistance, pressure drop, and pressure effort) of the airflow in the upper airway decreased in these responders, except in one case [31]. In the two studies that used statistical methods to analyze CFD results, the velocity, wall shear stress, wall static pressure, pressure drop, and pressure effort of the airflow in the upper airway decreased significantly after MMA [28, 30]. However, based on these studies, we do not obtain any information on the aerodynamic characteristics of the upper airway in the non-responders to MMA surgery. By including also non-responders in these kinds of studies, more insight in the underlying mechanism of non-response to MMA surgery from an aerodynamic perspective is provided.

The application of MAD is a promising treatment modality, but the reported success rates with MAD are limited [39, 40]. There are two different MAD designs used in the selected studies, which makes a comparison of effects on aerodynamics characteristics of airflow in the upper airway more difficult [16, 18]. The MAD is thought to act primarily by advancing the mandible during sleep [11], however, the mechanism of the action of the MAD on the upper airway patency is still speculative [41]. Based on the selected studies, the airway resistance [16], the velocity, and the wall static pressure [18] changed with MADs in situ. The selected studies suggested that the MAD could improve the ventilation of the upper airway by improving the aerodynamic characteristics of the upper airway in the OSA patients [16, 18]. However, in the study using statistical methods, only the airway resistance decreased significantly in responders and increased significantly in non-responders [16]. The above suggestion should therefore be applied in a prudent way.

*Comparison of aerodynamic characteristics between responders and non-responders to MAD*

In responders to MAD, aerodynamic characteristics of the airflow, such as velocity, wall static pressure, and airway resistance, decreased with the MAD in situ [16, 18]. In non-responders, the wall static pressure and airway resistance of the airflow increased with the MAD in situ [16, 18]. However, only one aerodynamic characteristic (viz. airway resistance) of the airflow in the upper airway decreased significantly in responders and increased significantly in non-responders to MAD [16]. Both studies on MAD therapies concluded that we can predict the treatment outcome by CFD [16, 18]. However, once starting an MAD treatment for OSA patients, it does not make sense to predict the treatment outcome by comparing the aerodynamic characteristics with and without MAD in situ, because OSA patients have to undergo the imaging procedure twice, resulting in an increase of the radiation exposure for the patients in studies in which CT and CBCT were applied. From a clinical point of view, it is more interesting to investigate if CFD analysis can be used to predict the treatment outcome in OSA patients before starting therapy.

*The correlation between treatment response and the change in aerodynamic characteristics of the upper airway*

Previous studies suggested that based on MRI images, the change in upper airway morphology alone, such as volume enlargement, will not be adequate for clinical prediction of treatment response [18, 42]. Using statistical methods, a decrease in the airway resistance with MAD in situ correlated significantly with a decrease in AHI [16]. Also, a decrease in the velocity after MMA had a significant correlation with a decrease in AHI [28]. It was suggested that if there was a significant decrease in airway resistance with MAD in situ, or in velocity after MMA, we can also expect a decrease in AHI, which indicates that the OSA patient is responding to the treatment [16, 28]. Therefore, it seems that, in addition to anatomical characteristics, the change in the aerodynamic characteristics in the upper airway may add more information to understand the treatment response. However, more studies with sufficient statistical analyses are needed to test the correlation between treatment response and the change in the aerodynamic characteristics of the upper airway.

None of the included nine studies compared the aerodynamic characteristics of the upper airway between responders and non-responders at baseline, which can help to recognize the non-responders before starting a treatment and therefore prescribe the optimal treatment



modality for the OSA patients. Therefore, it is strongly suggested that studies comparing the aerodynamic characteristics of the upper airway between responders and non-responders to MMA surgery and to MAD treatment at baseline should be carried out in the future. This kind of research may increase the success rate of MMA surgery and MAD treatment, thereby improving the cost-effectiveness of these treatments [16].

### **Conclusion**

In conclusion, this systematic review suggests that MMA surgery and MAD treatment may improve several aerodynamic characteristics of the upper airway by CFD analysis. However, due to several limitations of the selected studies, there is not enough evidence yet to support CFD analysis as a useful tool to predict the treatment outcome in OSA patients before starting these therapies.

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## Chapter 9

### **A novel imaging technique to evaluate airflow characteristics in the upper airway of an obstructive sleep apnea patient**

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## **A novel imaging technique to evaluate airflow characteristics in the upper airway of an OSA patient**

**Abstract:** We report about a novel imaging technique for airflow analysis, particle image velocimetry (PIV), used in a moderate obstructive sleep apnea (OSA) patient. By measuring the airflow characteristics in the upper airway at different protrusion positions, the effect of mandibular advancement device (MAD) on OSA was further understood.



## Introduction

Obstructive sleep apnea (OSA) is a sleep-related breathing disorder, often associated with a compromised upper airway space and an increase in upper airway collapsibility [1]. Excessive daytime sleepiness, snoring, and reduction in cognitive functions are among the common symptoms of OSA [2]. The consequences of OSA are increased cardiovascular morbidity, neurocognitive impairment, and overall mortality [2].

Mandibular advancement devices (MADs) have been recommended as a primary treatment option in mild to moderate OSA patients and in severe OSA patients who do not tolerate continuous positive airway pressure (CPAP) [3]. However, there is no definitive conclusion on the relation between the mandibular protrusion position and the improvement of the OSA symptoms. Ferguson et al., suggested that a large mandibular protrusion will lead to a large decrease in OSA events [4], while Aarab et al., found no significant difference in efficacy between MADs set at 50% protrusion position and at 75% protrusion position [5]. In this case report, it is hypothesized that the airflow characteristics in the upper airway are different at different protrusion positions, viz, the larger the protrusion position, the better the ventilation of the upper airway. Particle image velocimetry (PIV) is a novel imaging technique, which can show the airflow characteristics in the upper airway. By investigating the airflow characteristics in the upper airway at different protrusion positions using PIV, the effect of MAD therapy on OSA can be further understood from the perspective of aerodynamics.

The aim of this case report is to evaluate the airflow characteristics in the upper airway of an OSA patient at different protrusion positions using PIV.

## Case Report

A 35-year-old male OSA patient with no medical history (body mass index = 25.4 kg/m<sup>2</sup>), whose main complaint was snoring at night, was treated with an adjustable MAD (Erkodent, Baden-Württemberg, Germany). There was no change in his weight and sleep habit during the treatment. Based on polysomnography (PSG) at baseline, apnea occurred during both REM sleep and non-REM sleep. The total apnea-hypopnea index (AHI) was 17 events/hour, supine AHI was 28.7 events/hour, and the oxygen desaturation index (ODI) was 4.9. Epworth Sleepiness Scale (ESS) score was 11. Computed tomography (Discovery CT 750, General

Electric Healthcare, Milwaukee, USA) scans were taken both at baseline (without the MAD in situ) and with the MAD in situ at 50% and 75% of the maximal protrusion positions, while the patient was awake during free-breathing. The exposure settings were 120 kV, 30 mA, 0.516 pitch. Based on the CT images, three transparent air-filled acrylic upper airway models from the hard palate plane to the vocal cord plane were made by rapid prototyping as follows: 1. The solid upper airway models were based on one sagittal slice of the CT images at the mid-sagittal plane. This slice was expanded to a width of 10 mm to be a three-dimensional (3D) model; 2. Then these solid models were adjusted on the platform of a vacuum pressure molding machine (Biostar, Scheu Dental, Iserlohn, Germany) and coated with a transparent acrylic sheet; 3. After the acrylic was hardened, the solid models were removed and the transparent acrylic models of the upper airway were created. Subsequently, airflow characteristics in these three upper airway models were visualized separately by PIV using the following procedure: 1. Spherical glass micro-particles with a diameter of 0.5-5  $\mu\text{m}$  were placed in the flow field (water) as tracing particles; 2. The rate of the flow (water) was set at 103 ml/s, corresponding to an airflow rate of 125 ml/s [6]; 3. The trajectory of particles in the water was recorded by taking two photos of the upper airway models shortly after each other and exported to an image processing device; 4. From the known time difference and the measured displacement of the micro-particles, the velocity is calculated [7]. Based on the velocity field and the formula

$$\vec{w} = \nabla \times \vec{u}$$

where  $\vec{w}$  is the vorticity,  $\nabla$  is the del operator and  $\vec{u}$  is the velocity, the vorticity, which indicates the amount of turbulence in a fluid, is calculated. The inspiration phase is mimicked by allowing the flow (water) going through from the hard palate plane to the vocal cord plane, while the expiration phase is mimicked by allowing the flow (water) going through from the vocal cord plane to the hard palate plane (Figure 1).

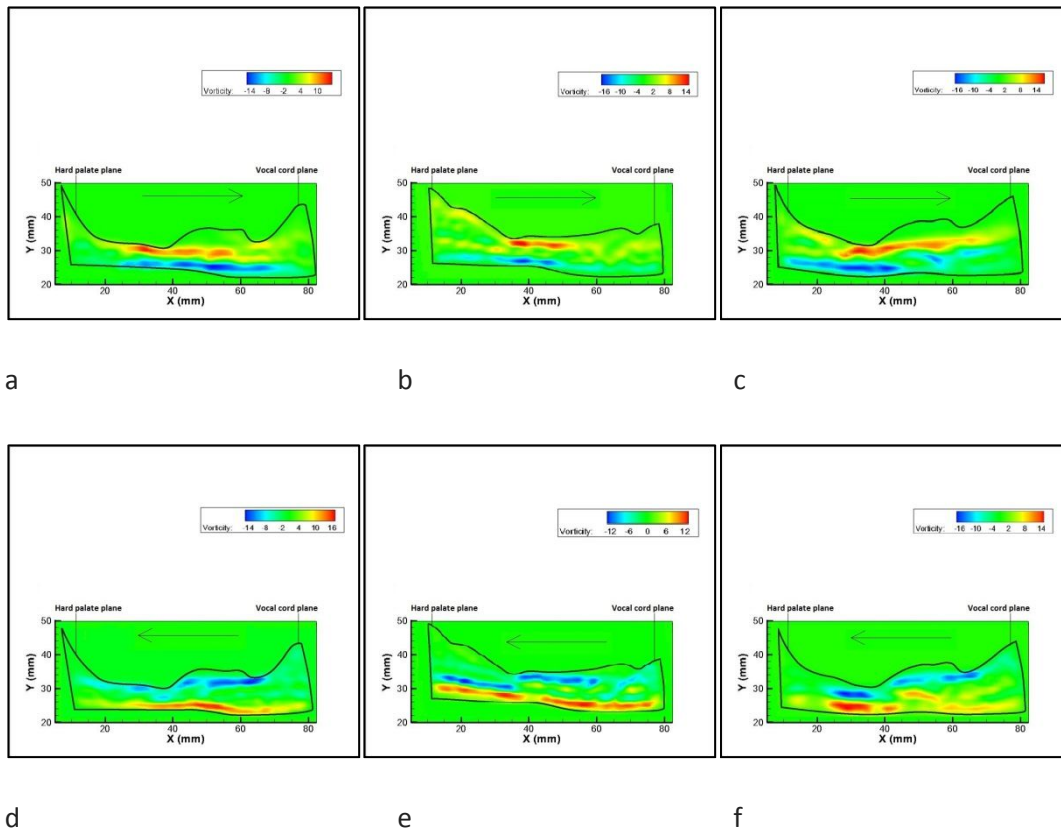


Figure 1 Vorticity field of the upper airway models at baseline during inspiration (a), at 50% protrusion position during inspiration (b), and at 75% protrusion position during inspiration (c). Vorticity field of the upper airway models at baseline during expiration (d), at 50% protrusion position during expiration (e), and at 75% protrusion position during expiration (f). The arrows show the direction of the flow: → inspiration; ← expiration. X axis: length of the model; Y axis: width of the model.

For this patient, the funnel-like upper airway at baseline was gradually changed into a cylinder-like one at 75% protrusion position. The airflow characteristics (vorticity profiles) in the upper airway of this OSA patient at different protrusion positions were shown in Figure 1. During inspiration, from baseline to 50% protrusion position, the maximum vorticity decreased from 16 to  $14 \text{ s}^{-1}$ , while from 50% to 75% protrusion position it remained the same (Figure 2). During expiration, from baseline to 50% protrusion position, the maximum vorticity decreased from 16 to  $12 \text{ s}^{-1}$ , and from 50% to 75% protrusion position it increased from 12 to  $14 \text{ s}^{-1}$  (Figure 2). The clinical record of this patient was used to determine whether there is an improvement of the patient's symptoms. With the MAD *in situ* at 50% and 75% protrusion position, the main complaint of this patient, viz., snoring, was improved.

However, with the MAD *in situ* at 75% protrusion position, this patient reported some side-effects, such as tenderness in the temporomandibular joint region upon awakening. As his main sleep apnea symptom was improved to an acceptable level at 50% protrusion position, he was prescribed the MAD at 50% protrusion position. This patient was followed up two years after treatment by filling the ESS questionnaire, and his ESS score was 6.

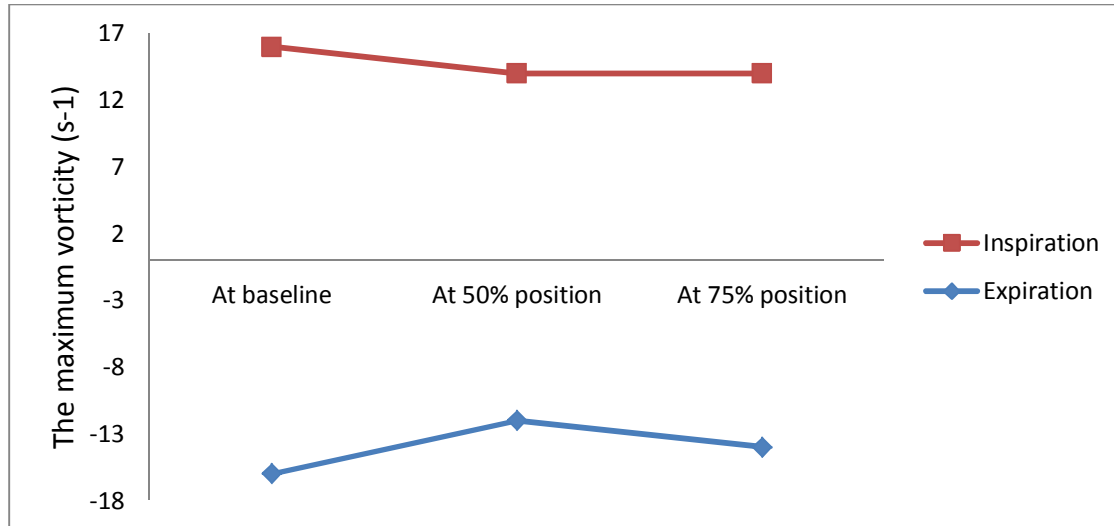


Figure 2 The maximum vorticity in the upper airway models during inspiration and expiration at three different protrusion positions

## Discussion

In our study, PIV was used to evaluate airflow characteristics (vorticity profiles) in the upper airway between the hard palate plane and the vocal cord plane at different mandibular protrusion positions.

For this patient, the funnel-like upper airway at baseline gradually changed into a cylinder-like one at 75% protrusion position. Compared with the cylinder-like upper airway, resistance of the funnel-like upper airway was greater, and more turbulence, quantified by the maximum vorticity, was observed (Figure 1). The turbulence increases the air pressure on the upper airway wall, which could cause tissue edema [8]. Besides, it is hypothesized that as tissues surrounding the upper airway are exposed to the abnormal airflow, such as high negative inspiratory pressure, in the long term, the anatomy of these tissues may change, e.g., enlargement of the tongue or the soft palate. These adaptive changes make the

upper airway narrower, which is unfavorable for air ventilation and causes a predisposition to OSA.

Vorticity is a mathematical concept used in fluid dynamics to describe the amount of turbulence in a fluid, which is equivalent to the curl of the fluid velocity [9]. The location of the maximum vorticity always occurs near the walls of the models and accompanies flow separations caused by sudden variations of the cross-sectional area perpendicular to the direction of the airflow. For OSA patients, the location of the maximum vorticity is the site where the axial cross-sectional area of upper airway changes significantly. Besides, vorticity is also a way to show the ventilation of the model, and by analyzing the distribution of vorticity contours, the ventilation of the upper airway can be determined in OSA patients [10]. During respiration, the maximum vorticity of the airflow was smaller with the MAD at 50% protrusion position *in situ* than without the MAD *in situ*, which indicates an improvement in ventilation of the upper airway with a MAD *in situ*. Compared to 50% protrusion position, the maximum vorticity at 75% protrusion position did not decrease during inspiration and it even increased during expiration. Therefore, the ventilation of the upper airway did not improve further (Figure 2). Besides, the symptoms of this patient were improved at both 50% and 75% protrusion position, but this patient reported more side-effects with the MAD at 75% protrusion position *in situ*. These results corroborate the findings of a previous study by Aarab et al., that there was no significant difference between the MAD set at 50% of the maximal protrusion and 75% of the maximal protrusion in the reduction of the apnea-hypopnea indices [5].

Only without the MAD *in situ* a polysomnography (PSG) of this patient was recorded, and not with the MAD *in situ* at 50% and 75% protrusion positions, which would have provided stronger evidence for the clinical application of this novel imaging technique. However, the patient reported improvement of the OSA symptoms with the MAD at 50% and 75% protrusion positions, which is consistent with the outcome of the PIV analysis. In this case report, there is a high radiation dose from the CT scans. For future study, it is recommended to use other imaging modalities such as cone beam computed tomography which has relatively lower radiation dose along with adequate contrast between the soft tissue and empty space to show the upper airway. The upper airway model used in the PIV analysis is made of rigid acrylic, which is different from the real upper airway. For future studies, it is

suggested to set up upper airway models using specific materials that could mimic more closely the behavior of the upper airway. The upper airway is a complex 3D structure and its airflow property is intricate. Another limitation of this case report is that only the airflow characteristics on the mid-sagittal plane of the upper airway were investigated. Modelling airflow properties within the complex 3D upper airway would require rather extensive computing resources, which could be incorporated in a future study. Notwithstanding those limitations, PIV is a promising tool to visualize the upper airway resistance, which is important in further understanding both the pathogenesis of OSA and the working mechanism of the MAD. For example, in clinical trials, this technique can be used to investigate the airflow characteristics between OSA patients and their controls or to compare the change of the airflow characteristic during different treatment modalities in OSA patients.

## Conclusion

The ventilation of the upper airway of this OSA patient was improved most with the MAD in situ at 50% protrusion position. PIV is a promising tool in evaluating airflow characteristics in the upper airway of the OSA patients.

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## **Chapter 10**

### **General discussion**





## General discussion

The pathogenesis of obstructive sleep apnea (OSA) is complicated and as yet not fully clarified [1]. Anatomical and aerodynamic characteristics of the upper airway are assumed to play an important role in the pathogenesis of OSA [2]. At the start of the research described in this thesis, it was unclear which anatomical and aerodynamic characteristics, obtained with three-dimensional (3D) imaging, were the most relevant ones in the upper airway collapse of OSA patients and in the treatment outcome of mandibular advancement device (MAD) therapy. Further, the reliability and accuracy of upper airway analysis based on 3D imaging had not yet been determined. Therefore, the two main aims of this thesis were: 1. to determine the reliability and accuracy of upper airway analysis based on 3D imaging (**Chapters 2-4**); and 2. to determine the most relevant anatomical and aerodynamic characteristics of the upper airway in the pathogenesis of OSA and in the treatment outcome of MAD therapy in OSA patients (**Chapter 5-9**).

In this chapter, the methodological aspects of this thesis and the main research outcomes are discussed in a broader context, and suggestions for future research are made.

## Methodological considerations

### *3D imaging in upper airway analysis*

3D upper airway measurements can be used to investigate the role of the upper airway morphology in the pathogenesis of OSA and in the treatment outcome of MAD therapy in OSA patients [3]. Therefore, it is important to determine the upper airway morphology in a reliable and accurate way. To date, there is a variety of imaging devices available for the depiction of the upper airway morphology [4], as well as a large number of software programs for the analysis of the upper airway morphology (at least 18 in 2011) [5]. However, the reliability and accuracy of upper airway analysis based on 3D imaging had not yet been determined. Therefore, we estimated the reliability and accuracy of the most commonly used imaging devices and software programs for the analysis of the upper airway. The five imaging devices and three software programs tested in this thesis were able to produce reliable results (**Chapters 3-4**). In Chapters 3-4, we determined that cone beam computed

tomography (CBCT) can be an accurate alternative to multiple multi-detector row computed tomography (MDCT) for the assessment of the upper airway, and that all three software programs can be used to analyze the upper airway morphology accurately. However, all imaging devices and all software programs underestimated the actual upper airway dimensions, which is in good agreement with previous studies [6-10]. As the measurement deviations from the gold standard were very small (measurement errors ranging from 1.1% to 10.8%), we argue that the influence of this inaccuracy on the measurements of the upper airway dimensions can be neglected (**Chapters 3-4**). Therefore, we assume that this inaccuracy did not affect our conclusions in **Chapters 5-9**. The advantages of CBCTs over MDCTs are the lower costs of these devices and the lower radiation dose to the patient [11, 12]. Therefore, we recommend using CBCTs for the determination of the upper airway morphology in research settings.

#### *Aerodynamic techniques in upper airway analysis*

Based on mathematical models of the upper airway derived from 3D images, both computational fluid dynamics (CFD) and particle imaging velocity (PIV) can be used to simulate the aerodynamic characteristics in the upper airway. However, both techniques have several limitations. Both CFD and PIV analyses are time consuming [13], and both techniques are difficult to perform and to understand for a researcher without a profound knowledge of engineering. Further, both analyses are based on 3D images, such as MDCT or CBCT images, which means that patients have to receive radiation prior to use of this technique. Finally, like for every new technique, before being applied in research settings, these aerodynamic methods should be validated. To our best knowledge, only in two studies CFD analysis was validated using a physical 3D airway model in vitro [13, 14]. However, the upper airway model used in these validation experiments was made of transparent rigid acrylic, which is different from the flexible upper airway in reality. Further, there are no studies on the validation of PIV analysis in the upper airway analysis. For future CFD and PIV validation studies, it is recommended to construct upper airway models using specific materials that could mimic the behavior of the upper airway during sleep. These future validation studies will determine if these techniques can indeed be used to investigate the aerodynamic characteristics of the upper airway in the pathogenesis of OSA and in the treatment outcome of MAD therapy in OSA patients.

### *Patients' condition during 3D imaging*

During the 3D imaging procedure, both the position of the patients (viz., supine versus non-supine) and their wake state could influence the upper airway morphology [15, 16]. It is obvious that most patients do not always sleep in their supine position. At this moment, there are no studies on the comparison of the upper airway morphology in different sleep positions based on 3D imaging [17]. However, there are studies comparing the upper airway morphology between upright and supine positions [15, 18]. Sutthiprapaporn et al. found that the anterior-posterior and lateral dimension of the minimum cross-sectional area ( $CSA_{min}$ ) of the upper airway was larger in the upright position than in the supine position [18]. Van Holsbeke et al. found that airway resistance decreased by 26.5% in the upright position [15]. Although we realize that the upper airway dimensions are probably smaller in the supine position than in the non-supine positions, the conclusions of our comparison studies ("OSA patients versus controls", **Chapters 5-6**; and "responders versus non-responders", **Chapters 7-8**) are not affected by this methodological aspect, because all participants underwent the CBCT imaging in the supine position.

OSA only occurs during sleep, and OSA patients experience little or no problems with their breathing while awake [19]. The morphology of the upper airway during sleep is different from that while awake [2]. Due to a loss of muscle tone during sleep, a narrowing of the upper airway can occur [20]. However, it is extremely difficult to take images during natural sleep, so that this is only scarcely performed in small sample sizes ( $N=1-20$ ) [21-23]. In these studies, participants had to sleep in an MRI device for five hours [21] or 90 minutes [23], which is not comparable to an overnight sleep study and also induced extra costs and time investment [21-23]. In this context, drug-induced sleep could be an alternative option [24]. Drug induced sleep endoscopy (DISE) is an evaluation technique that involves the assessment of individuals under pharmacologic sedation designed to simulate natural sleep, utilizing fiberoptic endoscopy to examine the upper airway [25]. Therefore, DISE allows a dynamic examination of the upper airway morphology in a sleeping OSA patient [26]. However, the main limitation of DISE is that there is currently no universally accepted DISE classification system for analyzing anatomic levels/structures and severity of obstruction [27-29]. Besides, drugs used for sedation can have inhibitory effects on airway muscle tone and ventilator drive, thereby potentially confounding the imaging results [24]. In our studies, the patients underwent the imaging procedure while awake. We hypothesize that the

difference between both groups in our comparison studies (“OSA patients versus controls”, **Chapters 5-6**; and “responders versus non-responders”, **Chapters 7-8**) is influenced in a comparable way during sleep and while awake, which would minimize the effect of sleep on the comparison of these groups.

#### *Conclusion of the methodological consideration*

We realize that ideally, we would like to have dynamic images of the upper airway during the natural sleep of an OSA patient to understand the role of upper airway morphology in the pathogenesis of OSA. However, CBCT images of the upper airway taken in a supine position and during the awake state have at least taught us that there are indeed differences in upper airway morphology and in the aerodynamic characteristics between OSA patients and their controls that may explain the collapse of the upper airway in OSA patients (**Chapters 5-6**). Moreover, based on these images, we learned that there is no difference in upper airway morphology between responders and non-responders, but OSA patient with a short maxillary length and a small maxillomandibular enclosure size may respond better to MAD treatment (**Chapter 7**) (see below).

#### **OSA patients versus controls**

In this thesis, we found that a small  $CSA_{min}$  of the upper airway is the most relevant anatomical characteristic related to the pathogenesis of OSA (**Chapter 5**), and that a high resistance during expiration ( $R_{ex}$ ) of the airflow in the upper airway is the most relevant aerodynamic characteristic related to the pathogenesis of OSA (**Chapter 6**). Further, we found a negative correlation between the  $CSA_{min}$  and the  $R_{ex}$  of the upper airway. Therefore, it is hypothesized that in OSA patients, the smaller  $CSA_{min}$  will result in a higher  $R_{ex}$  of the upper airway and will therefore yield a higher risk of collapse during sleep. Based on current literature, several anatomical and non-anatomical factors may contribute to the small upper airway size in OSA patients. It was suggested that maxillary and mandibular malformations, such as retrognathia and micrognathia, are likely to have direct etiological roles in OSA by reducing the upper airway size [30-33]. Furthermore, neuromuscular abnormalities, such as muscle dysfunction, could also influence the upper airway size [34]. Besides, a relatively small change in lung volume also has an important effect on the upper airway size in OSA patients [35, 36]. Some neuroventilatory factors, such as unstable ventilatory control (high

loop gain) [37-39] and a low respiratory arousal threshold [40-42], also play an important role in OSA pathogenesis for certain patients.

The interaction between the above factors and the upper airway morphology may ultimately determine the presence or absence of OSA as well as its severity [38]. Insight in the relative contribution of these different pathophysiological factors to the upper airway collapse may help us in characterizing different phenotypes of OSA patients [38, 43, 44]. These kind of studies will help prescribing targeted therapies for OSA patients according to their specific characterization [38, 40]. For example, for patients with upper airway muscle dysfunction, treatments such as hypoglossal nerve stimulation [45] and muscle training exercises [46, 47] might be helpful [40]. From the perspective of prevention of OSA, several strategies can be applied to reduce the risk of having OSA. For example, for the overweight population, effective strategies to achieve long-term weight loss could be a strategy to prevent OSA [48]. For the children with disproportionate craniofacial anatomy, such as maxillary constriction, rapid maxillary expansion might be helpful to prevent OSA in adulthood [49, 50].

### **Responders versus non-responders**

MADs are thought to act primarily by advancing the mandible during sleep [51], and by improving several aerodynamic characteristics of the upper airway (**Chapter 8**) [13, 52]. However, the response to MADs varies among the OSA patients [53]. In this thesis, we found no significant difference in the anatomical characteristics of the upper airway between responders and non-responders to MADs at baseline (**Chapter 7**). Some previous studies also found no difference [54, 55], while others found that the upper airway anatomy of non-responders to MADs was different from that of responders [56-64]. Moreover, as to upper airway morphology, both wider [60-62] and narrower [56, 63, 64] upper airway were said to be beneficial for OSA patients [58]. These inconsistent results may be due to variations in the definition of treatment success, in the design of the MAD (titratable or single-jaw position), in the configuration of samples, in the use of different imaging techniques, and in the mandibular position [40, 53, 58, 65, 66]. Therefore, well designed prospective studies with a larger sample size are needed to determine the role of the upper airway morphology in the treatment response to MADs in OSA patients.

Due to the multifactorial nature of OSA pathogenesis, the treatment outcome of MADs could be influenced by many factors [67]. For clinical practice, it is important to know if different phenotypes of the responders to MADs are present. Sutherland et al. summarized different phenotypes of the responders to MADs based on the following four aspects: clinical characteristics, polysomnographic characteristics, craniofacial structure, and physiological characteristics [68]. Less obese, younger OSA patients were more likely to respond to MADs [68]. Several polysomnographic characteristics, such as less severe OSA [68] and NREM or non-stage dependent OSA rather than REM-predominant OSA [68, 69] may be indicators for the responders to MADs. Besides, several craniofacial skeletal features, such as cranial base angle, mandibular plane angle, and hyoid to mandibular plane distance, were also related to treatment response [30, 70, 71]. Moreover, from a physiological viewpoint, most responders were those who had a less collapsible airway [1, 72] and primarily oropharyngeal collapse [73]. However, although clinical characteristics, craniofacial structure, and PSG characteristics of OSA may be related to treatment response, in clinical practice, these factors are not reliable for selecting individual patients for MAD treatment [1, 56, 69, 74]. To the best of our knowledge, it is still a challenge to identify responders to MAD by using a simple, reliable, and cost-effective phenotypic models, which should be addressed in future studies.

## Conclusions

The following conclusions can be drawn from this thesis:

1. The methodology of landmark localization and upper airway measurements used in our study shows an excellent reliability and can thus be recommended in the upper airway analysis on CBCT images. **(Chapter 2)**
2. Significant differences were observed in the volume and cross-sectional area measurements of the upper airway by using different MDCT and CBCT scanners. The Siemens MDCT and the Vatech CBCT scanners were more accurate than the GE MDCT, NewTom 5G, and Accuitomo CBCT scanners. In clinical settings, CBCT scanners offer an alternative to MDCT scanners in the assessment of the upper airway morphology. **(Chapter 3)**

3. All three software packages used in this study offered reliable volume, minimum cross-sectional area, and length measurements of the upper airway. The upper airway length measurements were the most accurate results in all software packages. All software packages underestimated the upper airway dimensions of the anthropomorphic phantom. **(Chapter 4)**
4. Based on a systematic review, we concluded that the most relevant anatomical characteristic of the upper airway related to the pathogenesis of OSA is a small minimum cross-sectional area. **(Chapter 5)**
5. The most relevant aerodynamic characteristic of the upper airway in the collapse of the upper airway in OSA patients is airway resistance during expiration ( $R_{ex}$ ). Therefore, the repetitive collapse of the upper airway in OSA patients may be explained by a high  $R_{ex}$ , which is related to the  $CSA_{min}$  of the upper airway and to the volume of the upper airway. **(Chapter 6)**
6. OSA patients with a short maxillary length and a small tongue area may respond better to MAD treatment than patients with a large maxillary length and a large tongue area. However, after controlling for the effect of BMI, no significant difference in the tongue area between responders and non-responders was present. **(Chapter 7)**
7. Maxillomandibular advancement (MMA) surgery and MAD therapies improve several aerodynamic characteristics of the upper airway. However, due to several limitations of the selected studies in our systematic review, there is not enough evidence yet to support computational fluid dynamics (CFD) analysis as a useful tool to predict the treatment outcome in OSA patients before starting these therapies. **(Chapter 8)**
8. The ventilation of the upper airway of our OSA patient was improved most with the MAD *in situ* at 50% protrusion position. Particle imaging velocimetry (PIV) is a promising tool in evaluating airflow characteristics in the upper airway of the OSA patients. **(Chapter 9)**

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## **Chapter 11**

### **Summary**



## Summary

Obstructive sleep apnea (OSA) is a sleep-related breathing disorder, often associated with oxygen desaturations and arousals from sleep. OSA is a major public health problem, affecting a significant portion of the population, approximately 3-7% of adult men and 2-5% of adult women. The critical factors that play a role in the pathogenesis of OSA and the treatment outcome of OSA are still not completely clear. The aim of this thesis, therefore, was to determine the role of the upper airway in the pathogenesis of OSA, as well as in the treatment outcome of OSA.

Three-dimensional upper airway measurements could be used to further investigate the role of the upper airway in the pathogenesis of OSA. However, the upper airway measurements must be reliable and accurate. For this reason we have carried out an investigation into the reliability and accuracy of the procedures of upper airway measurements. The methodology of landmark localization and upper airway measurements used in our study showed an excellent reliability and can thus be recommended for the upper airway analysis (**Chapter 2**). With regard to the accuracy of different CT scanners, we found that cone beam computed tomography (CBCT) and multi-detector row computed tomography (MDCT) scanners generally underestimated the upper airway dimensions, which is most probably due to the partial volume effect of the segmentation process. This underestimation, however, is small and probably not of clinical relevance. CBCT scanners can offer adequate clinical accuracy for the assessment of the upper airway (**Chapter 3**). To determine the accuracy of different software programs, we developed an anthropomorphic phantom of the upper airway as the gold standard. Three software programs (Amira®, Ondemand3D®, 3Diagnosis®) were used to perform upper airway measurements and all of them underestimated the upper airway dimensions by 2.1 - 10.8% (**Chapter 4**).

The above procedures of upper airway analysis investigated in the previous chapters (**Chapters 2-4**) have been applied to clinical research. In a systematic review, we found that the most relevant anatomical characteristic of the upper airway related to the pathogenesis of OSA is a small minimum cross-sectional area. Upper airway with a small cross-sectional area has an increased tendency toward obstruction of the upper airway (**Chapter 5**).



In addition to the anatomical characteristics of the OSA patients, we have investigated the aerodynamic characteristics of the upper airway in OSA patients. Using computational fluid dynamics (CFD), we found that the airway resistance during expiration is the most relevant aerodynamic characteristic of the upper airway related to the pathogenesis of OSA (**Chapter 6**). We also compared the craniofacial anatomy between responders and non-responders to mandibular advancement device (MAD) therapy and found that OSA patients with a short length of the maxilla and a small maxillomandibular enclosure size may respond better to MAD than patients with a large maxillary length and a large maxillomandibular enclosure size (**Chapter 7**).

Based on a systematic review, we concluded that maxillomandibular advancement (MMA) surgery and MAD may improve several aerodynamic characteristics (viz. airway resistance, velocity, and wall static pressure) of the upper airway (**Chapter 8**). Using particle imaging velocimetry (PIV), we found that the ventilation of the upper airway of an OSA patient improved most with the MAD in situ at 50% protrusion position (**Chapter 9**). These findings help us further understand the role of the upper airway in the pathogenesis of OSA, and its effects on the treatment outcome in OSA patients from the perspectives of both anatomy and aerodynamics (**Chapter 5-9**).

In the general discussion (**Chapter 10**), we present the limitations of the various studies and make suggestions for future research.

The conclusions of this thesis can be summarized as follows:

1. The methodology of upper airway measurements used in this study can be reliably used to perform upper airway analysis on CBCT images (**Chapter 2**).
2. CBCT scanners offer an alternative to MDCT scanners in the assessment of the upper airway morphology. All devices produced dimensions of the upper airway that are smaller than the real dimensions, although this difference is probably clinically irrelevant (**Chapter 3**).
3. All three software programs used in this study can offer reliable measurements of the upper airway, but underestimate the dimensions of the upper airway (**Chapter 4**).

4. The minimum cross-sectional area of the upper airway is the most relevant anatomical characteristic in the occurrence of OSA **(Chapter 5)**.
5. A higher airway resistance during expiration is the most relevant aerodynamic characteristic of the airflow in the pathogenesis of OSA **(Chapter 6)**.
6. Before controlling for BMI, OSA patients with a shorter maxillary length, a smaller maxillomandibular enclosure size, and a smaller tongue area may respond better to MAD treatment than patients with a longer maxillary length, a larger maxillomandibular enclosure size and a larger tongue area. After controlling for BMI, there was no longer a significant difference in the tongue area between responders and non-responders. **(Chapter 7)**.
7. MMA surgery and MAD therapy can improve the aerodynamic characteristics of the upper airway in OSA patients **(Chapter 8)**.
8. The effect of MAD therapy at different protrusion positions for an OSA patient can be analyzed by particle imaging velocimetry **(Chapter 9)**.



## **Chapter 12**

### **Samenvatting**



## Samenvatting

Obstructieve slaapapneu (OSA) is een slaapgerelateerde ademhalingsstoornis, vaak geassocieerd met zuurstoftekort en verstoring van de slaap. OSA is een belangrijk probleem in de volksgezondheid en treft een aanzienlijk deel van de bevolking; ongeveer 3-7% van de volwassen mannen en 2-5% van de volwassen vrouwen. De kritische factoren die een rol spelen bij de pathogenese van OSA en bij de behandeluitkomst van OSA zijn nog niet helemaal duidelijk. Het doel van dit proefschrift was dus om de rol van kenmerken van de bovenste luchtweg in de pathogenese en in de behandeluitkomst van OSA te bepalen.

Drie-dimensionale metingen van de bovenste luchtweg kunnen worden gebruikt om de rol van de bovenste luchtweg in de pathogenese van OSA verder te onderzoeken. De metingen van de bovenste luchtwegen moeten echter betrouwbaar en accuraat zijn. Om deze reden hebben we een onderzoek uitgevoerd naar de betrouwbaarheid en nauwkeurigheid van de procedures van de luchtwegmetingen. De methodologie van lokalisatie van meetpunten en van de metingen van de bovenste luchtweg in onze studie bleek een uitstekende betrouwbaarheid te hebben en kan dus worden aanbevolen voor analyse van de de bovenste luchtweg (**Hoofdstuk 2**). Met betrekking tot de nauwkeurigheid van verschillende CT-scanners, vonden we dat cone beam computed tomography (CBCT) en multi-detector row computed tomography (MDCT) scanners over het algemeen de bovenste luchtweg afmetingen onderschatten, hetgeen waarschijnlijk het gevolg is van het *partial volume effect* van het segmentatie proces. Deze onderschatting is echter klein en waarschijnlijk niet van klinische relevantie. CBCT scanners kunnen voldoende klinische nauwkeurigheid bieden voor de beoordeling van de bovenste luchtweg (**Hoofdstuk 3**).

Om de nauwkeurigheid van verschillende softwareprogramma's te bepalen, ontwikkelden we een antropomorf fantoom van de bovenste luchtweg als de gouden standaard. Drie softwareprogramma's (Amira®, Ondemand3D®, 3Diagnosis®) werden gebruikt om de bovenste luchtwegmetingen uit te voeren en ze onderschatten de afmetingen van de bovenste luchtweg met 2.1 - 10.8% (**Hoofdstuk 4**).

De procedures voor de analyse van de bovenste luchtweg zoals gepresenteerd in de vorige hoofdstukken (**Hoofdstukken 2-4**), zijn toegepast in klinisch onderzoek. In een systematische review bleek dat het meest relevante anatomische kenmerk van de bovenste luchtweg in

verband met de pathogenese van OSA een kleine minimale doorsnede is. Een luchtweg met een kleine doorsnede heeft een verhoogde neiging tot obstructie van de bovenste luchtweg **(Hoofdstuk 5)**.

Naast anatomische eigenschappen van OSA-patiënten hebben we de aërodynamische eigenschappen van de bovenste luchtweg in OSA-patiënten onderzocht. Met behulp van *computer fluid dynamics* (CFD) vonden we dat de luchtwegweerstand tijdens het uitademen de meest relevante aërodynamische karakteristiek van de bovenste luchtweg is die verband houdt met de pathogenese van OSA **(Hoofdstuk 6)**. Wij vergeleken ook de craniofaciale anatomie tussen respondenten en niet-responders bij *mandibular advancement device* (MAD) therapie en het bleek dat OSA-patiënten met een korte lengte van de maxilla en een klein maxillomandibulair volume beter reageren op MAD dan patiënten met een grote maxillaire lengte en een groot maxillomandibulair volume **(Hoofdstuk 7)**.

Gebaseerd op een systematisch review, konden we concluderen dat een maxillomandibulaire protrusie (MMA) operatie en MAD verschillende aërodynamische eigenschappen kunnen verbeteren (bijv. luchtwegweerstand, lichtsnelheid en statische wanddruk) van de bovenste luchtweg **(Hoofdstuk 8)**. Met behulp van partikelbeeldvormende velocimetrie (PIV) vonden we dat de doorstroming in de bovenste luchtweg van een OSA-patiënt het meest verbeterde met de MAD in situ bij 50% protrusie **(Hoofdstuk 9)**.

Deze bevindingen helpen ons de rol van de bovenste luchtweg in de pathogenese van OSA verder te begrijpen alsmede de effecten op de behandeluitkomst van OSA-patiënten vanuit zowel anatomisch als aerodynamisch perspectief **(Hoofdstuk 5-9)**.

In de algemene discussie **(Hoofdstuk 10)** presenteren wij de beperkingen van de verschillende studies en doen we suggesties voor toekomstig onderzoek.

De conclusies van dit proefschrift kunnen als volgt worden samengevat:

1. CBCT-afbeeldingen kunnen betrouwbaar worden gebruikt om metingen van de bovenste luchtweg uit te voeren **(Hoofdstuk 2)**.
2. Driedimensionale datasets verkregen met CBCT-scanners zijn vergelijkbaar met die verkregen met MDCT-scanners. Alle apparaten produceren afmetingen van de

bovenste luchtweg die kleiner zijn dan de echte afmetingen, hoewel dit verschil waarschijnlijk klinisch irrelevant is (**Hoofdstuk 3**).

3. Dedicated software programma's kunnen betrouwbare metingen van de bovenste luchtweg bieden, maar onderschatten de afmetingen van de bovenste luchtweg (**Hoofdstuk 4**).
4. De minimale doorsnede van de bovenste luchtweg is het meest relevante anatomische kenmerk in het vóórkomen van OSA (**Hoofdstuk 5**).
5. Een hogere luchtwegweerstand tijdens het uitademen is het meest relevante aërodynamische kenmerk van de luchtstroom in de pathogenese van OSA (**Hoofdstuk 6**).
6. Zonder correctie voor BMI, lijkt het dat OSA-patiënten met een kortere maxillaire lengte, een kleiner maxillomandibulair volume en een kleinere omtrek van de tong beter reageren op MAD-behandeling dan patiënten met een langere maxillaire lengte, een groter maxillomandibulair volume en een grotere omtrek van de tong. Na correctie voor BMI, zijn er geen verschillen tussen responders en niet-responders (**Hoofdstuk 7**).
7. MMA-operatie en MAD-therapie kunnen de aërodynamische eigenschappen van de bovenste luchtweg in OSA-patiënten verbeteren (**Hoofdstuk 8**).
8. Het effect van MAD-therapie bij verschillende protrusieposities voor een OSA-patiënt kan worden geanalyseerd door middel van *particle imaging velocitometry* (**Hoofdstuk 9**).





## **Curriculum Vitae**

### Curriculum Vitae

Hui Chen was born in Chengwu, Heze, Shandong, China on March 13, 1989. In 2005, she obtained her high school diploma at No.1 high school, Chengwu, China. In the same year, she started her dentistry study at Binzhou Medical University. After graduating as a dentist with *cum laude* in 2010, she joined the 3-year master program of orthodontics in Shandong University. In 2013, she graduated as an orthodontist and joined the PhD program in the department of Oral Radiology and the department of Oral Kinesiology at the Academic Centre for Dentistry under the supervision of Prof.Dr. Paul van der Stelt, Prof.Dr. Frank Lobbezoo, Prof.Dr. Jan de Lange, and Dr. Ghizlane Aarab. She is an active researcher in 3D imaging of the upper airway in obstructive sleep apnea.

## PhD Portfolio



## PhD Portfolio

### PhD training summary

Part		ECTS point
<b>Course</b>	a. Course on scientific integrity	2
	b. Course statistics and Methodology	3
	c. Course Writing and presenting in English	4
	d. Oral Biology	4
	e. Grant writing	1
	f. Epidemiology & Evidence Based Practice in Dentistry and Oral Health Care	3
<b>Congress</b>	a. Congress visits	10
<b>Supervision</b>	a. Guidance and supervision by the supervisors	10
<b>Total</b>		37

### Expertise and Experience

- (1) Orthodontist/Dentist
- (2) Image Processing.
- (3) 3D Printing.
- (4) Finite element analysis.

### Presentations and Awards

- (1) 2017: World Sleep 2017 congress, Prague, Czech Republic: Differences in three-dimensional craniofacial anatomy between responders and non-responders to mandibular advancement splint treatment in obstructive sleep apnea patients (Poster presentation accepted).

(2) 2017: 26th American Academy of Dental Sleep Medicine Annual Meeting, Boston, USA: Aerodynamic characteristics of the upper airway: obstructive sleep apnea patients versus control subjects (Poster presentation).

(3) 2017: 21st Congress of the International Association of Dento-Maxillo-Facial Radiology, Kuoshiung, Taiwan, China: Anatomical and functional modeling of the upper airway in obstructive sleep apnea patients and controls (Oral presentation; **Research Award, Travel Grant**).

(4) 2016: 3D Printing in Healthcare, Amsterdam, the Netherlands.

(5) 2016: Mimics Innovation Conference, Leuven, Belgium.

(6) 2016: 25th European Congress of Dental-maxillofacial Radiology, Cardiff: Reliability and accuracy of imaging software for three-dimensional analysis of the upper airway on cone beam CT. (Oral presentation; **Research Award**)

(7) 2015: 20th International Academy Dental-maxillofacial Radiology Congress, Santiago, Chile: Upper airway analysis: reliability of anatomical landmark localization and of 3-dimensional measurements. (Oral presentation; **finalist of the Research Award**)

(8) 2015: 2nd Junior Meeting of European Academy Dental-maxillofacial Radiology, Freiburg, Germany: Three-dimensional imaging of the upper airway anatomy in obstructive sleep apnea: a systematic review. (Oral presentation)

(9) 2014: 24th European Academy Dental-maxillofacial Radiology Conference, Cluj, Romania: Simulation of airflow in the upper airway of obstructive sleep apnea by particle image velocimetry (Poster presentation).

(10) 2012: 14th International Symposium on Dentofacial Development and Function (XIVth DFDF), Beijing, China: A novel porcine acellular dermal matrix scaffold used in periodontal regeneration.

(11) 2012: 11th National Congress on Orthodontics of China (11th NCO), Beijing, China

(12) 2012: Orthodontic Forum of Peking University, Beijing, China

### **Professional Memberships**

(1) Member of the European Academy Dental-maxillofacial Radiology (EADMFR)

(2) Member of the International Academy Dental-maxillofacial Radiology (IADMFR)

(3) Member of the American Academy of Dental Sleep Medicine (AADSM)

(4) Member of World Sleep Society (WSS/WASM)

(5) Board Member of PhD council of University of Amsterdam (UvaPro) (2014-2015)

(6) Board Member of PhD council of ACTA (ACTAPro) (2014-2015)

## Scholarship and Grant

- (1) 2006-2007: National Scholarship; Ministry of Education of China; 8,000 CNY
- (2) 2007-2008: National Endeavor Fellowship; Ministry of Education of China; 5,000 CNY
- (3) 2008-2009: National Scholarship; Ministry of Education of China; 8,000 CNY
- (4) 2009-2010: National Endeavor Fellowship; Ministry of Education of China; 5,000 CNY
- (5) 2013.11-2017.10: Chinese Scholarship Council. Support for PhD project. 57,600 EUR
- (6) Main investigator: The role of race in the pathogenesis of obstructive sleep apnea: Asians versus Caucasians. Koninklijke Nederlandse Akademie van Wetenschappen (KNAW) en Nederlandse Organisatie voor Wetenschappelijk Onderzoek (NWO) (Project number: 530-5CDP12; 26,700 EUR)

## Organizer and Speaker of international exchange program between China and the Netherlands

- (1) 2014: National Continuing Education Program (Dental-maxillofacial radiology) in Jinan, China; Course on dento-maxillofacial radiology in Qingdao, China;
- (2) 2016: National Continuing Education Program (Oral kinesiology and oral radiology) in Jinan, China;
- (3) 2017: National Continuing Education Program (Oral kinesiology) in Jinan, China.

## Co-operation Partners

- (1) 2013-present: Department of Orthodontics, Shandong University, China
- (2) 2013-present: Department of Oral and Maxillofacial Surgery, Academic Medical Center (AMC), the Netherlands
- (3) 2014-present: Department of Orthodontics, University of Sydney, Australia
- (4) 2014-present: 3D Innovation Lab, Department of Oral and Maxillofacial Surgery/Oral Pathology, VU University Medical Center (VUmc) Amsterdam, The Netherlands
- (5) 2016-present: Division of Image Processing, Department of Radiology, Leiden University Medical Center, Leiden, the Netherlands



## Publication list

- (1) **Chen, H**, Aarab G, de Ruiter MH, de Lange J, Lobbezoo F, van der Stelt PF. Three-dimensional imaging of the upper airway anatomy in obstructive sleep apnea: a systematic review. *Sleep Medicine* 2016; 21: 19-27.
- (2) **Chen H**, Aarab G, Parsa A, de Lange J, van der Stelt PF, Lobbezoo F. Reliability of three-dimensional measurements of the upper airway on cone beam computed tomography images. *Oral surgery, oral medicine, oral pathology and oral radiology* 2016; 122: 104-10.
- (3) **Chen H**, van Eijnatten M, Wolff J, de Lange J, van der Stelt PF, Lobbezoo F, Aarab G. Reliability and accuracy of imaging software for three-dimensional analysis of the upper airway on cone beam CT. *Dentomaxillofacial Radiology* 2017; 46: 20170043.
- (4) **Chen H**, van Eijnatten M, Aarab G, Forouzanfar T, de Lange J, van der Stelt PF, Lobbezoo F, Wolff J. Accuracy of MDCT and CBCT in three-dimensional evaluation of the upper airway morphology. *European Journal of Orthodontics* 2017; 1-6. doi:10.1093/ejo/cjx030
- (5) **Chen H**, Aarab G, Liu J, Yu, Guo J, van der Stelt PF, Lobbezoo F. A novel imaging technique to evaluate airflow characteristics in the upper airway of an obstructive sleep apnea patient. *Clinical Case Report* 2016. doi:10.1002/ccr3.716
- (6) Guo J, **Chen H**, Wang Y, Cao CB, Guan GQ. A novel porcine acellular dermal matrix scaffold used in periodontal regeneration. *International Journal of Oral Science* 2013; 5: 37-43.

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