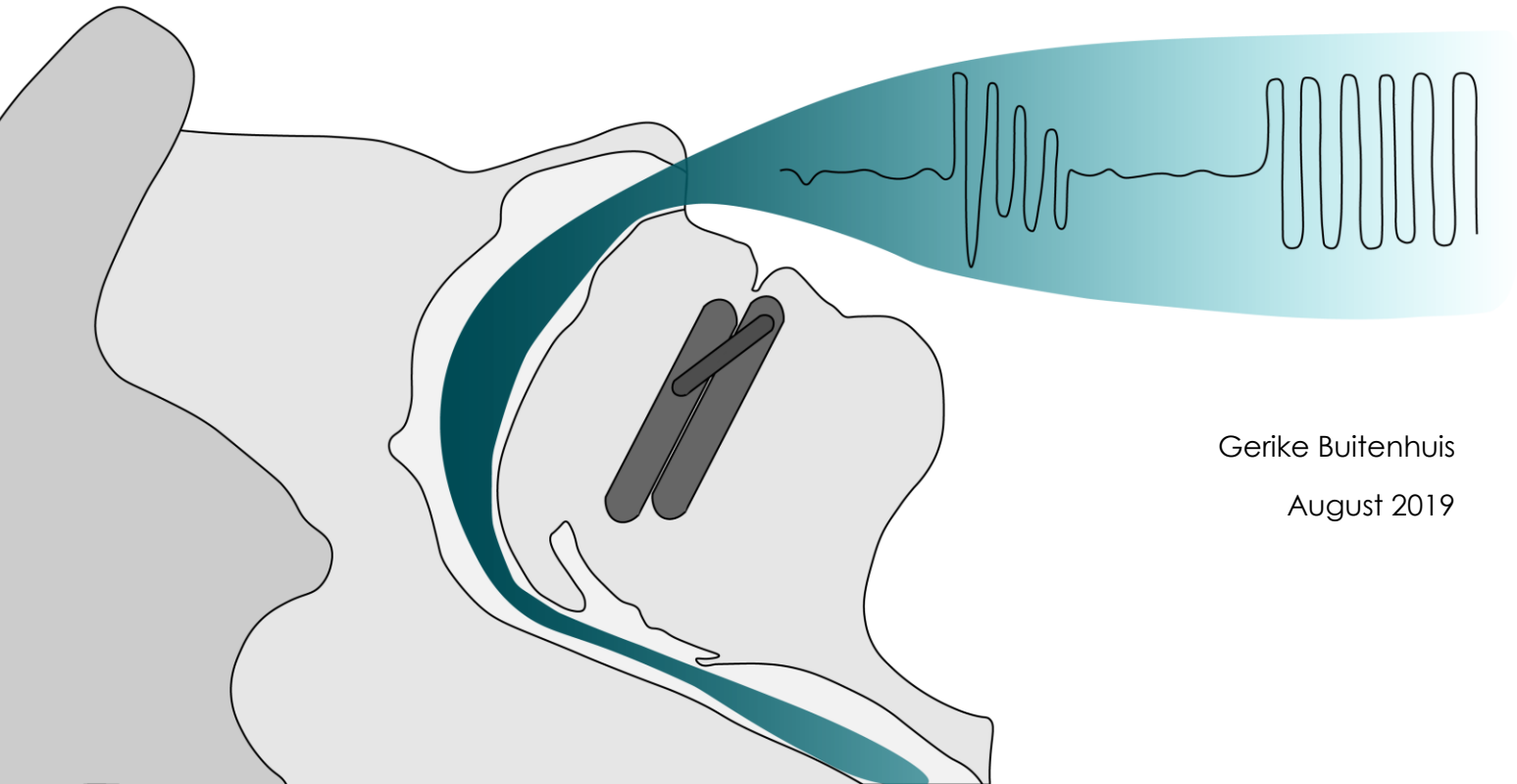
Use of upper airway measurements for the prediction of successful mandibular advancement device therapy both in protrusion and retraction of the mandible in patients with obstructive sleep apnoea

Master's thesis



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Abstract

Introduction: Obstructive sleep apnoea syndrome (OSAS) is a sleep-related breathing disorder which is present in about 2-7% of the middle-aged men and women. In patients with mild OSAS, the mandibular advancement device (MAD) is the preferred therapy and in patients with moderate OSAS, it is one of the treatment options. A MAD protrudes the mandible forward, causing an increased upper airway volume. However, MAD therapy is only completely successful in around 48% of the patients. On top of that, a MAD is custom-made and the titration period takes a couple of months. Therefore, a predictive method for the effectiveness of MAD therapy is desirable. At the moment, no clinical acceptable prediction methods exist. Lung function measurements are a possibility to assess the upper airway in OSAS patients. In this study, the use of flow and resistance parameters obtained by the forced oscillation technique (FOT), negative expiratory pressure (NEP) and spirometry are investigated for the prediction of successful MAD therapy.

Methods: Twenty-three patients with OSAS were included. Patients were 18 years or older and have an initial apnoea-hypopnoea index of 15 or higher. The patients have (had) a MAD therapy with optimal titration. Patients were included at the moment when they were referred by the special dentistry for a control poly(somno)graphy or when they have had a control poly(somno)graphy within the last year and a half. During the visit to the hospital, three different lung function tests were performed; spirometry, FOT and NEP. During these measurements, the patient breathed through an adjustable mouthpiece, which protrudes or retracts the mandible. The measurements were performed twice while the subject was in a supine position; with the mandible completely protruded and with the mandible completely retracted. After the measurements, a questionnaire was filled in to evaluate the subject's experience. Flow, pressure and resistance parameters were obtained. The absolute and relative differences in these parameters between the measurements with the mandible in a completely protruded and retracted position were used as predictive value for MAD success.

Results: There were no significant differences in spirometry parameters between the MAD successful and non-successful group. Two parameters of the NEP differed significantly between the successful and non-successful group. Multiple parameters of the FOT differed significantly between the two groups. Especially the parameters of the maximal fast in- and expiration differed significantly between the two groups with an area under the curve between 0.72 and 0.83. Most of these parameters included the linear approximation between the specific parameters (based on both the resistance and reactance values) and the inspiratory volume. The user experience did not differ between the MAD successful and non-successful group.

Conclusion: None of the spirometry parameters are suitable as predictors for MAD success. Two parameters of the NEP differed significantly between the MAD successful and non-successful group and could possibly in the future be used to predict MAD success. Multiple parameters of the FOT differed significantly between the two groups and have the potential to be used as predictors for MAD success. Further research should focus on the FOT as a screening method and on developing a multivariate model based on FOT parameters for the prediction of MAD success.

List of abbreviations

AHI	Apnoea-Hypopnoea Index
AUC	Area Under the Curve
AX	Area under the Reactance Curve
BMI	Body-Mass Index
Ca	Capacitance
C_{max}	Maximum coefficient of respiration approximation trendline
CO_2	Carbon Dioxide
CPAP	Continuous Positive Airway Pressure
C_{Rmax}	Maximum coefficient of the resistance curve
C_{Xmin}	Minimum coefficient of the reactance curve
DISE	Drug-Induced Sleep Endoscopy
EFL	Expiratory Flow Limitation
EMG	Electromyogram
ERS	European Respiratory Society
ERV	Expiratory Reserve Volume
FEV1	Forced Expiratory Volume in one second
FIV1	Forced Inspiratory Volume in one second
FOT	Forced Oscillation Technique
FRC	Functional Residual Capacity
Fres	Resonance Frequency
FVC	Forced Vital Capacity
I	Inertance
IOS	Impulse Oscillometry System
IVC	Inspiratory Vital Capacity
MAD	Mandibular Advancement Device
MEF50	Expiratory Flow rate at 50% of vital capacity
MST	Medisch Spectrum Twente
MIF50	Inspiratory Flow rate at 50% of vital capacity
NEP	Negative Expiratory Pressure
NPV	Negative predictive value

OSAS	Obstructive Sleep Apnoea Syndrome
$PaCO_2$	Arterial carbon dioxide pressure
P_{crit}	Critical closing pressure
PFT	Pulmonary Function Test
PPV	Positive predictive value
P_{tm}	Transmural Pressure
VAS	Visual analog scale
$\dot{V}_{max}$	Maximum absolute peak flow in the second half of the impulse segment
$\dot{V}_{min}$	Minimum absolute peak flow in the first half of the impulse segment
$\dot{V}_{opposite}$	Opposite reaction in flow of the respiratory system
R5	Resistance at 5 Hz
R5-20	Resistance at 5 Hz minus the resistance at 20 Hz
R20	Resistance at 20 Hz
RCMP	Remotely Controlled Mandibular Positioner
R_{neg}	Negative resistance
ROC	Receiver Operating Characteristic
Rrs	Resistance of the respiratory system
RV	Residual Volume
$\Delta \dot{V}$	Drop in flow after the onset of NEP
$V_{0.2}$	Volume exhaled during the first 0.2 seconds after NEP application or during the first 0.2 seconds of the previous three expirations
$V_{0.5}$	Volume exhaled during the first 0.5 seconds after NEP application or during the first 0.5 seconds of the previous three expirations
VC	Vital Capacity
X5	Reactance at 5 Hz
Xrs	Reactance of the respiratory system
Z_{rs}	Respiratory impedance

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Chapter 1 – Introduction

Obstructive sleep apnoea syndrome (OSAS) is a sleep-related breathing disorder which is present in about 2-7% of middle-aged men and women[1, 2]. OSAS is characterized by repetitive collapse of the upper airway during sleep[3, 4]. The diagnosis of OSAS is based on an overnight poly(somno)graphy measurement by calculating the apnoea-hypopnoea index (AHI)[5]. The AHI is the average number of disturbed breathing events per hour of sleep and OSAS is often defined as an AHI ≥5 with associated symptoms or an AHI ≥15 regardless of the presence of symptoms. Associated symptoms include excessive daytime sleepiness, fatigue, and impaired cognition. Several mechanisms are important in the appearance of OSAS, of which the upper airway anatomy is believed to be the most important[6]. Increased soft tissue or a small bony compartment surrounding the airway results in an anatomically small pharyngeal airway[7]. During sleep, muscle activity is reduced and the anatomically small pharyngeal airway increases the change of repetitive airway collapses. Untreated OSAS is a risk factor for the development of cardiovascular, central nervous system and endocrine system disorders[5].

The gold standard therapy for severe OSAS is continuous positive airway pressure (CPAP) therapy[8]. However, more than 40% of patients do not endure or are not compliant with CPAP therapy[9]. Another therapy for the treatment of OSAS is a mandibular advancement device (MAD)[3]. MAD therapy is considered as a primary intervention in patients with mild OSAS (AHI: 5-15) and one of the optional treatments in patients with moderate OSAS (AHI: 15-30), or those who refuse or cannot tolerate CPAP therapy[10, 11]. The MAD protrudes the mandible forward, causing an increased upper airway volume[3]. MAD therapy can only be applied in patients with a sufficient mandible and dental condition, which makes it an unsuitable therapy in approximately 33% of the OSAS patients[12]. Furthermore, MAD therapy is only completely successful in around 48% of the patients[13]. Since the implementation of effective MADs takes a long time and the costs of MAD are high, a predictive method for the effectiveness is desirable[8, 14]. Currently, the most used method to predict the effect of MAD therapy is the use of drug-induced sleep endoscopy (DISE)[15]. However, the DISE is a complex and costly method and it requires sleep-induction, therefore, DISE is less suitable as a screening tool for clinical application[16]. Since the upper airway is of key importance in OSAS, lung function measurements evaluating the upper airway could be a clinically acceptable screening method. Possible upper airway measurements are spirometry for assessing in- and expiratory flow, the forced oscillation technique (FOT) for measuring differences in respiratory resistance and negative expiratory pressure (NEP) for measuring the effect of negative pressure on the expiratory flow.

In light of all the above, the primary objective of this study is: to predict the success of MAD therapy in OSAS patients by using resistance and flow parameters obtained by spirometry, FOT, and NEP both in protrusion and retraction of the mandible. Secondary objectives are to evaluate the experience of subjects per measurement and the time it takes to perform the different measurements and to obtain additional parameters from spirometry, FOT, and NEP for the prediction of successful MAD therapy.

Chapter 2 – BACKGROUND

This chapter is subdivided into three parts. The first subchapter '*Clinical background*' is divided into five sections. The first section introduces the physiological background of the upper airway. In the second section, the upper airway during sleep is elaborated. In the third part, the pathophysiology of obstructive sleep apnoea is discussed. Fourthly, the clinical treatment options are mentioned. Finally, different predictive methods for MAD therapy are discussed.
The second subchapter '*Technical background*' introduces the general working mechanisms of the three different lung function measurements used in this study: spirometry, FOT and NEP.

Subchapter 2A – Clinical background

Section 2A.1 – Anatomy and physiology of the upper airway

The upper airway is a structure that is usually divided into four anatomical subsegments; the nasopharynx, velopharynx, oropharynx, and the hypopharynx, Figure 1[17, 18]. These structures form a passage for air movement from the nose to the lungs. Approximately twenty muscles surround the upper airway, which interact in a complex fashion to ensure the patency of the airway. The walls of the upper airway are formed by soft tissue structures, including the tonsils, soft palate, uvula, tongue and lateral pharyngeal walls. The mandible and the hyoid bone are the craniofacial bony structures that determine mainly the cross-sectional area of the upper airways.

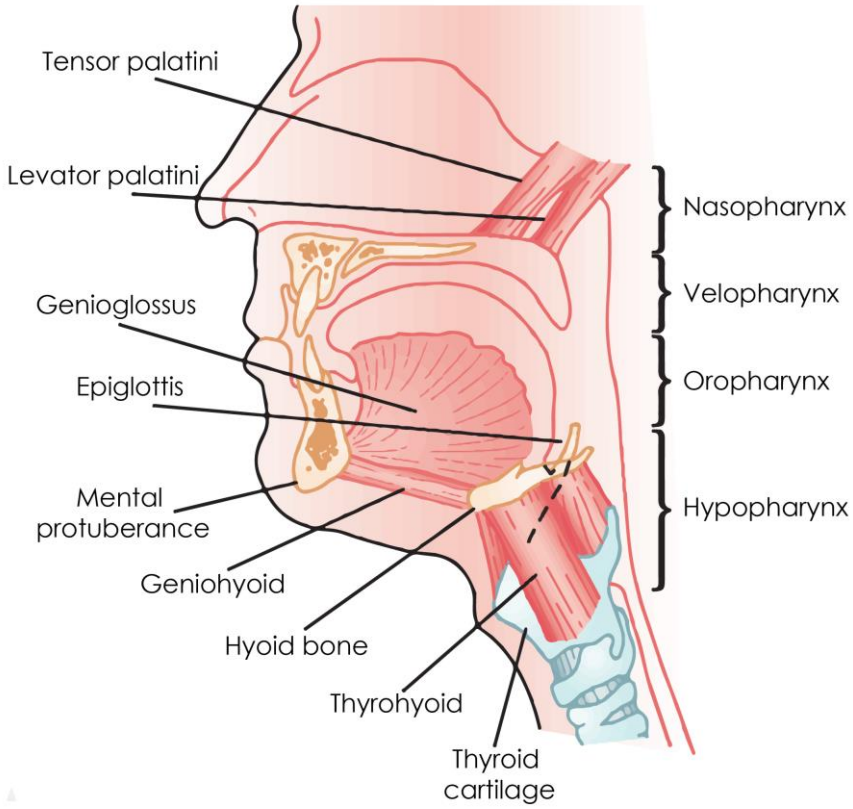


Figure 1 – Anatomy of the upper airway and the main segments, adapted from [18].

The cross-sectional area of the airway depends on the pressure balance, also called the transmural pressure (P_{tm}). The P_{tm} is the pressure difference over the airway wall. In other words, it is the difference between the pressure in the airways (intraluminal pressure) and the

pressure outside the airways, which can be generated by the contracting forces of the upper airway dilator muscles. During inspiration, a negative intraluminal pressure is generated by the diaphragm causing a reduction in pharyngeal cross-sectional area. This negative pressure also causes an airflow (inspiration), which further reduces the intraluminal pressure (Bernoulli's principle) and therefore the pharyngeal cross-sectional area. The reduction of the cross-sectional area depends on the compliance of the airway walls and opposing dilating forces[7]. The pharyngeal patency during wakefulness is in large part attributable to continuous neuromuscular control by the central nervous system[18]. The pharyngeal dilator muscles prevent upper airway collapse as well as the longitudinal traction on the airway resulting from lung inflation[7].

Section 2A.2 – Upper airway changes during sleep

The sleep state is associated with a decrease in neuromotor output to pharyngeal muscles. When this occurs against the background of anatomic abnormalities of the upper airway, the pharyngeal airway can become severely narrowed or closed[18]. In this case, the negative intrathoracic pressure can result in a complete collapse of the upper airway. The P_{tm} at which this occurs is called the critical closing pressure (P_{crit}). The same collapse can also occur due to increased extra-luminal pressure, for example, adipose tissue surrounding the upper airway. Besides the decreased neuromotor output to pharyngeal muscles, gravity also has an important influence on pharyngeal airway patency during sleep in a supine position. Due to gravity, the tongue and soft palate move posteriorly, reducing the oropharyngeal area, thereby increasing the supraglottic airway impedance and collapsibility[17].

Section 2A.3 – Diagnosis and definition of Obstructive Sleep Apnoea Syndrome

OSAS is a disorder with repetitive pharyngeal collapses during sleep[6]. A collapse could be complete, causing an apnoea or partial, causing a hypopnoea. Patients with OSAS report snoring, witnessed apnoeas, waking up with a choking sensation, and excessive sleepiness. Other common symptoms are non-restorative sleep, difficulty initiating or maintaining sleep, fatigue or tiredness, and morning headache[6].

The diagnosis of OSAS can be made with a polysomnography or a polygraphy. A polysomnography is an overnight sleep investigation in a laboratory where amongst others, sleep stages, nasal airflow, thoracic, and abdominal effort and body position can be measured[19]. A polygraphy measurement is a less comprehensive investigation and is always performed at home. The diagnosis of obstructive sleep apnoea is primarily based on the AHI, in which an apnoea is defined as a drop in the nasal pressure of ≥90% for ≥10 seconds, and a hypopnoea as a drop in nasal pressure of ≥30% for at least 10 seconds with a drop in saturation of ≥ 3% or an arousal[20, 21]. During a polygraphy, an arousal cannot be measured since there is no electroencephalography measurement present. So not all hypopnoeas are detected. The time a patient is in sleep can also not be measured with a polygraphy. These two limitations of the polygraphy result possibly in lower AHI compared to the AHI measured with a polysomnography. OSAS is often defined as an AHI ≥5 with associated symptoms or an AHI ≥15 regardless of the presence of symptoms. OSAS is considered as mild when the AHI is ≥5 and <15, it is considered as moderate when the AHI ≥15 and <30[5]. When the AHI is ≥30 OSAS is considered as severe.

Untreated OSAS causes daytime sleepiness, impaired cognition, increased risk of a motor vehicle accident and affects the quality of life[4, 6, 22]. On the long-term, untreated OSAS is linked to systemic hypertension, stroke, myocardial infarction, and diabetes mellitus[6]. There exists also an association between OSAS and epilepsy[5]. In a large 10-year prospective

study, untreated severe OSAS independently increased the odds of fatal and nonfatal cardiovascular events[5]. However, Mcevoy et al. studied in a randomised control trial the effect of CPAP on cardiovascular events in OSAS patients[23]. They did not find any significant differences in cardiovascular events between the group who received CPAP and the usual-care group.

Section 2A.4 - Pathophysiology and risk factors of Obstructive Sleep Apnoea Syndrome

Several mechanisms are important in the appearance of OSAS. In this section, the airway anatomy, pharyngeal dilator muscle function, lung volume, arousal threshold, and the respiratory regulatory system quantified by the loop gain are discussed as mechanisms that contribute to airway collapses. These mechanisms are previously described by Eckert et al. as the main mechanisms underlying OSAS[22]. Additionally, the risk factors for the appearance of OSAS are discussed.

Airway anatomy

Primarily, OSAS is considered to be a problem of the upper airway anatomy[6]. Increased soft tissue surrounding the airway (e.g. an increased amount of fat surrounding the neck), a small bony compartment surrounding the airway or physical structures that fill the airway lumen (e.g. tonsils or adenoids) results in an anatomically small pharyngeal airway[7]. An anatomically small pharyngeal airway leads to an increased likelihood of pharyngeal collapse. It is expected that this effect is amplified by the fact that a small pharyngeal airway results in an increased flow, which leads to increased negative pressure (following Bernoulli's principle) and a further decrease in the cross-sectional area. However, Verbraecken et al. discussed this hypothesis. They suggested that during inspiration, the upper airway muscles compensate for the negative pressure since it is shown that during inspiration there is more enlargement of the upper airway. It is at the end of expiration that the airway narrows and is most at risk for collapse. This could be due to the tissue pressure which could be larger compared to the intra-luminal pressure at the end of expiration[24]. During wakefulness, the airway is held open by the high activity of the airway dilator muscles. During sleep, the muscle activity is reduced and the airway might collapse.

Pharyngeal dilator muscle function

During wakefulness, OSAS patients compensate for the anatomically compromised upper airway through reflexes of the upper airway dilator muscle activity. These muscles are active during inspiration and less active during expiration or they have a similar level of activity throughout the respiratory cycle[7]. The most studied muscle is the genioglossus, which is an inspiratory muscle. Primarily three neural inputs control the genioglossus muscle. First, the negative pressure in the airway activates mechanoreceptors located in the larynx, resulting in a nerve activation and ultimately increased output to the genioglossal muscle. Thus, an event that threatens airway patency will lead to increased negative pressure and therefore activation of the genioglossal muscle to counter the threat. Second, neurons in the medulla (which generates the respiratory pattern) also influence genioglossal activation. During inspiration, the genioglossal muscles are activated a few milliseconds before the diaphragm is activated to withstand the negative pressure. Third, neurons that modulate arousal, influence upper airway motoneurons such as hypoglossal motoneurons. This increases muscle activity of the hypoglossal muscle. With these three inputs, pharyngeal muscle activity is linked to negative pressure in the airway, respiration, and arousal state[7]. During sleep, these control mechanisms are changed substantially. The negative-pressure reflex is reduced and

the ‘wakeful’ input to the muscles is diminished during sleep, which explains the loss of tonic activity. The respiratory input is likely maintained during sleep. Thus, a reduced negative-pressure reflex and ‘wakeful’ input result in a fall in pharyngeal muscle activity during sleep. The airway becomes vulnerable and is more likely to collapse[7, 22].

Lung volume

Lung volume might also be of influence for pharyngeal patency[6, 7, 22]. The lung volume stabilises the respiratory control system by buffering the blood gases from changes in ventilation. The functional residual capacity is decreased during sleep and therefore contribute to the sleep-related collapse. This effect is amplified in patients with abdominal obesity since abdominal obesity attributes to a decrease in lung volume[25]. Besides, a decrease in lung volume results in a diaphragm and thorax that are moved towards the head. This decreases the caudal traction on the upper airway and therefore results in a more collapsible airway. Thus, during sleep, a decrement in lung volume can occur by changes in posture (upright to supine position). As a result, the upper airway becomes more vulnerable to collapses.

Arousal threshold

Another potentially important factor for the appearance of OSAS is the propensity to arouse from sleep, also called the arousal threshold[6]. A low arousal threshold (wake up easily) is believed to be of influence in the appearance of OSAS. After arousal, most people hyperventilate briefly due to an increased ventilatory response, and carbon dioxide (CO_2) concentration in blood can fall. The low CO2 concentration reduces the respiratory drive to just below the normal (eupnoeic) level when sleep resumes and the upper airway dilator muscles activity is reduced which could lead to a collapse of the airway. So, a low arousal threshold destabilizes breathing and perpetuate apnoea severity.

Loop gain

OSAS patients have a breathing pattern whereby periods of normal respiration are alternated with periods of obstructive breathing events and arousals[7, 22]. The respiratory control stability is believed to play an important role in the pathogenesis of OSAS and consists of a feedback system. This feedback system consists of three elements: chemoreflex sensitivity, muscle activity, and gas exchange, Figure 2.

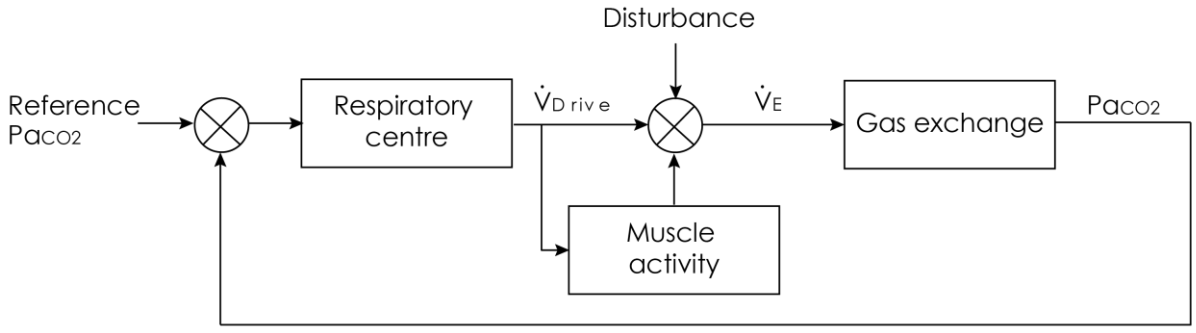


Figure 2 – Respiratory feedback control system. The input for the respiratory centre is the arterial CO_2 pressure ($PaCO_2$) and the output is the respiratory drive ($\dot{V}_{Drive}$). The $\dot{V}_{Drive}$ influences the respiratory minute volume $\dot{V}_E$ and muscle activity. The muscle activity also influences the $\dot{V}_E$ together with other disturbances (i.e. arousal or sleep stage). The gas exchange determines the $PaCO_2$ for a given $\dot{V}_E$[26].

Through negative feedback, a disturbance can be restored. For example, a disturbance causes a decrease in respiratory minute volume and therefore for an increase in $PaCO_2$. This is sensed in the chemoreceptors and compared to a reference value of the $PaCO_2$. The error signal to the respiratory centre causes a signal to the respiratory muscles to increase respiration (increase in respiratory drive). The increased respiration will decrease the $PaCO_2$ via gas exchange. In this feedback loop, the respiratory centre describes the change in respiratory drive to a change in $PaCO_2$. An increased respiratory drive causes an increase in muscle activity and an increased respiratory minute volume. The gas exchange describes how fluctuation in respiratory minute volume changes the $PaCO_2$. The stability of this respiratory feedback control system (the respiratory centre and gas exchange) can be described with the 'loop gain'. The loop gain defines how responsive or sensitive this system is to a disturbance in breathing (e.g., arousal). An elevated loop gain is believed to be related to increased oscillations from the respiratory regulation centre in the brainstem, which may increase the tendency for obstructive apnoeas. For example, the upper airway muscles are responsive to the respiratory system. When the activity of the respiratory system increases (increase in the respiratory drive), the upper airway muscles activity also increases. So, during an unstable ventilatory control, the activity of the pharyngeal muscles will also be unstable. Moreover, during a decreased respiratory drive, the activity of the pharyngeal muscles is also decreased and this can promote upper airway collapse. An obstructive apnoea amplifies this effect. During an obstructive apnoea (disturbance), the respiratory minute volume is zero and the $PaCO_2$ rises. In case of an elevated loop gain, the respiratory control system is very sensitive to this disturbance and increases the respiratory drive[27]. The airway is collapsed so the respiratory minute volume cannot increase and the $PaCO_2$ and respiratory drive keep increasing. When the airway reopens at the termination of the apnoea, the respiratory drive determines the degree of hyperventilation. The hyperventilation results in a decreased $PaCO_2$ which results again in a low respiratory drive. This low respiratory drive affects the upper airway muscles and the muscle tone is reduced. The reduced muscle tone causes again an obstructive apnoea. On top of this, an elevated loop gain may increase the respiratory response to arousal. This may drive the $PaCO_2$ below the level at which respiration stops (apnoea threshold) and an obstructive or central apnoea could occur.

Risk factors

Two important risk factors for OSAS are obesity and being male[6, 22]. Obesity affects the anatomy of the upper airway as fat is deposited in surrounding structures, therefore it increases the likelihood of airway collapse. Moreover, obesity might also decrease the lung volume and therefore destabilizes breathing and increases airway collapsibility as stated above. Men tend to gain weight more centrally compared to women, resulting in more fat stored in the upper airway structures and the abdomen. Studies also suggest that men have a longer airway than women, which could also be an explanation for the increased propensity for airway collapse in men.
Older persons have a loss of elastic recoil in the lung and a loss of collagen in the airways and might therefore also have a more easily collapsible airway. Genetic factors which influence the craniofacial anatomy are also of influence for the development of OSAS. For example, persons with retrognathia (posterior position of the mandible) have a higher risk to develop OSAS[28]. Menopause is also a risk factor and could be related to weight gain and a redistribution of body fat to central regions. Moreover, postmenopausal women have a lower level of progesterone which has respiratory stimulant properties, this increases the change on airway collapses[29]. Smoking is also linked with OSAS, although the exact mechanism is not clear.

Section 2A.5 – Treatment of Obstructive Sleep Apnoea Syndrome

CPAP is the treatment of choice for patients with OSAS[6]. The positive airway pressure maintains a positive pharyngeal transmural pressure, which prevents airway collapse. Moreover, CPAP increases end-expiratory lung volume, which stabilises the upper airway. However, more than 40% of patients do not endure or are not compliant with CPAP therapy[9].

Another therapy for the treatment of OSAS is a MAD. MAD therapy is preferable to CPAP in some patients with mild or moderate OSAS, or those who refuse or cannot tolerate CPAP therapy[6, 10, 11]. The MAD protrudes the mandible forward, causing an increased upper airway volume[3]. A challenge with MAD therapy is that several visits to a dentist are needed for optimal titration, and a satisfactory outcome can only be judged after a titration period of several months[6]. MAD therapy can only be applied in patients with a sufficient mandible and dental condition, which makes it an unsuitable therapy in approximately 33% of the OSAS patients[12]. Furthermore, MAD therapy is only completely successful in around 48% of the patients[13].

Conservative measures can also be helpful, especially in patients with mild OSAS[12]. Conservative measures include loss of weight, alcohol abstinence, stop smoking, and avoid sedative medicines. In the case of position-dependent OSAS, positional treatment could be helpful. These patients have an AHI in a supine position that is at least twice as high compared to other sleeping positions. This is due to the tongue and palatal structures that move posteriorly due to gravitational effects, which generates more positive tissue pressure and lead to collapse[7]. For these patients, prevention of supine position during sleep could be helpful.

Section 2A.6 – Prediction of the effect of mandibular advancement device therapy

Since MAD therapy is only completely successful in around 48% of the patients, titration of a MAD is time-consuming, and the costs of a MAD are high, a predictive method for the effectiveness is desirable[8, 14]. An easy method for the prediction of effective MAD therapy is described by Tsuiki et al[30]. They investigated the body mass index (BMI) and the Mallampati score as predictors for MAD therapy effectiveness in mild OSAS patients (5< AHI ≤15). The Mallampati score evaluates the state of crowding in the oropharyngeal region caused by a large tongue and/or small craniofacial bony enclosure. The Mallampati score is scored with a number between 1 and 4, as shown in Figure 3[31].
The BMI and Mallampati score were significantly higher in patients not responding to MAD therapy with a sensitivity/specificity of 63/67% and 80/57% respectively.

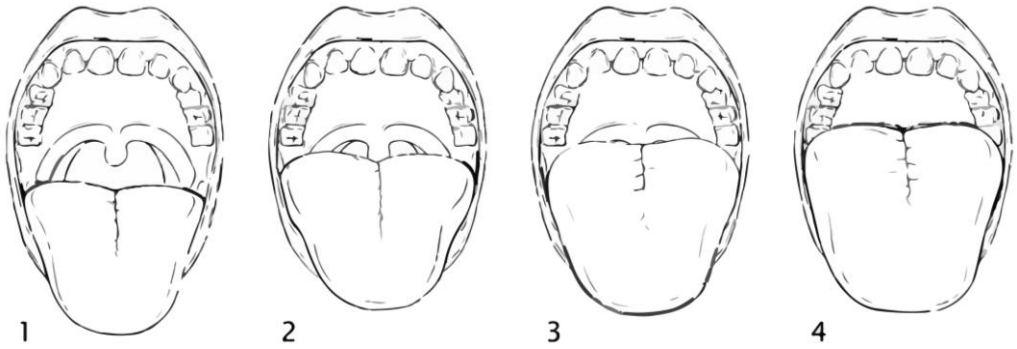


Figure 3 - Mallampati score. Class 1: Faucial/tonsillar pillars, uvula and soft palate are all visible. Class 2: Partial visibility of the faucial/tonsillar pillars, uvula, and soft palate. Class 3: Base of the uvula, soft and hard palate visible. Class 4: Only hard palate is visible. The figure is adapted from [31].

De Corso et al. investigated the use of drug-induced sleep endoscopy (DISE) as a screening tool for the successfulness of MAD therapy in patients with OSAS[15]. A MAD with an advanced level of 4 till 5 mm was used and the successfulness was defined as obstructive events better or absent for at least 3 min, associated with endoscopic evidence of improved airway patency at one or more sites of obstruction by at least 50%. In this study, a MAD was successful in 53.8%. MAD success was defined as an AHI < 5 or a reduction of AHI ≥ 50%. By using DISE as a selection tool, the MAD was successful in 71.4% of the patients selected for MAD therapy. Huntley et al. also suggests that improvement in the retrolingual and retropalatal airway size during DISE while trusting the mandible forward is predictive of successful treatment with a MAD, defined as an AHI <20 and at least 50% improvement from baseline[32]. Vroegop et al. also used DISE as a screening tool for MAD therapy in OSAS patients[33]. When the MAD application during DISE results in a partially or completely resolved upper airway collapse the consecutive MAD therapy was successful in 69% of the patients. Success was defined as a reduction in AHI of ≥50%. Besides the prediction of MAD success, DISE was also used to determine the collapse pattern of the upper airways. The site of collapse was used as a predictor of treatment response. The presence of a palatal collapse, for example, was associated with treatment response, whereas the presence of a hypopharyngeal collapse was associated with less favourable treatment outcomes. Since DISE is a complex and costly method and it requires sleep-induction, DISE is a less suitable screening tool for the clinical application. So other success-prediction tools are desirable. Chan et al. investigated the use of nasopharyngoscopy as a prediction mechanism of MAD success[34]. They found a significantly larger increase in the cross-sectional area of the velopharynx after application of a MAD in responders compared to non-responders with a positive predictive value of 79% and a negative predictive value of 81%. MAD responders were defined as patients with a reduction in AHI of ≥ 50%. Zeng et al. used rhinomanometry to measure nasal resistance in responders and non-responders of MAD therapy[35]. They found a significantly higher baseline nasal resistance in the MAD non-responders group compared to the responders' group. Responders were defined based on a reduction in AHI of ≥ 50%. Tsai et al. investigated the use of a remotely controlled mandibular positioner (RCMP) as a prediction mechanism of MAD success[36]. They hypothesized that the successful elimination of respiratory events and oxygen desaturation by a mandibular protrusion with the RCMP during sleep predicts MAD therapy success based on different success criteria. Specificity and sensitivity of 89% and 90% were found respectively for this prediction method in which success is defined as an AHI ≤ 15.

Recently, Bamagoos et al. investigated the dose-dependent effect of mandibular advancement on different OSAS phenotypes[37]. MAD success was defined as a 50% reduction in AHI after two months of acclimatisation on the MAD at the maximal comfortable protruded position. They determined the P_{crit}, genioglossus electromyogram (EMG) and the pharyngeal muscle effectiveness and airflow for three different positions of the mandible (neutral position, 50% and 100% of maximal protrusion). P_{crit} decreased across the three different mandible positions. MAD non-responders had a greater reduction in P_{crit} compared with responders from 0 till 50% of the maximal protrusion. In contrast, from 50-100% of maximal protrusion, MAD responders experienced a greater P_{crit} reduction compared to non-responders. There was no difference in genioglossus responsiveness and pharyngeal muscle effectiveness between MAD responders and non-responders. These findings suggest that MAD therapy works primarily by passively improving pharyngeal anatomy and, thereby, its function.

Subchapter 2B – Technical background

Section 2B.1 – Spirometry

Spirometry is a test that measures how individuals inhale and exhale airflow and calculates volume as a function of time[38]. The patient breathes through a mouthpiece with a pneumotachograph connected measuring flow based on a pressure difference over a resistance[39]. The following parameters can be measured with spirometry:

- Vital capacity (VC): the maximum amount of air that can be inhaled after maximal slow
- Forced vital capacity (FVC): the maximum amount of air that can be exhaled when blowing out as fast as possible after a maximal inspiration.
- Forced expiratory volume in one second (FEV1): volume expired in the first second of maximal expiration after a maximal inspiration.
- Maximum expiratory flow at 50% of vital capacity (MEF50)
- Maximum inspiratory flow at 50% of vital capacity (MIF50)
- Inspiratory vital capacity (IVC): the maximum amount of air that can be inhaled when inhaling fast after a slow maximal expiration.
- Forced inspiratory volume in 1 second (FIV1): volume inspired in the first second of maximal inspiration after a slow maximal expiration.

Based on these parameters, several parameters can be calculated. Most used is the FEV1/FVC ratio, which is as a measure for the degree of obstruction. To obtain information about the upper airway, the following parameter can be calculated:

- Ratio of Expiratory Flow rate at 50% of vital capacity to the Inspiratory Flow rate at 50% of vital capacity (MEF_{50}:MIF_{50}).

References values for these parameters are based on age, sex, height and ethnic origin[39]. For the reference values, the values of the European Coal and Steel Community are used. An example of a normal forced flow-volume curve is shown in Figure 4A. The positive curve represents the forced maximum expiration and the negative curve represents the maximum inspiration. During these measurements, the patient needs to keep blowing until the volume-time trace reaches a plateau with <50 mL being exhaled in 2 seconds[39]. The performer of the measurements has to check whether the results are acceptable and reproducible according to the European Respiratory Society (ERS) criteria[38, 39]. Acceptability of the results is based on the following criteria:

- The measurement is free of artefacts (i.e. coughing, early termination or cut-off).
- The start is good (the volume at the start of the measurement is less than 5% of FVC or less than 150 mL, whichever is greater).
- The exhalation is complete (the duration of expiration is at least 6 seconds or an end-expiratory plateau must be present, i.e. the volume measured within the last two seconds must not exceed 50 mL).

The reproducibility of the best two measurements of minimal three measurements is then checked according to the following criteria:

- Variability of FVC is less than or equal to 150 mL or within 5% of each other.
- Variability of FEV1 is less than or equal to 150 mL or within 5% of each other.
- The last measurement is not the best measurements.

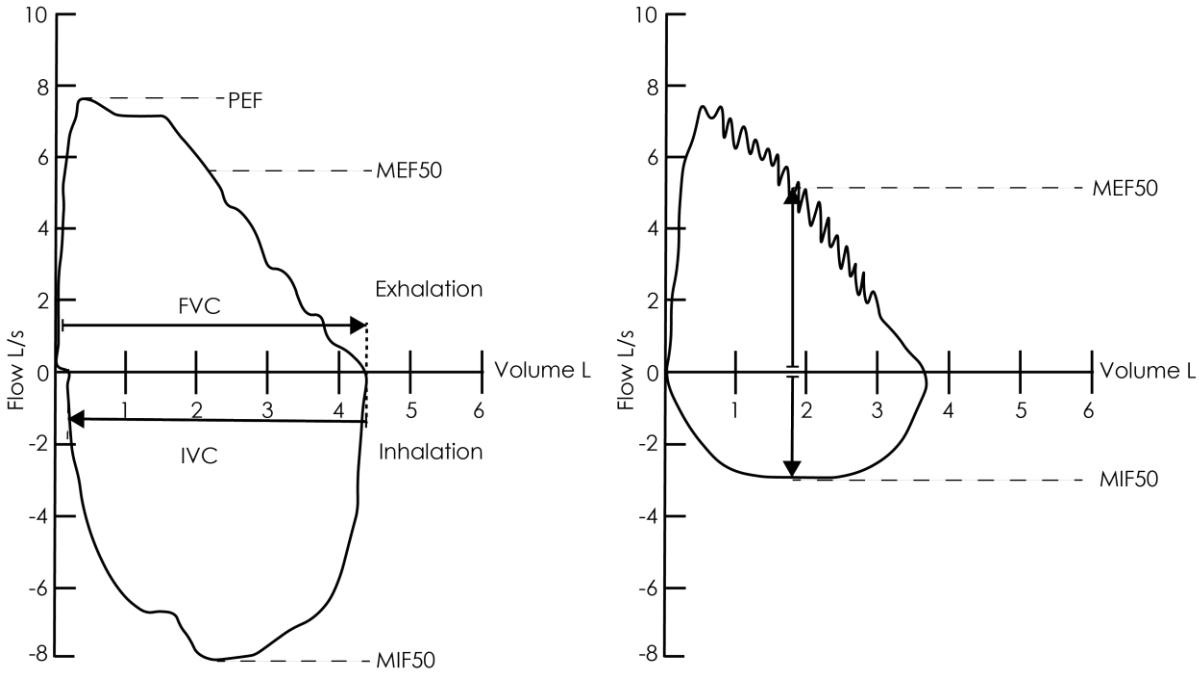


Figure 4 - Flow-volume curves A) normal person[38] B) Example of a patient with obstructive sleep apnoea[40]. IVC = Inspiratory volume, FVC = Forced vital capacity, MEF50 = expiratory flow rate at 50% of vital capacity, MIF50 = inspiratory flow rate at 50% of vital capacity, PEF = Peak expiratory flow.

In OSAS patients two abnormalities in the flow-volume curves are described, also shown in Figure 4B[40]. The first abnormality is 'saw-toothing' or flow oscillations occurring at regular intervals on the inspiratory and/or expiratory limbs of the flow-volume loop. This abnormality corresponds to the fluttering of the superfluous pharyngeal tissue or loss of upper airway muscle tone. The second abnormality is the MEF_{50}:MIF_{50} greater than one, due to a reduced MIF_{50} (as a sign of an extrathoracic obstruction[38]). This increased ratio may indicate upper airway obstruction. Zeng et al. used the flow-volume curve to predict the MAD treatment outcome in OSAS patients[41]. Spirometry was performed by the OSAS patients and the MEF_{50}, MIF_{50} and the MEF_{50}:MIF_{50} were determined. All patients underwent MAD treatment and patients were defined as MAD responders when a decrease of more than 50% in AHI was present after 6 weeks. Zeng et al. found significant differences in MIF_{50} and MEF_{50}:MIF_{50} between responders and non-responders. By using a MEF_{50}:MIF_{50} ratio greater than 0.7, the positive predictive value was 83% with a negative predictive value of 58%. By combining this with a cut off of MIF_{50} <0.6 L/second positive and negative predictive values of 89 and 76% respectively were found.

Section 2B.2 – Forced Oscillation Technique

FOT is a technique in which external pressure is applied to the respiratory system via a mouthpiece to determine the mechanical response of the respiratory system[42-44]. The external pressure is applied during normal breathing. The FOT equipment includes a loudspeaker to generate the oscillatory signals; a pneumotachograph and pressure transducers to measure pressure and flow and a mouthpiece, as shown in Figure 5[43].

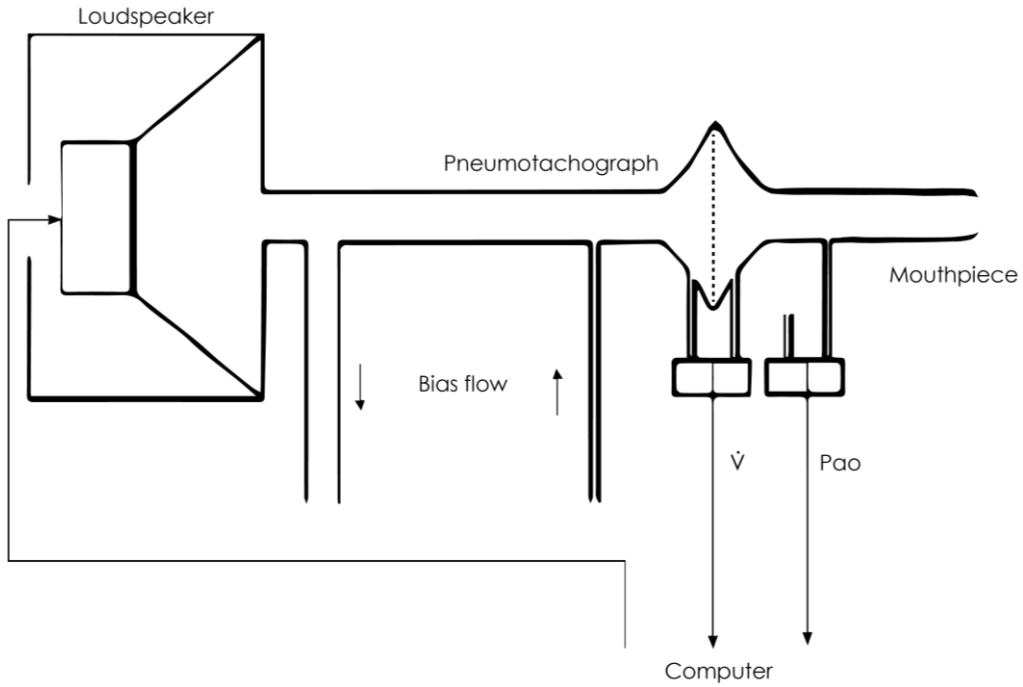


Figure 5 - Set up of a forced oscillation technique, with $\dot{V}$ the output flow, determined by a pressure difference over a known resistance yielding flow and Pao the pressure at the airway opening. Bias flow is optional to flush the dead space. The loudspeaker applies the oscillations to the airways. This figure is adapted from [43].

Possible input pressures are pseudorandom-noise and an impulse-shaped signal, of which the last one is used in the impulse oscillation technique (IOS). Based on the measured flow ($\dot{V}_{rs}$) and pressure (P_{rs}) signals, the respiratory input impedance (Z_{rs}) can be determined. This is possible by discriminating the pressure and flow signals from the underlying respiratory signals. When the pressure and flow signals corrected from the underlying respiratory signals are obtained, a Fourier transform of the pressure and flow signal can be made. By dividing the Fourier transform of the pressure signal by the Fourier transform of the flow signal, the Z_{rs} is obtained, as shown in formula 1. The impedance is a reflection of all the forces that hinder airflow into and out of the lungs[45].

$$Z_{rs}(f) = \frac{P_{rs}(f)}{\dot{V}_{rs}(f)} \quad (1)$$

The obtained impedance can be described with a real part, the resistance (R_{rs}), and an imaginary part, the reactance (X_{rs}) term, as shown in formula 2. In these formulas, ω is the angular frequency, which is equal to $2\,\pi f$.

$$Z_{rs}(f) = R_{rs}(f) + jX_{rs}(f) \quad (2)$$

$$Z_{rs}(f) = R_{rs}(f) + \omega I - \frac{1}{\omega Ca} \quad (3)$$

The respiratory impedance consists of:

- Resistance as a function of frequency (R(f)): this is a measure of the energy dissipation in the respiratory system[46]. It contains contributions from energy dissipation in the lung and chest wall tissues and increases as the airways narrow[47]. Heterogeneous constriction and/or disease of the small airways commonly leads to characteristic

changes in the shape of the resistance curve. The resistance increases above normal values in case of a proximal or distal airway obstruction.

- Reactance as a function of frequency (X(f)): this is a measure of the energy conservation in the respiratory system, which includes the elastic fibres in the lung (lung compliance) also called the capacitance (Ca), and the inertive forces (I) related to the acceleration and deceleration of the column of air in the airway tree as well as the lung tissues[46]. The capacitance is defined to be negative in sign and is most prominent at the low frequencies. The inertance is positive in sign and dominates the higher frequencies. Low-frequency reactance becomes more negative in most lung disease and is particularly sensitive to obstructions in the small airways.

An example of the resistance and reactance of the respiratory system is shown in Figure 6[43]. Based on these impedance data, the following parameters could be determined:

- Low-frequency resistance (R_5): indicative of the overall resistance of the respiratory system.
- Mid-frequency resistance (R_{19} or R_{20}): indicative of the resistance of the conducting airways.
- Frequency dependence of resistance (R_{5-19} or R_{5-20}): indicative of changes in the shape of R(f) that are typically associated with heterogenous obstruction and small airway disease.
- Low-frequency reactance (X_5): Indicative of overall elasticity (i.e. loss or increase of compliance) of the lungs and obstruction of small airways.
- Resonance frequency (f_{res}): The frequency at which X(f) is zero. Indicative of overall elasticity of the lungs and obstruction of small airways.
- Reactance Area (AX): Area under the reactance curve from the frequency at 5 Hz till the resonance frequency. It is an indicator of small airway obstruction.

It is suggested that the low frequencies (2-4 Hz) represent the properties of the peripheral respiratory system whereas the higher frequencies (>20 Hz) represent the properties of the proximal conducting airways[43]. It has been shown that the airway resistance measured with a plethysmograph is increased in OSAS patients[48]. Lorino et al. showed a significant decrease in airway resistance (at the extrapolated 0 Hz frequency) measured with FOT after application of a MAD in forwarding position[49].

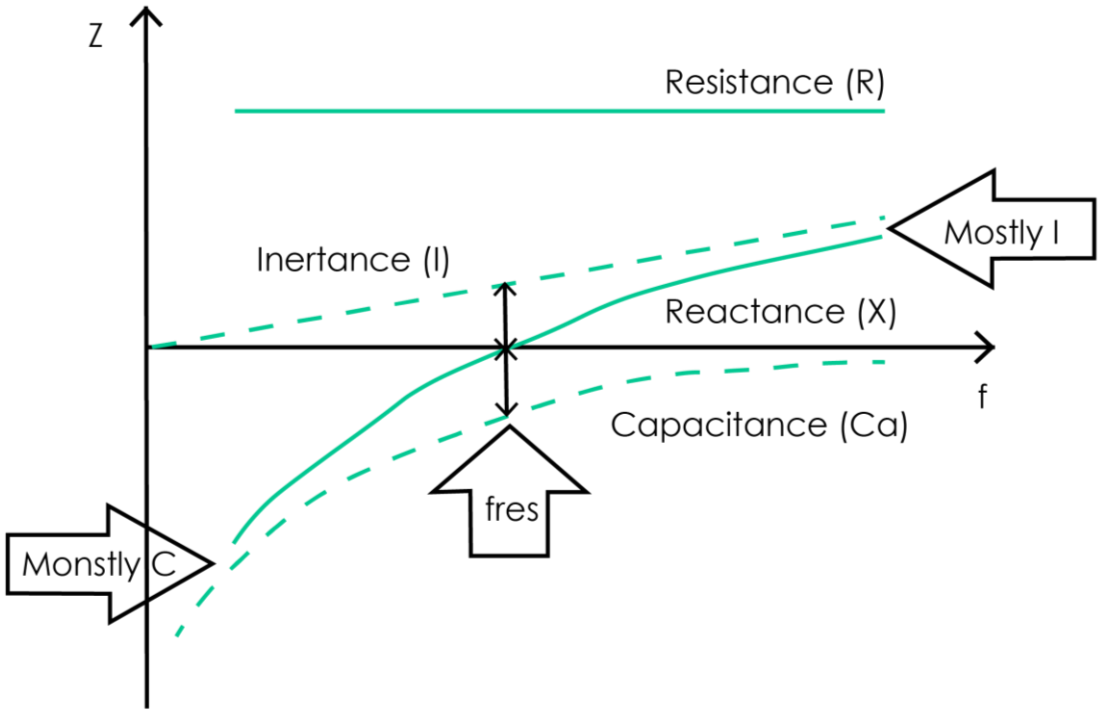


Figure 6 - Resistance (Rrs) and reactance (Xrs) of the respiratory system as a function of the oscillation frequency[46, 50]. At low frequencies the capacitance (C) dominates and at high frequencies the inertance I) dominates the reactance curve. Fres is the point where the reactance curve crosses the x-axis and is called the resonance frequency. Below the Fres, the elastic properties of the lung (capacitance) dominate, whereas, above the Fres, inertance dominates. This figure is adapted from [46].

Section 2B.3 - Upper airway flow limitation by negative expiratory pressure

Since one of the main problems in OSAS patients is the increased collapsibility of the upper airway, a prediction of this disorder could be done by determining the response to a NEP[51]. During a NEP test, a negative pressure is generated by a Venturi device connected to a tank of compressed air and applied at the early onset of expiration. A pneumotachograph is connected to the mouthpiece and the flow and mouth pressure are measured.
In a healthy person, the increase in pressure gradient between the alveoli and the airway opening should result in increased expiratory flow. However, OSAS patients are flow limited and NEP application does not increase the flow during the terminal portion of tidal expiration[52]. Upper airway collapsibility could be evaluated based on the following parameters:

- The ratio between expiratory tidal volume exhaled during the first 0.2 s after NEP application ($V_{0.2}$) as a percentage of the first 0.2 or 1 s of the mean expiratory volume of the 3 breaths preceding NEP application ($V_{0.2}/V_{0.2}$ and $V_{0.2}/V_{1.0}$)[53, 54]. Only the first 0.2 s are taken to avoid influences of reflexes and voluntary reactions to the NEP stimulus. A low ratio corresponds with a more collapsible upper airway.
- The ratio between expiratory tidal volume exhaled during the first 0.5 s after NEP application ($V_{0.5}$) as a percentage of the first 0.5 or 1 s of the mean expiratory volume of the 3 breaths preceding NEP application ($V_{0.5}/V_{0.5}$ and $V_{0.5}/V_{1.0}$)[53, 54].
- The drop in the flow ($\Delta\dot{V}$), as shown in Figure 7[51]. After the onset of NEP, a spike in the flow is present, followed by a $\Delta\dot{V}$. The $\Delta\dot{V}$ is caused by an increase in resistance of the upper oropharyngeal structures.

- The percentage of expired tidal volume over which the NEP-induced flow did not exceed the previously measured spontaneous flow (percentage below)[55]. Baydur et al. found a higher percentage in OSAS patients compared to controls.

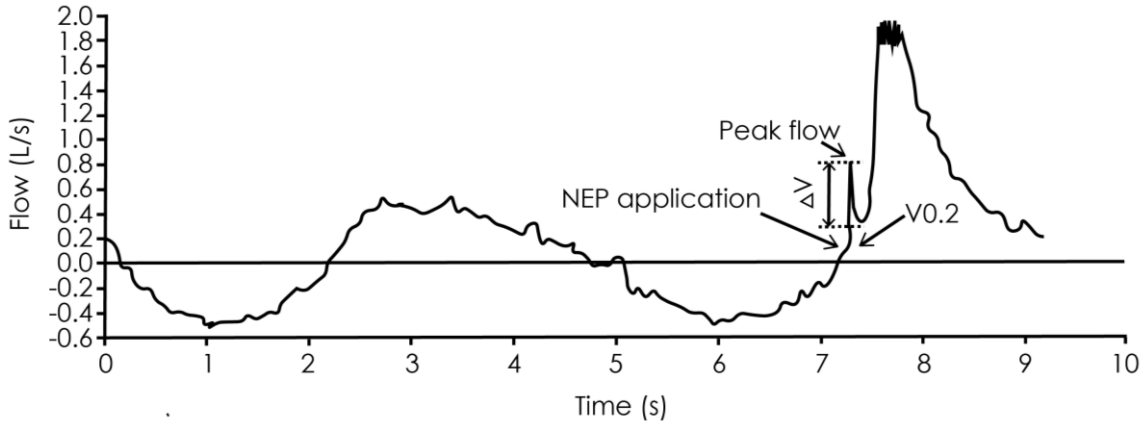


Figure 7 - Evaluation of upper airway collapsibility by the negative expiratory pressure test. Upper airway collapsibility is determined based on expiratory volume in 0.2 seconds $V_{0.2}$ and as the flow drop $\Delta\dot{V}$ [56].

Chapter 3 – Methods

This chapter describes the method of this study and consists of five subchapters.

In the first subchapter, the patient population and the inclusion method of this study are described. In the second subchapter, the study design is discussed. The measurement devices are discussed in the third subchapter. In the fourth subchapter, the analysis methods are described. In the fifth subchapter, the main, secondary, and other study parameters are described and this chapter ends with the statistical analysis in the sixth subchapter.

Subchapter 3A – Subjects

Patients with OSAS and MAD therapy were recruited for this study. The specific inclusion criteria were an age of ≥ 18 years, an AHI of ≥ 15 on the first poly(somno)graphy, a signed informed consent prior to participation and a scheduled control poly(somno)graphy measurement after titration of MAD therapy or a control poly(somno)graphy within the last year and a half from the beginning of this study. Patients were excluded if they were unable to read and/or understand the Dutch language, having a control polygraphy after initial polysomnography or having control polysomnography after an initial polygraphy. There were two ways a patient could be included in this study. In the first place, inclusion took place by the special dentistry department. The special dentist asked during a control appointment whether the patient was interested to participate in the study. When the patient showed interest, the patient received a patient letter about the study, and an appointment for the informed consent and the different measurements were made. In the second way, patients were recruited from the medical database of the department of special dentistry. Patients who met the inclusion criteria, have (or have had) a MAD therapy with optimal titration and have had a control poly(somno)graphy within the last year and a half, received a letter and a patient information letter from their treating physician. Patients could contact the coordinating investigator to schedule an appointment when they were willing to participate. When there was no reaction from the patients within 14 days, the coordinating investigator contacted the patients to ask whether they were interested to join the study or not. When they were interested and wanted to participate, an appointment for the measurements was scheduled. Based on a limited time and the number of patients having MAD therapy and an initial AHI ≥ 15, it was chosen to include 25 patients. With 25 patients and equal distribution in patients with successful and non-successful MAD therapy, a positive or negative predictive value of 0.8 could be demonstrated with a confidence interval from 0.59 to 0.92. Due to the limited time, we found these numbers acceptable for this study. The study was approved by the medical ethics committee of Twente (Enschede, the Netherlands) and the local board of directors of Medisch Spectrum Twente (MST).

Subchapter 3B – Study design

At the day of the visit, demographic data were collected, the neck circumference was measured and it was documented whether retrognathia was present. The Mallampati score was determined in a sitting position. The patient was asked whether he or she experienced regular nasal obstruction and whether he or she gained or lost weight in the period from the first poly(somno)graphy (initial poly(somno)graphy) until the study measurements. The medical and smoke history of the patients were asked as well as the current health state. After the demographic data was obtained, the measurements started. The measurements were divided into three different measurements. An adjustable mouthpiece was used to enable protrusion and retraction of the mandible. The measurements were performed with the mandible in the maximal comfortable retracted and maximal comfortable protrusive position. The measurements were performed with the patient in a supine position on a flat

examination bench. An overview of the study design is shown in Figure 8. The different measurements included:

- NEP measurement (A): The patient had to breathe normally in the NEP device. Five breaths with NEP application were performed.
- FOT measurement (B): In the first part (B-I) of the measurement, the patient breathed normally in the IOS while supporting their cheeks and blocking nasal airflow with a nose clip[46]. The patient was instructed to put his tongue under the mouthpiece to ensure that the tongue did not obstruct the breathing pathway. Three measurements of 30 seconds were performed. In the second part (B-II) the patients had to completely inhale and exhale slowly. Again, three measurements of 30 seconds were performed. In the last part (B-III), the patients had to completely inhale and exhale as fast as possible until at least 5 breaths were executed. The measurement was also performed three times.
- Spirometry (C): Three fast maximal in- and expirations were performed. The patient was instructed to inhale completely and at the maximum of inhalation, to exhale as fast and completely as possible. After which, a fast and complete inhalation followed. The measurements had to be acceptable and reproducible as described in section 2B.1 - Spirometry.

After the three measurements in a supine position, standard spirometry in the sitting position was performed. First, the vital capacity of the patient was determined. The patient was instructed to first completely exhale and then completely inhale slowly. Additionally, a fast maximal in- and expiration manoeuvre was executed in the same way as described above. A detailed description of the measurement protocol can be found in chapter 8 (Appendices 'Subchapter A – measurement protocol').

Type of measurement	Measurement A "NEP"		Measurement B "FOT"						Measurement C "Spirometry"		Control "Spiro Control"
Position of the mandible	Retracted	Protruded	B-I		B-II		B-III		Retracted	Protruded	Without adjustable mouthpiece
			Retracted	Protruded	Retracted	Protruded	Retracted	Protruded			
Time (min)	5	5	5	5	5	5	5	5	5	5	5
Position	Supine										Sitting

Figure 8 - Configuration of the measurements (A, B, C, and control), the duration of the measurements in minutes and the position of the patient. B-I is the FOT measurement while breathing normally, B-II is during maximal slow in- and expiration and B-III is during a maximal fast in- and expiration.

After all measurements, the patient answered a visual analog scale (VAS)-questionnaire (see chapter 8 Appendices 'Subchapter B – VAS-questionnaire') to evaluate their experience with the different measurements and breathing through the adjustable mouthpiece.

Subchapter 3C – Measurement devices and data analysis

In this subchapter, the different measurement devices and data analysis are described. Starting with the adjustable mouthpiece which the patients wore during the measurement followed by the measurement equipment and data analysis of the spirometry, FOT, and NEP. All data were analysed in MATLAB (version 2018a, Mathworks, Natick, MA, USA).

Section 3C.1 - Adjustable mouthpiece

During the spirometry, FOT, and NEP measurements the patient breathed through an adjustable mouthpiece. The adjustable mouthpiece was designed in SolidWorks 2016 (Dassault Systèmes Solidworks Corporation, Waltham, MA, USA) and included two small blocks where the teeth can rest, of which one block is adjustable as can be seen in Figure 9. The 3D-images of the adjustable mouthpiece can be found in chapter 8 (Appendices 'Subchapter C – 3D-images adjustable mouthpiece'). Measure lines were incorporated into the design, to be able to control the mandible position.

The adjustable mouthpiece was 3D printed in Dental LT Clear Resin material (Formlabs GmbH, Berlin, Germany) which is Class IIa long-term biocompatible and has a high resistance to fracture and wear. The material is non-toxic, water-resistant and can be disinfected with ethanol. The adjustable mouthpiece was printed with a Formlabs 3D printer, which is a stereolithography/resin printer. The adjustable mouthpiece was attached airtight to the spirometry, FOT, and NEP equipment.

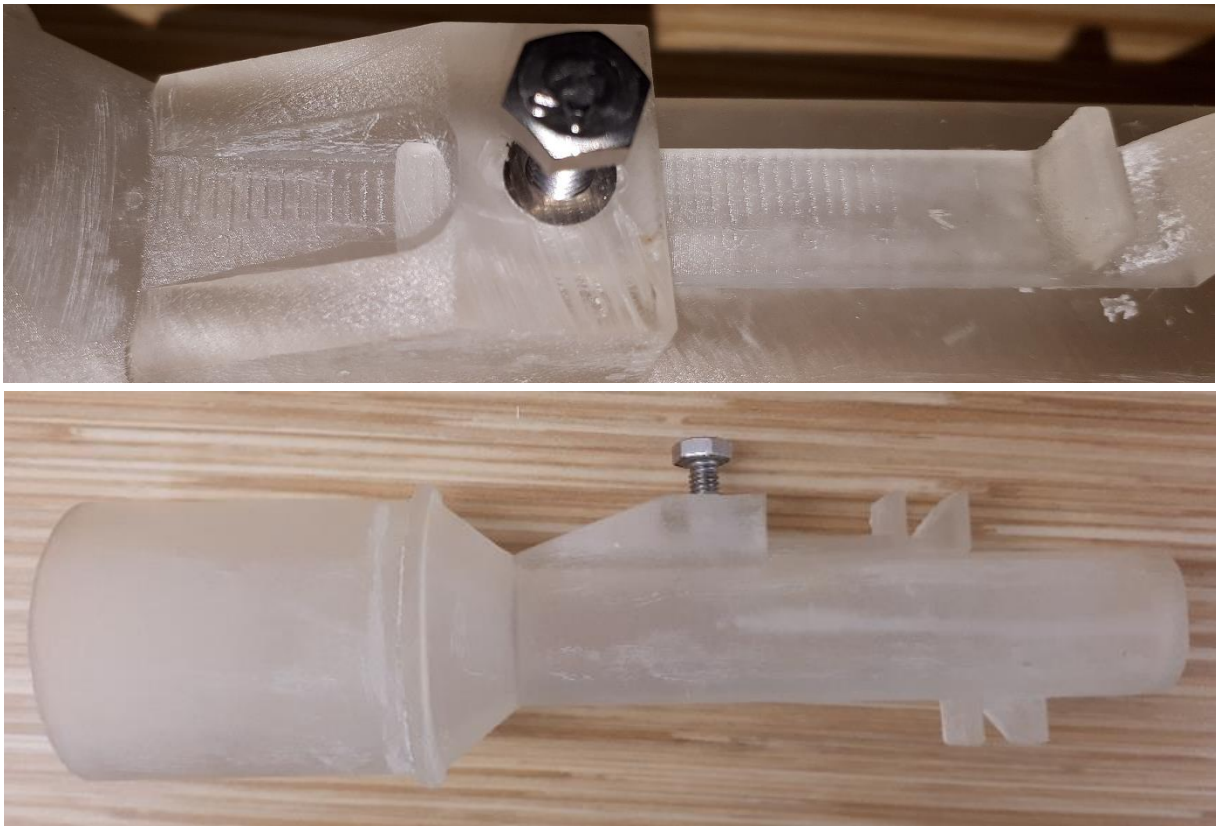


Figure 9 - Adjustable mouthpiece with a close-up of the measure lines.

The adjustable mouthpiece was used to hold the mandible in a protruded or retracted position during the different measurements. A picture of these two different positions of the mandible is shown in Figure 10.

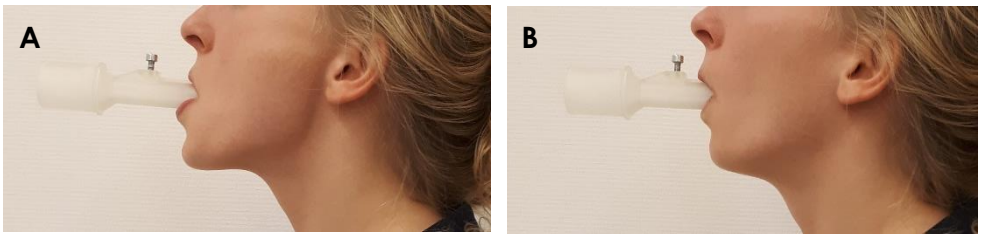


Figure 10 – Adjustable mouthpiece with the mandible in protruded (A) and retracted (B) position.

Section 3C.2 - Spirometry

For the spirometry measurements, a Masterscreen Pulmonary Function Test (PFT) system (Vyaire Medical, Mettawa, IL, USA) was used. The flow was measured by a pneumotach with a range of 0 to ± 20 L/s and accuracy of ± 2% or 0.2 L/s (for 0.2 to 12 L/s) and a resolution of 10 mL/s[57]. The volume was determined based on software integration within the range of ±20 L and accuracy of ± 3% or ± 0.05 L (for 0.5 to 8 L). The pressure was measured with a pressure sensor based on a piezoresistive element with a range of ± 20 kPa, and an accuracy of ± 2 % and a resolution of 0.01 kPa. The spirometry parameters were obtained by the built-in software of the Masterscreen PFT System. The flow was integrated to obtain the volume.

Data analysis of maximal fast in- and expiration

The start of a maximal fast in- and expiration manoeuvre was determined by extrapolation. The new 'time zero' from back extrapolation defines the start for all timed measurements. The largest slope averaged over an 80-ms period is used, as shown in Figure 11 (adapted from Miller et al.)[38]. The point where the largest slope crosses the x-axis is used as new time zero and as a start point for the FEV1. The FEV1 was determined by taking the volume one second after the new time zero. In the same way, the FIV1 was calculated. So a new time zero was determined based on the largest slope of the inspiration. The FIV1 was calculated by taking the volume one second after the new time zero of the inspiration.

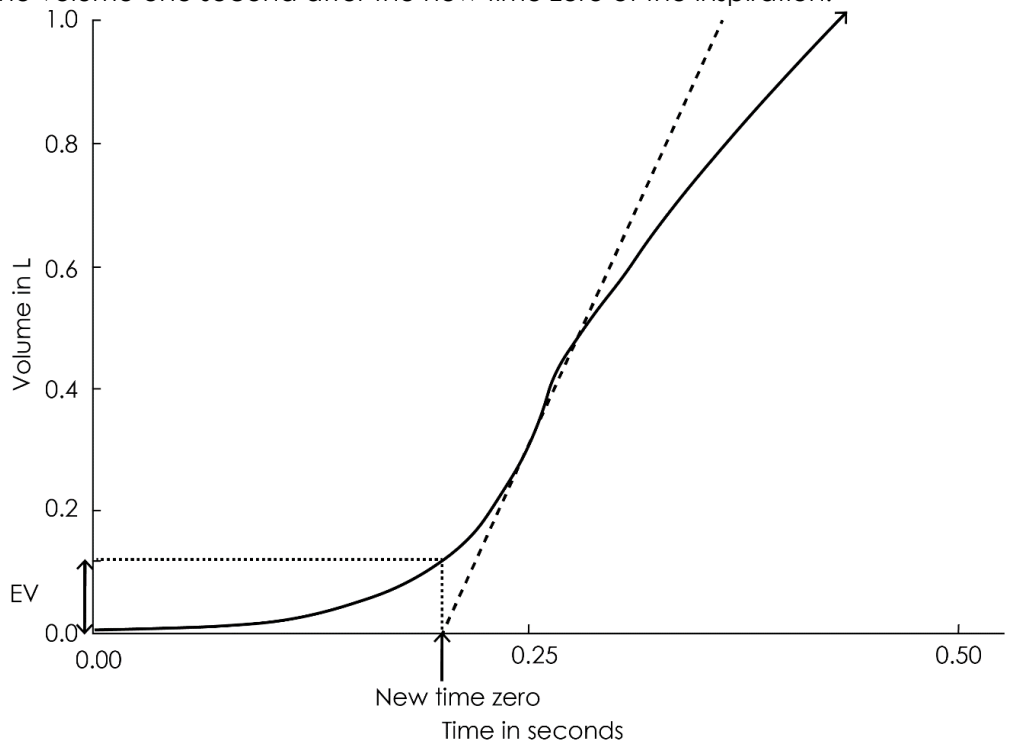


Figure 11 – Early part of subject's volume-time curve. Back extrapolation is performed based on the steepest part of the curve, where the flow is peak expiratory flow (PEF), to determine the new 'time zero. Back extrapolated volume (EV) is 0.123 L. Figure adapted from Miller et al.[38]

The FVC was determined by taking the difference between the maximum volume (at the start of expiration) and the minimum volume after maximal expiration. MIF50 and MEF50 were determined by searching the flows corresponding to respectively 50% of the inspiratory and expiratory vital capacity. The FEV1:FIVC was determined by taking the ratio of the largest FEV1 and the largest FIVC. The ratio MEF50:MIF50 was obtained by dividing the MEF50 by the MIF50. For every signal, multiple fast maximal in- and expiration manoeuvres were performed. The maximum values for every parameter were determined.

Data analysis vital capacity

The IVC was determined by taking the difference between the minimum in volume at the start of the IVC manoeuvre and the maximum in volume at the end of the IVC manoeuvre.

Section 3C.3 - Forced oscillation technique

The FOT measurements were performed with the Jaeger MasterScreen IOS (Vyaire Medical, Mettawa, IL, USA). A loudspeaker generated impulses in alternating directions with a frequency range of 0 and 100 Hz[42, 58]. The impulse length was 40 ms and the accuracy of the signal is < ±2%. The flow was measured by a pneumotachograph and the pressure was measured by pressure transducers. The data was stored with a sampling frequency of 200 Hz.

Data analysis forced oscillation technique

The analysis of the FOT signals was based on the script build by Huisintveld[59]. The flow was integrated to obtain the volume. An example of a flow and pressure signal during normal breathing is shown in Figure 12. The volume was obtained by integration of the flow signal.

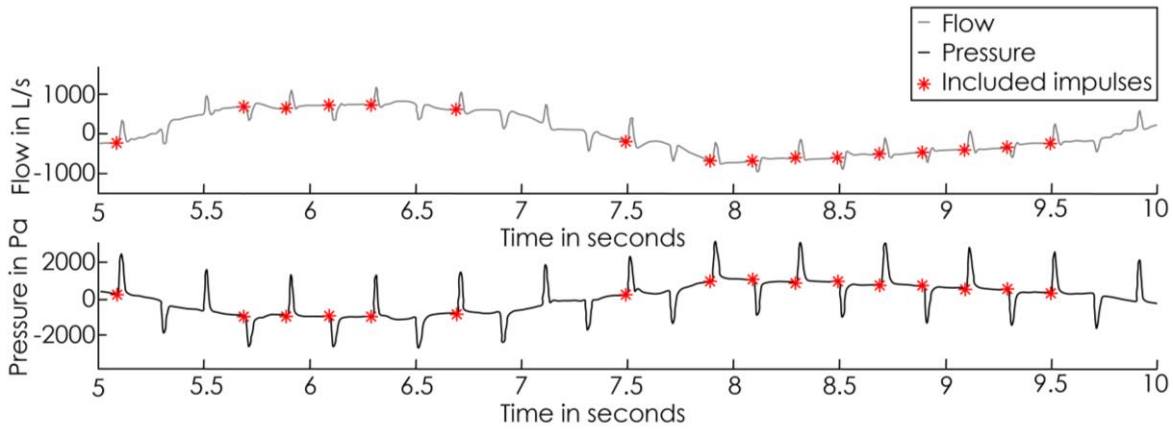


Figure 12 - Flow and pressure signal during a forced oscillation technique measurement during normal breathing. The red markings indicate impulses that met the criteria to be included in the analysis.

All pulses superimposed on the breathing were divided into different segments with the same length, which was done by making use of the start positions of the impulses. Respiration was filtered out of the impulse segments by fitting a linear line to the begin and end of the segment and subtracting this line from the data. Every measurement was repeated three times. When the impulse and response of the respiratory system were separated from the underlying respiration, a fast Fourier transform was applied to all the different pressure and flow segments. All frequencies lower than 3 Hz or higher than 35 were filtered out. The impedance of every segment was obtained by dividing the Fourier transform of the pressure signal by the Fourier transform of the flow signal. The resistance was obtained by taking the real part of the impedance and the reactance was obtained by taking the imaginary part of the impedance. After calculation of the impedances for every segment, the results were checked for reliability. The results could be unreliable if the superimposed impulses were poorly separated from the underlying respiratory signal. Criteria were based on the manual of the MS-IOS system, the report of Huistinveld and visual inspection of the data[42, 59]. Impulse

segments that did not comply with one or more of the following reliability criteria were removed:

- The maximum coefficient of linear approximation of the respiration (C_{max}) should not exceed 1500 mL/s^2, because of the dominance of the underlying respiratory signal.
- The resistance should not be negative (R_{neg}) at any frequency as this is physically impossible.
- The minimum absolute peak flow in the first half of the impulse segment ($\dot{V}_{min}$) should be at least 200 mL/s to prevent a very low value in the nominator for the calculation of the impedance.
- The maximum absolute peak flow in the second half of the impulse segment ($\dot{V}_{max}$) was allowed to be 200 mL/s. Higher flows in the second half of the impulse segment suggested other influences besides the reaction of the respiratory system to the impulse.
- There must be an opposite reaction in the flow of the respiratory system ($\dot{V}_{opposite}$); the sign of the flow had to change within the segment. A change in sign could suggest that a response from the respiratory system to the impulse is registered, and therefore that the segment was more reliable.
- The maximum coefficient of the resistance curve (C_{Rmax}) should not be bigger than 0.15 to correct for sharp changes and improbable bumps in the curve.
- The minimum coefficient of the reactance curve (C_{Xmin}) should not be smaller than -0.04 to correct for sharp changes and improbable bumps in the curve.

The number of removed segments was saved as well as the criteria that were not met in those cases. The resonance frequency was determined by searching for the frequency where the reactance is zero. The area under the reactance curve was determined by taking the area of the reactance from 5 Hz till the resonance frequency. The resistances at 5 and 20 Hz were determined by searching the resistance for the corresponding frequencies. By subtracting the resistance at 20 Hz from the resistance of 5Hz, the frequency dependence of the resistance was determined. The reactance at 20 Hz was determined by searching the reactance for the corresponding frequency. The mean was calculated for the resonance frequency, the area under the reactance curve, the resistance at 5 Hz and 20 Hz, the frequency dependence and the reactance at 20 Hz. Since these parameters differ for different inspiratory volumes, they were plotted against the inspiratory volume. For each patient, the lowest point in their inspiratory volume graph was taken as zero. A linear approximation of the relationship between the specific parameter and the inspiratory volume was performed. The y-intercept (interception with y-axis) and the coefficient (slope angle) were determined. An example of this analysis is shown in Figure 13.

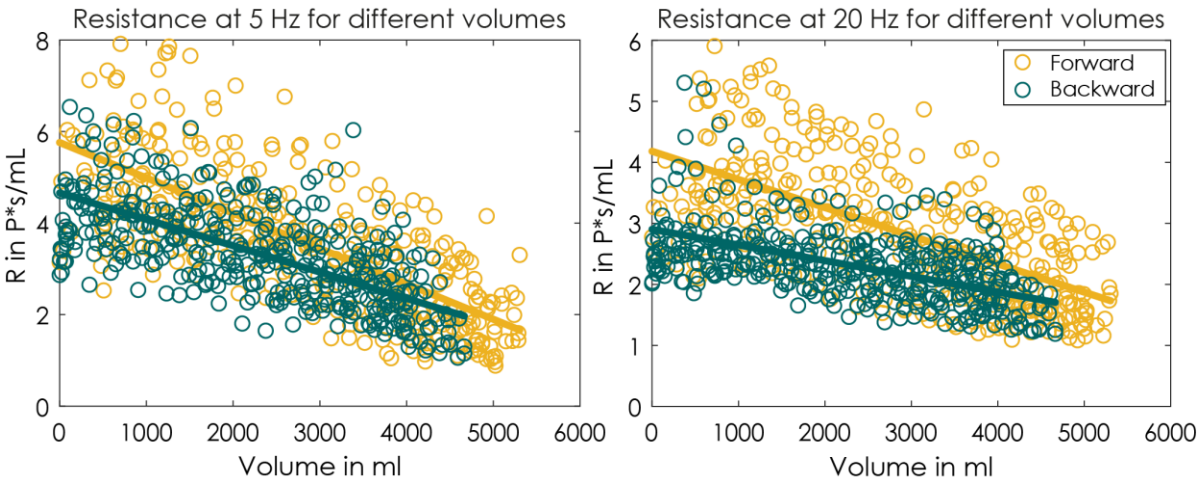


Figure 13 – A linear approximation of the relationship between the resistance parameters and the inspiratory volume. The start position (intersection with y-axis) and coefficient (slope angle) are determined.

These analyses were performed for normal breathing, maximal slow in- and expiration maximal fast in- and expiration (i.e. from total lung capacity to residual volume) and fast maximal in- and expiration. A pilot study showed that the above-mentioned reliability criteria could not be used for maximal fast in- and expiration since these were developed for normal tidal breathing. No impulse segments met all the criteria during a maximal fast in- and expiration and therefore, the following reproducibility criteria were used for the maximal fast in- and expiration manoeuvres: C_{max} was deleted as reliability criteria, R_{neg}, $\dot{V}_{min}$, $\dot{V}_{opposite}$, C_{Rmax} and C_{Xmin} were not changed and $\dot{V}_{max}$ was increased to 400 mL/s.

Section 3C.4 - Negative expiratory pressure

The NEP measurements were performed with a custom-made device, Figure 14.

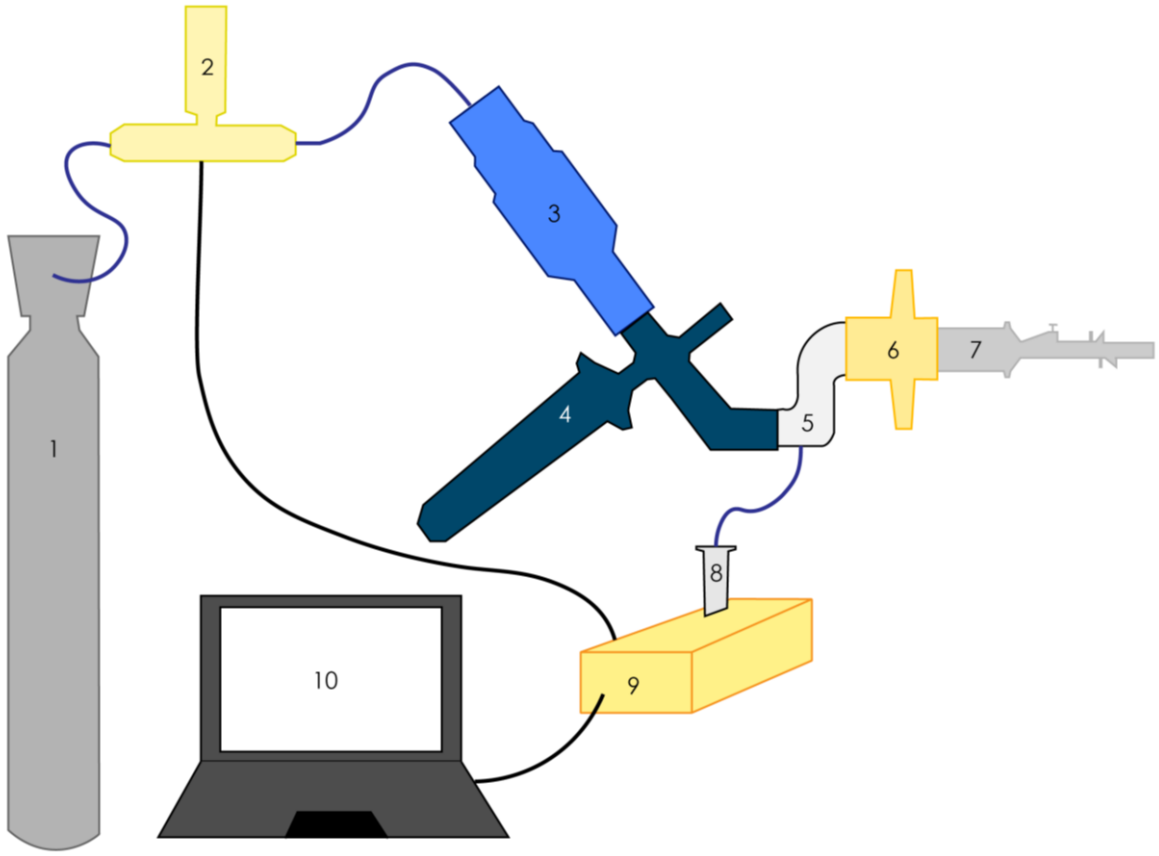


Figure 14 - Measurement set-up of the Negative Expiratory Pressure Measurement. 1) Gas bottle with pressurised air, 2) Solenoid valve, 3) Air amplifier, 4) Pneumotachograph, 5) Connector tubes, 6) Antibacterial filter, 7) Adjustable mouthpiece, 8) Syringe connected to a pressure sensor, 9) Box with Arduino microcontroller and a breadboard with electrical wiring, 10) Laptop displaying the measured signals.

An air amplifier (Meech air amplifier aluminium 25 mm, Oxfordshire, UK) is a device which created a negative pressure relative to atmospheric pressure using a Venturi effect generated by pressurised air delivered by a gas bottle. The pressurised air was regulated by a solenoid valve (JP Fluid Control CM-DA G1/4'', Tameson, Eindhoven, Netherlands), which provided precise control of the pressured air and therefore the negative pressure. The air amplifier was connected to the pneumotachograph (Vyaire Medical MasterScreen PFT System, Mettawa, IL, USA) which measured the flow and the pressure at the mouth. The flow was measured with a range of 0 to ± 20 L/s and an accuracy of ± 2% or 0.2 L/s (for 0.2 to 12 L/s) and a resolution of 10 mL/s[57]. The volume was determined based on software integration within the range of ±20 L and accuracy of ± 3% or ± 0.05 L (for 0.5 to 8 L). The pressure was measured piezoresistive with a range of ± 20 kPa relative to atmospheric pressure, an accuracy of ± 2 % and a resolution of 0.01 kPa. Data was saved using Jlab (version 2012, Terranuova Bracciolini, Italy) with a sampling frequency of 200 Hz. To detect when a patient was exhaling, a pressure sensor (Bosch Sensortec BMP085, Reutlingen, Germany) was connected to the breadboard (WBU-301, Wisher Enterprise Co. Taipei, Taiwan) which measured the mouth pressure. The solenoid valve and pressure sensor were controlled by an Arduino Uno microcontroller (Arduino UNO, New York, NY, USA). The NEP was operated by use of a script written in Arduino IDE (version 1.8.7). A person breathed through the adjustable mouthpiece. After at least three stable breaths, a NEP was applied during

inspiration. At the start of the following expiration, the solenoid valve opened within 30 ms and a negative pressure of -5 cm H_20 was applied for 1 second after which the valve closed automatically. A detailed description of the NEP set-up can be found in the report of van der Steen[60].

Data analysis negative expiratory pressure

The analysis of the NEP signals was based on the script build by van der Steen[60]. The flow was integrated to obtain the volume. An example of a flow and pressure signal is shown in Figure 15.

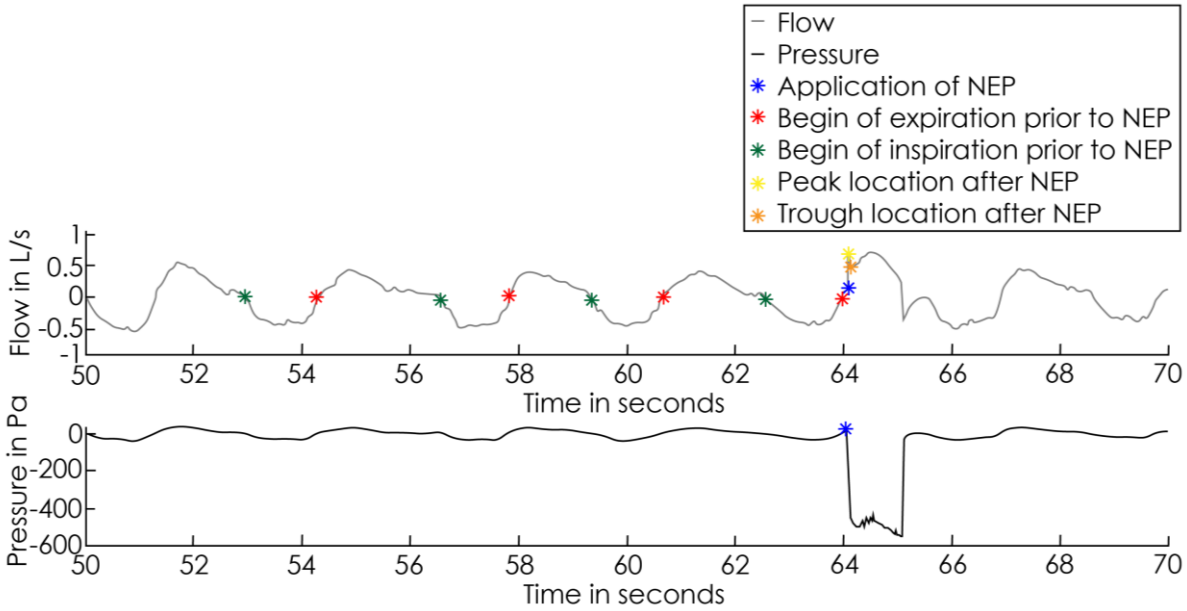


Figure 15 – Flow and pressure signal during a negative expiratory pressure (NEP) measurement. The breaths before the NEP application are marked as well as the point of application of NEP, the peak in the flow after NEP application and the trough in the flow after the peak.

In the pressure signal, the onset of NEP was searched. This was done by searching for a negative pressure, which decreased with a large angle of inclination. In the first 0.1 seconds after the application of NEP, a peak was searched. The height of the peak was saved. Between the location of the peak and 0.2 seconds after the application of NEP, a trough was searched. The begin of inspiration and expiration was determined based on the transitions in flow from negative to positive. The begin of the expiration in which the NEP was applied was also searched. The three breaths before the breath in which NEP was applied were saved. The mean flow was calculated of the three expirations before the breath in which NEP was applied. It was calculated when the flow of the NEP signal was smaller compared to the mean flow of the three preceding expiration. This was represented as a percentage of total time when NEP flow was smaller compared to the flow of the three preceding expirations. The time difference between the beginning of the expiration and the NEP application was also determined. To determine the $V_{0.2}/V_{0.2}$, $V_{0.5}/V_{0.5}$, the volume in respectively the first 0.2 and 0.5 seconds after NEP application divided by the mean volume of respectively the first 0.2 and 0.5 seconds of the three preceding expiration was calculated. To obtain the $V_{0.2}/V_{1.0}$,$V_{0.5}/V_{1.0}$, the volume of the first 0.2 and 0.5 seconds after NEP application was also divided by the mean volume of the first second of the three expirations preceding NEP application.

Subchapter 3D – Study parameters

The main study parameters answered the main objective: to investigate the resistance and flow parameters obtained by spirometry, FOT, and NEP in OSAS patients for the prediction of

successful MAD therapy. This is done by calculating the diagnostic accuracy, expressed as sensitivity, specificity, negative predictive value, and positive predictive value, for the different measurement parameters. The parameters of the different measurements are:

- Spirometry: relative difference between the ratios of the expiratory flow rate at 50% of vital capacity to the inspiratory flow rate at 50% of vital capacity (MEF_{50}:MIF_{50}) obtained by the MAD in maximal retracted and maximal protrusive position.
- FOT: absolute difference between the mid-frequency resistances (R_{20}) obtained by the MAD in maximal retracted and maximal protrusive position.
- NEP: absolute difference in flow drops ($\Delta\dot{V}$) as a percentage of the peak flows ($\%V_{peak}$) obtained by the MAD in maximal retracted and maximal protrusive position.

Successful MAD therapy is determined on the outcome of the control poly(somno)graphy measurement after the titration period of the MAD. Which is defined as a decrease in AHI of more than 50% and an AHI < 20 compared to the initial poly(somno)graphy measurement.

The secondary study parameters of interest are:

- The diagnostic accuracy of the different primary measurement parameters with the relative differences instead of the absolute differences between the prediction of MAD success.
- The experience of the subjects with the different tests. This will be evaluated with three questions (see Attachment F1).
- The diagnostic accuracy of the other spirometry parameters (FVC, FIVC, FIV1, FEV1, 'saw toothing', MEF50, MIF50, VC) for successful MAD therapy, by both calculating the absolute and relative differences between the results obtained by a MAD in maximal retracted and maximal protrusive position.
- The diagnostic accuracy of the other FOT parameters (R5, X5, $R_{5\text{-}20}$, $f_{res,}$ AX) for successful MAD therapy, by both calculating the absolute and relative differences between the results obtained by a MAD in maximal retracted and maximal protrusive position.
- The diagnostic accuracy of the other NEP parameters (the $V_{0.2}/V_{0.2}$, $V_{0.2}/V_{1.0}$, $V_{0.5}/V_{0.5}$, $V_{0.5}/V_{1.0}$, and percentage below) for successful MAD therapy. This is performed by both calculating the absolute and relative differences between the results obtained by a MAD in maximal retracted and maximal protrusive position.
- Additional study parameters are obtained by performing an explorable analysis on the spirometry, FOT, and NEP data. The diagnostic accuracy of these parameters as for successful MAD therapy is determined by both calculating the absolute and relative differences between the results obtained by the mandible maximal retracted and maximal protruded.
- The diagnostic accuracy of the different primary and secondary measurement parameters for an alternative definition of MAD success. This definition is also based on the control poly(somno)graphy measurement after the titration period of the MAD and is defined as an AHI < 10 with reduction of complaints.

Subchapter 3E – Statistical analysis

To answer the main research question, the diagnostic accuracy expressed as the sensitivity, specificity, negative predictive value, and positive predictive value for the three different measurement parameters described in 8.1 were determined. To assess different cut-off values for the sensitivity and specificity, a receiver operating characteristics (ROC) curve was

calculated. The sensitivity and specificity were determined based on the optimum cut-off value of both the sensitivity and specificity. The accuracy of the different measurement parameters was measured by the area under the curve (AUC). A value of 0.5 for the AUC indicates that the investigated parameter had no discriminatory ability between successful or not successful MAD therapy[61, 62]. An AUC between 0.5 and 0.6 is considered as a fail, an AUC between 0.6 and 0.7 as poor, an AUC between 0.7 and 0.8 as fair, an AUC between 0.8 and 0.9 as good and an AUC more than 0.9 as an excellent ability to discriminate[62]. A predictive parameter was considered to be clinical acceptable when a sensitivity of ≥ 80% and specificity of ≥ 60% was obtained.

Diagnostic accuracy (sensitivity, specificity, PPV, NPV, and AUC) was also determined for the secondary study parameters. The subject's experiences with the three different measurements were determined. An unpaired T-test or Mann-Whitney U test was performed as appropriate to evaluate whether there was a difference in convenience between the MAD successful group and the MAD unsuccessful group.

The other study parameters were the demographic parameters. These were analysed with descriptive statistics, calculating the mean and standard deviation or median and interquartile, whichever was appropriate. Additionally, the demographic parameters were compared between the successful and non-successful MAD therapy groups. Categorical data were analysed using the Chi-square test. Continuous data were analysed with the Student's t-test or Mann Whitney U test, whichever appropriate.

Statistical analysis was performed using IBM SPSS Statistics software (version 22, IBM Corp., Armon, NY, USA).

Chapter 4 – Results

In this chapter, the results of the study are discussed. In the first subchapter, the study population is discussed, in the second subchapter, the baseline characteristics of the included subjects are described. The third subchapter focusses on the results of the spirometry measurements, the fourth subchapter on the results of the FOT measurements and the fifth subchapter on the results of the NEP measurements. The sixth subchapter describes the results of the patient experiences of the measurements.

Subchapter 4A – Study population

Forty-six subjects were approached by the special dentistry or received a letter based on the database of the special dentistry. Of these, twenty-three patients were excluded. Six patients had no time to participate, two were rejected since they met the exclusion criteria (a control PG after an initial PSG), five patients did not show up for the appointment and ten patients had not given an explanation or there was another cause for exclusion. All subjects had an initial and control polygraph within 15 months of each other. One of the twenty-three patients switched to CPAP therapy, the other twenty-two patients were still using a MAD at the moment of the measurements. There were 14 patients with successful MAD therapy based on definition 1 (AHI < 20 and a reduction of ≥ 50% in AHI) as well as definition 2 (AHI < 10). 9 Patients had an unsuccessful MAD therapy based on both definitions. For both definitions of MAD success, there was one patient with successful MAD therapy, who was not successful based on the other definition of MAD success. All patients had an initial and control polygraph. Details regarding in- and exclusion can be found in Figure 16.

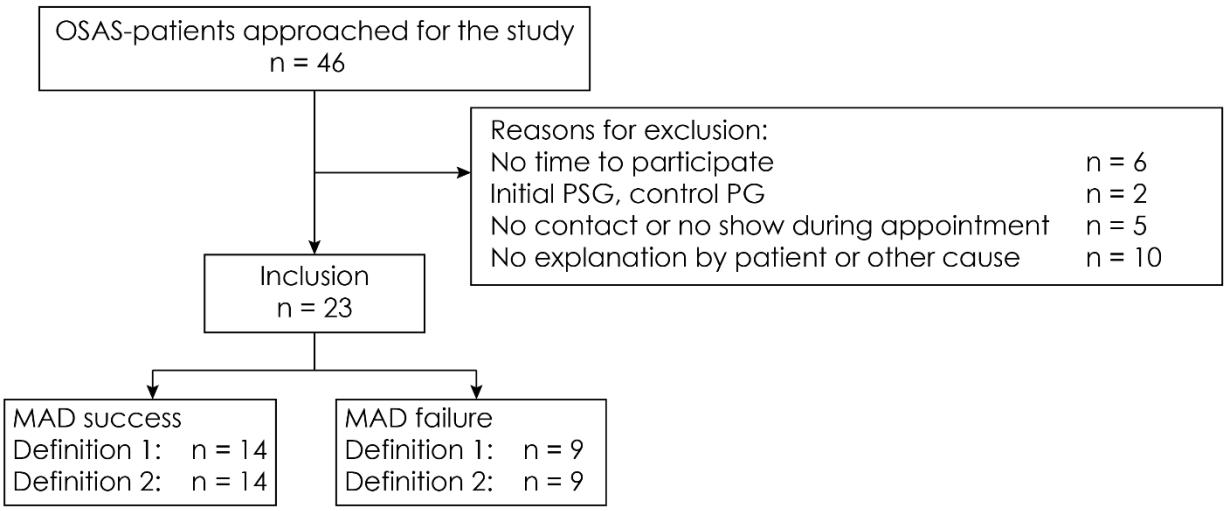


Figure 16 – Flow chart of patients included in the study. Mandibular Advancement Device success was based on two different definitions. Definition 1: a decline in the apnoea-hypopnoea index (AHI) of more than 50% and an AHI<20. Definition 2: an AHI<10.

Subchapter 4B – Patient characteristics

The mean age was 53.8 (±9.7) years and 87 % (20/23) was male. The mean BMI was 28.2 (±3.0) kg/m^2 and retrognathia was present in 21.7% (5/23). The median AHI at baseline was 17.7 (15.9-25.9) per hour. Mean AHI on the control sleep test after MAD titration was 8.6 (±4.1) per hour. There were no significant differences between the MAD successful and not successful group except for the control AHI (based on both definitions of MAD success). Based on the first definition of MAD success, the median control AHI in the successful group was 5.9 (4.0 - 7.9) whereas the median control AHI in the non-successful group was 11.3 (10.9-13.0). An overview of the baseline characteristics for the first definition of MAD success is presented in

Table 1. Baseline characteristics for the second definition of MAD success can be found in Table A.1 in chapter 8 (Appendices 'Subchapter D – Additional results').

Table 1 – Baseline characteristics of the successful MAD therapy group versus the non-successful MAD therapy group based on the first definition of MAD success

	All included patients (n=23)	Successful MAD therapy (n=14)	Non-successful MAD therapy (n=9)	P-value
Age (yrs)	53.8 (9.7)	54.5 (8.5)	52.7 (11.8)	0.69
Male gender (n)	20 (87)	11 (78.6)	9 (100)	0.25
BMI (kg/m^2)	28.2 (3.0)	28.0 (2.8)	28.4 (3.6)	0.78
Baseline AHI Total	17.7 (15.9 - 25.9)	19.3 (15.7 - 29.1)	17.7 (16.4 - 20.4)	0.59
Control AHI Total	8.6 (4.1)	5.9 (4.0 - 7.9)	11.3 (10.9 - 13.0)	<0.01*
Neck circumference (cm)	41.2 (2.3)	41.1 (2.7)	41.4 (1.6)	0.75
Retrognathia (n)	5 (21.7)	4 (28.6)	1 (10.0)	0.61
Mallampati Score				0.25
I	2 (8.7)	1 (7.1)	1 (11.1)	
II	13 (56.5)	6 (42.9)	7 (77.8)	
III	7 (30.4)	6 (42.9)	1 (11.1)	
IV	1 (4.3)	1 (7.1)	0 (0)	
Nasal obstruction	6 (26.1)	5 (35.7)	1 (11.1)	0.34
Weight gain (n)	1 (4.4)	1 (7.1)	0 (0)	1.00
Weight loss (n)	3 (13)	1 (7.1)	2 (22.2)	0.54
Smoking (n)	1 (4.3)	0 (0)	1 (11.1)	0.39
Packyears (yrs)	1.8 (0 - 8)	3.3 (0 - 8.6)	0 (0 - 16)	0.55
Medical history				
Cardiovascular (n)	2 (8.7)	1 (7.1)	1 (11.1)	1.00
COPD (n)	1 (4.3)	0 (0)	1 (11.1)	0.39
Asthma (n)	2 (8.7)	0 (0)	2 (22.2)	0.14
Tonsillectomy (n)	6 (26.1)	3 (21.4)	3 (33.3)	0.64
Position difference of adjustable mouthpiece (mm)	9.4 (4.2)	9.8 (4.8)	8.9 (3.1)	0.59

*Values are given in numbers (%), medians (interquartile ranges), or mean (standard deviations), yrs = years, n = number of patients, BMI = Body Mass Index, AHI = Apnoea-hypopnoea index, COPD = chronic obstructive pulmonary disease, * indicates significant difference between MAD successful and non-successful group.*

Subchapter 4C – Spirometry

To get an overview of the lung function of the patients, standard spirometry was performed. The results of this standard spirometry are presented in Table 2. When possible the percentage of the predictive value is given. The mean FVC of all patients was 5.10 (±1.37) litre which corresponds to 110% (±16.7) of the predicted value. The mean FEV1 was 3.78 (±1.10) litre which was 102% (±19.2) of the predicted value. The median and predicted values of the FEV1/FIVC was respectively 74.7 (68.6-77.4) and 96.6% (90.1-98.6). There were no significant differences between the MAD successful and non-successful group for both definitions of MAD success.

Table 2 – Normal spirometry parameters for the successful MAD therapy group versus the non-successful MAD therapy group.

	All included patients (n=23)	Successful MAD therapy (n=14)		Non-successful MAD therapy (n=9)		P-value	
		Def 1	Def 2	Def 1	Def 2	Def 1	Def 2
FVC (L)	5.10 (1.37)	4.94 (1.38)	4.76 (1.46)	5.34 (1.41)	5.62 (1.11)	0.52	0.13
FVC (% of predicted)	110 (16.5)	111 (13.9)	107 (18.5)	108 (20.8)	115 (12.8)	0.72	0.29
FEV1 (L)	3.78 (1.10)	3.67 (1.06)	3.46 (1.15)	3.95 (1.21)	4.28 (0.84)	0.17	0.06
FEV1 (% of predicted)	102 (19.2)	100 (92.9–119)	97.3 (21.5)	105 (91.3-116)	108.86 (13.3)	0.71	0.13
FEV1/IVC	74.7 (68.6-77.4)	74.5 (68.9-7.8)	71.2 (9.64)	74.8 (67.5-77.0)	75.4 (5.42)	0.80	0.19
FEV1/IVC (% of predicted)	96.6 (89.4-98.6)	96.7 (88.4-9.8)	96.6 (84.3-98.1)	95.6 (89.5-98.2)	96.0 (92.7-100)	0.45	0.57
FIV1 (L)	4.73 (1.37)	4.56 (2.97-.82)	4.42 (1.54)	4.50 (1.07)	5.23 (0.91)	0.83	0.13
IVC (L)	5.03 (1.35)	4.83 (1.39)	4.69 (1.42)	5.34 (1.31)	5.57 (1.11)	0.39	0.11
MIF50 (L/s)	6.33 (1.77)	6.19 (2.10)	5.94 (2.02)	6.54 (1.16)	6.93 (1.15)	0.62	0.15
MEF50 (L/s)	3.88 (1.64)	3.80 (1.63)	3.45 (1.74)	4.01 (1.74)	4.55 (1.28)	0.77	0.10
MEF50 (% of predicted)	79.8 (31.2)	80.4 (32.0)	73.3 (34.8)	79.0 (31.9)	90.0 (22.7)	0.92	0.18
MEF50/MIF50	0.63 (0.26)	0.63 (0.24)	0.60 (0.27)	0.62 (0.30)	0.68 (0.24)	0.91	0.46
Saw-toothing	2 (8)	2 (14.3)	2 (14.3)	0 (0)	0 (0)	0.50	0.50
VC (L)	0.52 (1.38)	5.00 (1.40)	4.84 (1.43)	5.49 (1.38)	5.74 (1.17)	0.42	0.12
VC (% of predicted)	107 (14.7)	108 (12.4)	105 (15.4)	107 (18.6)	112 (13.1)	0.91	0.23

Values are given in numbers (%), medians (interquartile ranges), or mean (standard deviations). Def 1 = first definition of MAD success, Def 2 = second definition of MAD success.

For the analysis of the spirometry parameters, the values of the normal (sitting) measurement were taken as baseline value (100%). The results of the mandible in a retracted and protruded position were determined as a percentage of baseline values. The difference of these percentages was taken by subtracting the percentage value of the measurement with the mandible in retracted position from the percentage value of the measurement with the mandible in protruded position, these differences are called the relative differences. Table 3 shows the results of this analysis.

Table 3 – Relative difference in spirometry parameters for the successful MAD (definition 1) therapy group versus the non-successful MAD therapy group. The results for the mandible in the protruded and retracted position were determined as a percentage of the values for the normal (sitting) measurement. The difference between these two percentages was taken and called the relative difference.

	All included patients (n=23)	Successful MAD therapy (n=14)	Non-successful MAD therapy (n=9)	P-value
Δ FVC (%)	0.84 (-1.13 - 1.74)	1.07 (-1.89 - 1.80)	-0.19 (-0.77 – 1.31)	0.66
Δ FEV1(%)	0.55 (-1.04 - 1.50)	0.32 (2.01)	0.44 (1.84)	0.89
Δ FEV1/FIVC (%)	-0.13 (-1.85 - 2.00)	0.34 (4.10)	0.47 (3.81)	0.94
Δ FIV1 (%)	0.00 (-2.25 - 5.90)	1.99 (12.08)	-0.70 (2.35)	0.43
Δ IVC (%)	0.27 (3.39)	0.35 (3.86)	0.15 (2.69)	0.88
Δ MIF50 (%)	3.53 (-3.59 - 7.93)	6.15 (0.97 - 9.13)	-1.85 (-3.92 – 1.92)	0.07
Δ MEF50 (%)	0.75 (-3.70 - 6.67)	-1.14 (-2.69 - 7.02)	2.09 (-6.79 - 7.70)	0,80
Δ MEF50/MIF50 (%)	-2.90 (17.50)	-6.84 (19.18)	3.23 (13.23)	0.15

Values are given in numbers (%), medians (interquartile ranges), or mean (standard deviations).

There were no significant differences between the MAD successful and non-successful group based on both definitions of MAD success for the relative and absolute differences. Results of these analyses can be found in Table A.2 and Table A.3 in chapter 8 (Appendices 'Subchapter D – Additional results').

There were no significant differences for the individual parameters (both in protruded and retracted position) between the MAD successful and non-successful group for the first and second definition of MAD success. An overview of the results of this analysis can be found in Table A.4 and Table A.5 in chapter 8 (Appendices 'Subchapter D – Additional results').

Subchapter 4D – Forced Oscillation Technique

For the FOT measurements, the results from the mandible in retracted position were subtracted from the results from the mandible in protruded position (absolute difference). The results of this analysis for the main parameters and the first definition of MAD success are presented in Figure 17. The exact numbers and p-values for the parameters for the first and second definition of MAD success can be found in Table A.6 in chapter 8 (Appendices 'Subchapter D – Additional results').

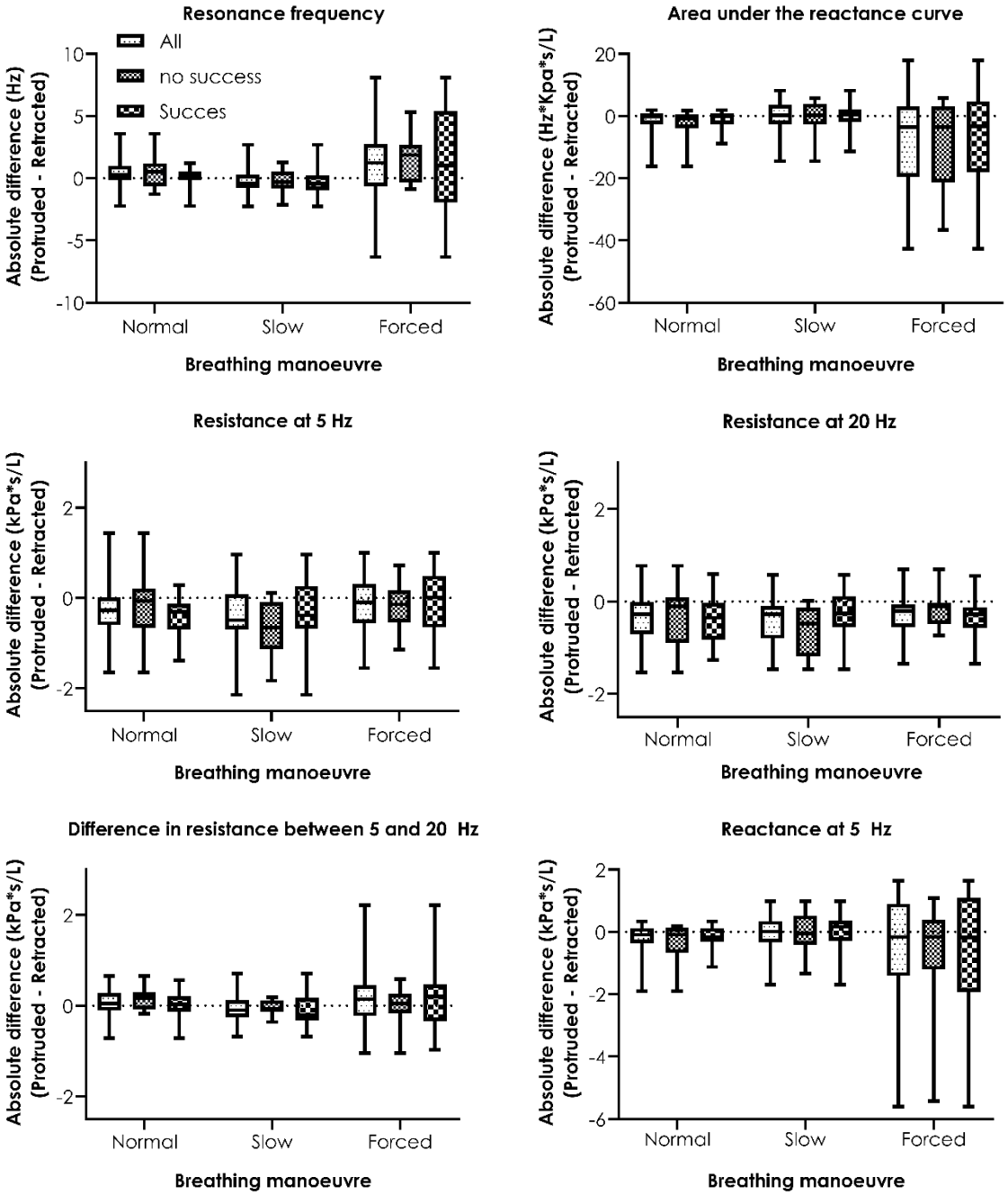


Figure 17 – Box plots of the absolute differences in main parameters for the normal, slow and fast maximal in- and expiration manoeuvres. The horizontal line in the box represents the median value, the width of the box represents the interquartile ranges and the error ranges indicates the minimum and maximum values.

There were no significant differences in absolute differences for all the investigated parameters between protruded and retracted position for the MAD successful and non-

successful group based on the first definition of MAD success. There were also no significant differences for the same analysis based on the second definition of MAD success, see Table A7 in chapter 8 (Appendices 'Subchapter D – Additional results'). There were also no significant results for the relative differences of these parameters between the mandible in protruded and retracted position for both definitions of MAD success. For the relative differences, the values in protruded position were taken as 100% and the relative difference is calculated with the mandible in a retracted position. The results of this analysis are present in Table A8 for the first definition of MAD success and in Table A9 for the second definition of MAD success in chapter 8 (Appendices 'Subchapter D – Additional results').

The individual and secondary parameters are also investigated as predictors for MAD success. The secondary parameters were analysed for every breathing manoeuvre separately. The results of all analysis can be found in Table A.10 and A.11 for the measurements with the mandible in protruded position and Table A.12 and A.13 for the mandible in a retracted position in chapter 8 (Appendices 'Subchapter D – Additional results').

Section 4D.1 – Normal breathing

By investigation of the different secondary parameters for normal breathing during the FOT measurement, there were no parameters that were significantly different between the MAD successful and MAD non-successful group based on the first definition of MAD success. For the second definition of MAD success, there were three parameters which differ significantly between the successful and non-successful group.

It was also investigated which parameters differed significantly between the MAD successful and non-successful group during normal breathing based on the second definition of MAD success. Three parameters differed significantly between these two groups. All these parameters were based on the airway resistance. The ROC-curves of these parameters are shown in Figure 18. The predictive values associated with the optimal cut-off are also enumerated in Table A.14 in chapter 8 (Appendices 'Subchapter D – Additional results').

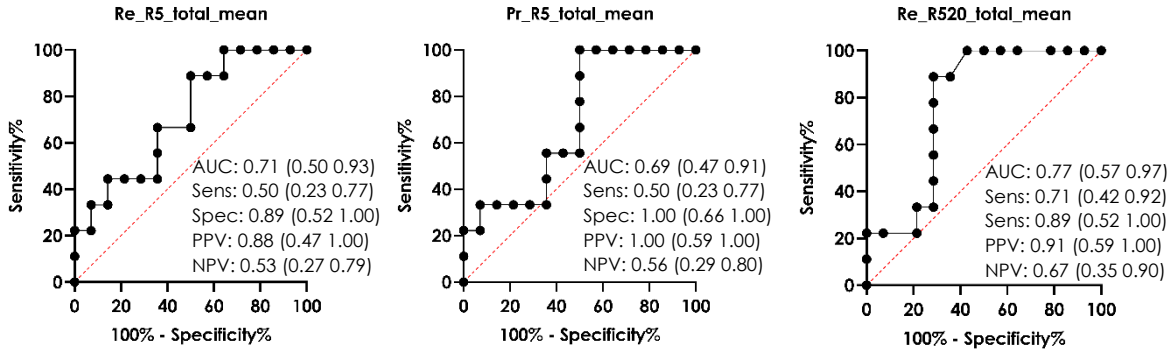


Figure 18 – Receiver Operating Characteristic (ROC)-curves of the FOT parameters during normal breathing which were significantly different between MAD successful and MAD non-successful group based on the second definition of MAD success. Re = retracted position of the mandible, Pr = protruded position of the mandible, R5 = resistance at 5 Hz, R520 = difference in resistance between 5 and 20 Hz, AUC = area under the curve, Spec = specificity, Sens = sensitivity, PPV = positive predictive value, NPV = negative predictive value with the 95% confidence interval.

Section 4D.2 – Maximal slow in- and expiration

It was investigated whether there were significant differences in the secondary parameters during a maximal slow in- and expiration during the FOT measurements between the MAD successful and non-successful group. Based on the first definition of MAD success, there were no significantly different parameters between the two groups. For the second definition of MAD success, four parameters differed significantly between the MAD successful and non-successful group. All of these parameters are related to the airway resistance. Three were related to the resistance at 5 Hz, and one to the resistance at 20 Hz. The ROC-curves of these parameters are shown in Figure 19. The values of this analysis are present in Table A.15 in chapter 8 (Appendices 'Subchapter D – Additional results').

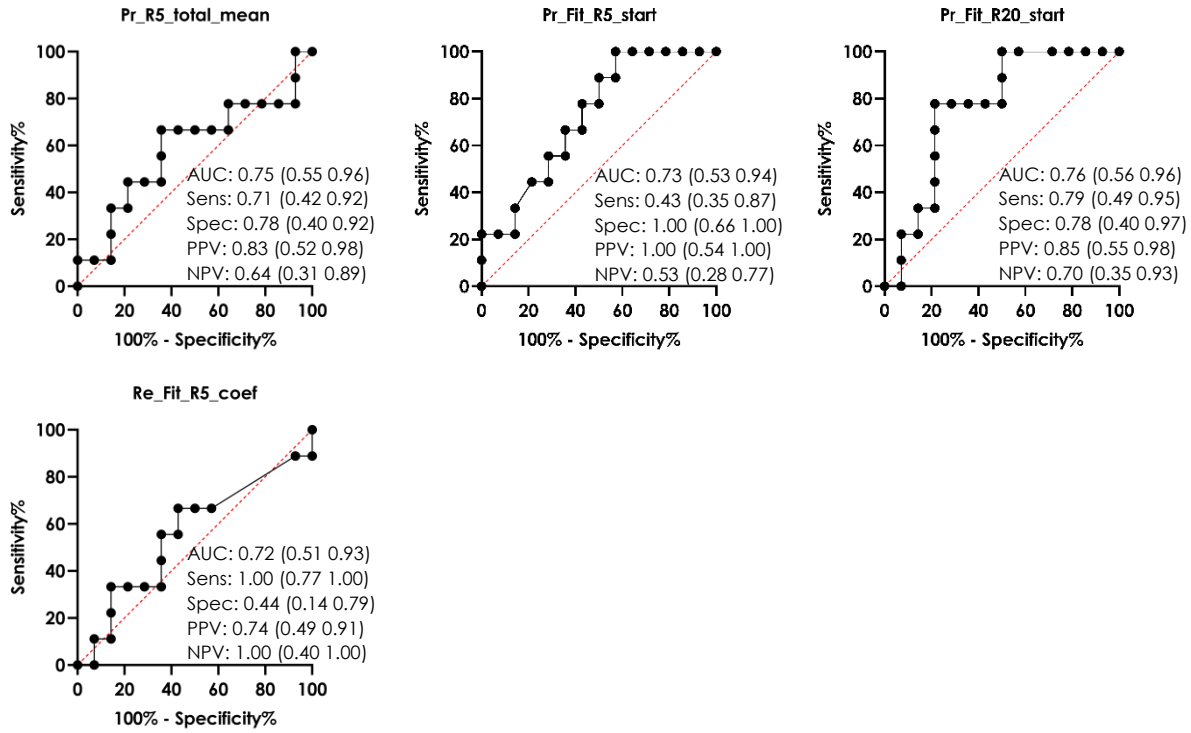


Figure 19 – Receiver Operating Characteristic (ROC)-curves of the FOT parameters during a maximal slow in- and expiration which were significantly different between MAD successful and MAD non-successful group based on the second definition of MAD success. Pr = mandible in protruded position, Re = mandible in retracted position, R5 = resistance at 5 Hz, R20 = resistance at 20 Hz, Fit = the linear approximation of the relationship between the parameter and the volume during breathing, start gives the y-intercept of this linear approximation and coef the coefficient, AUC = area under the curve, Spec = specificity, Sens = sensitivity, PPV = positive predictive value, NPV = negative predictive value with the 95% confidence interval.

Section 4D.3 – Maximal fast in- and expiration

For the maximal fast in- and expiration during the FOT measurements, it is also investigated whether there were significant differences in the secondary parameters between the MAD successful and non-successful group. Since there were many significant parameters, the results of this analysis are separated by the different positions of the mandible (protruded, retracted and the difference between those two).

Protruded position of the mandible

There were no significant differences for the mandible in protruded position between the successful and non-successful group based on the first definition of MAD success. Based on the second definition of MAD success, eleven parameters were significantly different between these two groups. Three were based on the resonance frequency, five on the resistance, three on the reactance and nine were related to the linear approximation of the

correlation between the specific parameter and the inspiratory volume. ROC-curves were made for these parameters, which are shown in Figure 20. A detailed description of the results of this analysis is present in Table A.16 in chapter 8 (Appendices 'Subchapter D – Additional results').

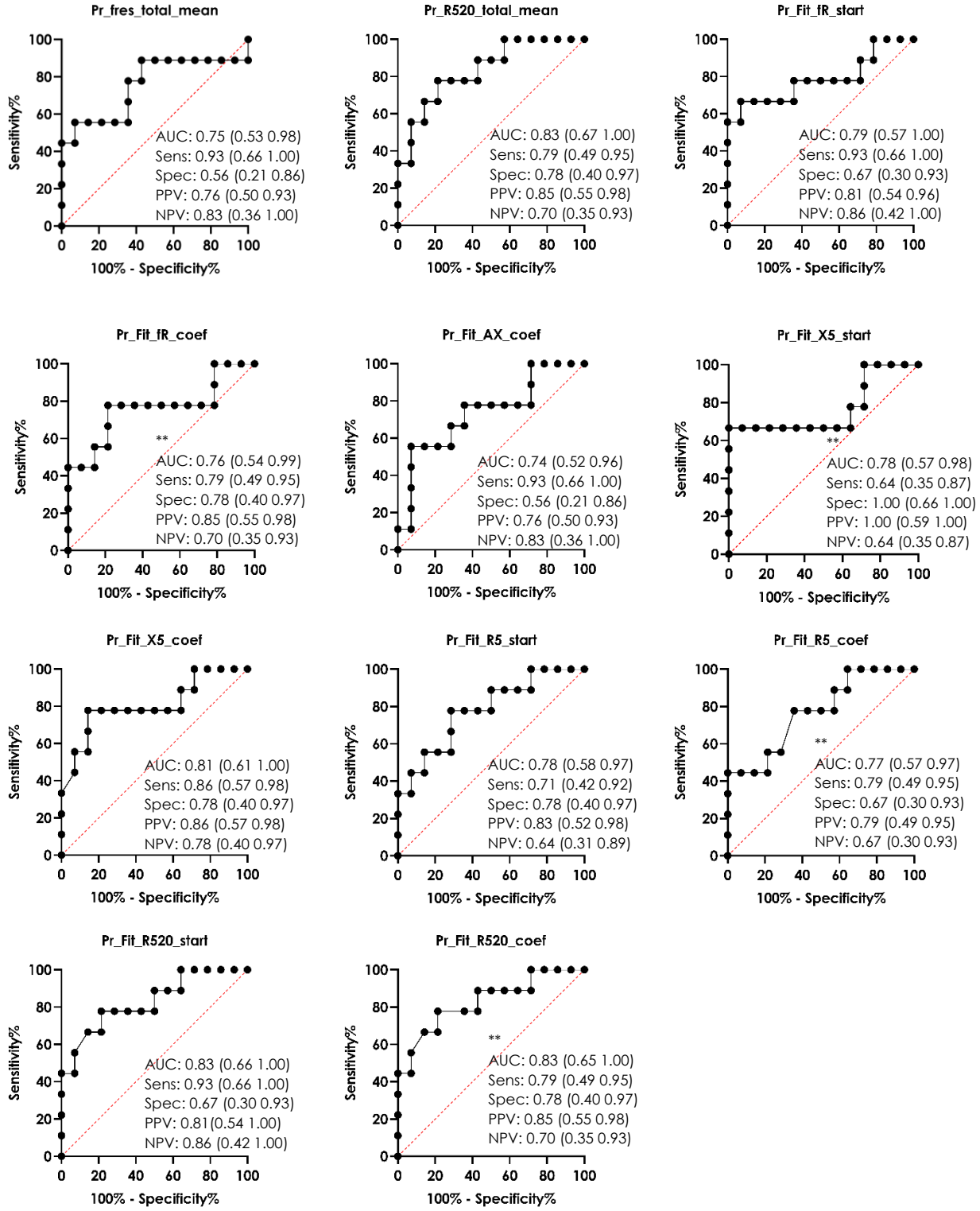


Figure 20 – Receiver Operating Characteristic (ROC)-curves of the FOT parameters during a maximal fast in- and expiration with the mandible in protruded position. The ROC-curves are shown from the parameters which were significantly different between MAD successful and MAD non-successful group based on the second definition of MAD success. Pr = mandible in protruded position, R5 = resistance at

5 Hz, R20 = resistance at 20 Hz, R520 = difference in resistance between 5 and 20 Hz (5Hz – 20Hz), fRes = resonance frequency, AX = area under the reactance curve, X5 = reactance at 5 Hz, Fit = the linear approximation of the relationship between the parameter and the volume during breathing, start gives the y-intercept of this linear approximation and coef the coefficient, AUC = area under the curve, Spec = specificity, Sens = sensitivity, PPV = positive predictive value, NPV = negative predictive value with the 95% confidence interval. ** These parameters predict MAD failure instead of success.

Retracted position of the mandible

For the mandible in a retracted position, one parameter differed significantly between the MAD successful and non-successful group based on the first definition of MAD success. The difference in resistance between 5 and 20 Hz was significantly different between the successful and non-successful group. A ROC-curve was made of this parameter and the results are shown in Figure 21. The exact values of this analysis are present in Table A.17 in chapter 8 (Appendices 'Subchapter D – Additional results').

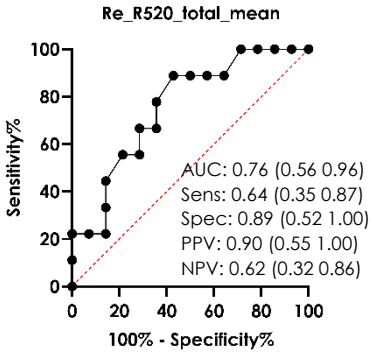
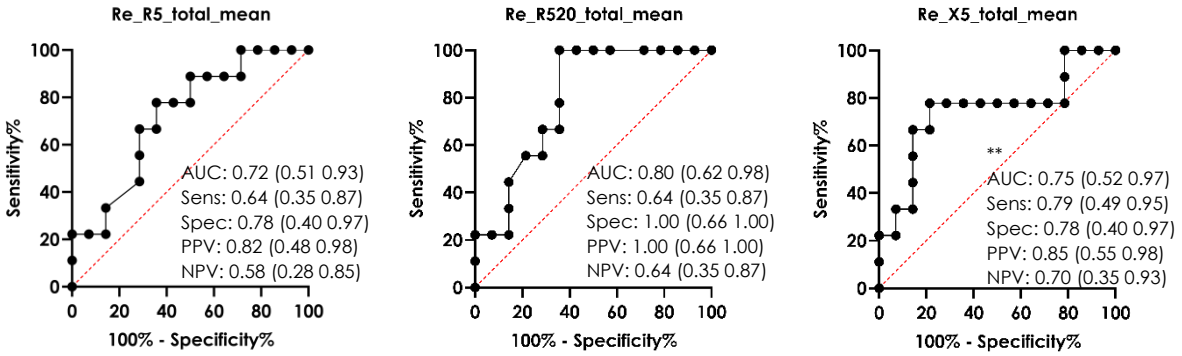


Figure 21 – Receiver Operating Characteristic (ROC)-curve of the FOT parameter during a maximal fast in- and expiration with the mandible in a retracted position. The ROC-curves are shown from the parameters which were significantly different between MAD successful and MAD non-successful group based on the first definition of MAD success. R520 = difference in resistance between 5 and 20 Hz (5Hz – 20Hz), AUC = area under the curve, Spec = specificity, Sens = sensitivity, PPV = positive predictive value, NPV = negative predictive value with the 95% confidence interval.

For the second definition of MAD success, thirteen parameters differ significantly between the successful and non-successful group. Six parameters were based on the resistance, five on the reactance, two on the resonance frequency and ten on the linear approximation of the correlation between the specific parameter and the inspiratory volume. ROC-curves are made of these parameters and are shown in Figure 22. The exact values of this analysis are present in Table A.17 in chapter 8 (Appendices 'Subchapter D – Additional results').



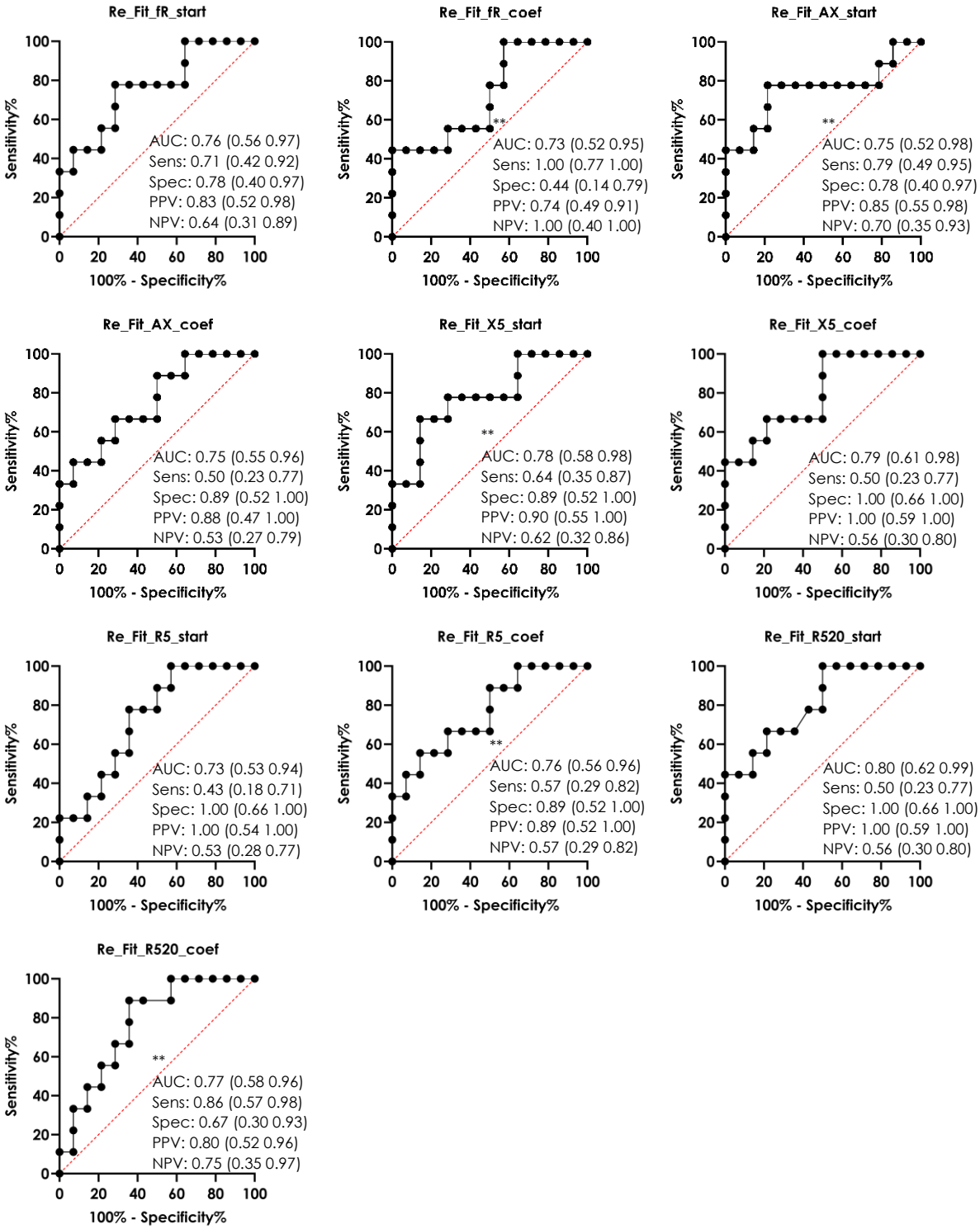


Figure 22 – Receiver Operating Characteristic (ROC)-curves of the FOT parameters during a maximal fast in- and expiration with the mandible in a retracted position. The ROC-curves are shown from the parameters which were significantly different between MAD successful and MAD non-successful group based on the second definition of MAD success. R5 = resistance at 5 Hz, R520 = difference in resistance between 5 and 20 Hz (5Hz – 20Hz), X5 = reactance at 5 Hz, AX = area under the reactance curve, fR = resonance frequency, Fit = the linear approximation of the relationship between the parameter and the volume during breathing, start gives the y-intercept of this linear approximation and coef the coefficient, AUC = area under the curve, Spec = specificity, Sens = sensitivity, PPV = positive predictive value, NPV = negative predictive value with the 95% confidence interval. ** These parameters predict MAD failure instead of success.

Difference in protruded and retracted position of the mandible

For the differences (absolute and relative) in secondary parameters, there were no significant differences between the MAD successful and no successful group based on the first definition of MAD success. For the second definition of MAD success, there were two parameters significant different between the successful and non-successful group. Both parameters are related to the linear approximation of the correlation between the specific parameter and the inspiratory volume. ROC-curves of these two parameters are shown in Figure 23 and the exact value can be found in Table A.18 in chapter 8 (Appendices 'Subchapter D – Additional results').

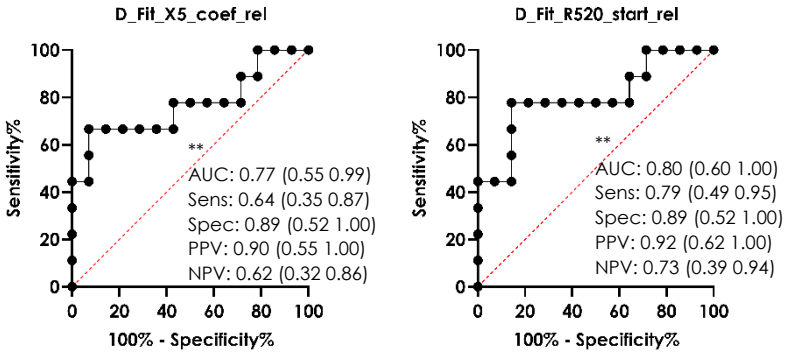


Figure 23 – Receiver Operating Characteristic (ROC)-curves of the FOT parameters during a maximal fast in- and expiration for the differences between the mandible in protruded and retracted position. The ROC-curves are shown from the parameters which were significantly different between MAD successful and MAD non-successful group based on the second definition of MAD success. R520 = difference in resistance between 5 and 20 Hz (5Hz – 20Hz), X5 = reactance at 5 Hz, Fit = the linear approximation of the relationship between the parameter and the volume during breathing, start gives the y-intercept of this linear approximation and coef the coefficient, AUC = area under the curve, Spec = specificity, Sens = sensitivity, PPV = positive predictive value, NPV = negative predictive value with the 95% confidence interval. ** These parameters predict MAD failure instead of success.

Subchapter 4E – Negative Expiratory Pressure

For the analysis of the NEP parameters, the relative and absolute difference between protruded and retracted position were investigated for the prediction of MAD success. The results of the relative differences between protruded and retracted are shown in Table 7. The results of the absolute differences are present in Table A.19 in chapter 8 (Appendices 'Subchapter D – Additional results'). There were no significant differences between the MAD successful and non-successful group except for the difference in mean and maximum delay. For both the absolute and relative differences, the difference in mean and maximum delay was significantly different between the MAD successful and MAD non-successful group based on the first definition of MAD success. Based on the second definition of MAD success, only the absolute difference in maximum delay was significantly different between the successful and non-successful group.

Table 7 – Relative differences in NEP parameters for the MAD successful and MAD non-successful group, based on the first definition of MAD success

	All included patients (n=25)	Successful MAD therapy (n=14)	Non-successful MAD therapy (n=9)	P-value
Δ Flow drop				
Median	-3.34 (-23.78 - 3.35)	-4.25 (-33.29 - 5.51)	-0.65 (-163.76 - 2.73)	0.85
Max	0.05 (-2.52 - 3.43)	-0.49 (-14.20 - 4.77)	0.24 (-0.87 - 2.87)	0.66
Δ Percentage below				
Median	25.00 (0.00 - 90.00)	0.00 (-34.38 - 97.21)	33.33 (12.50 - 72.52)	0.66
Max	18.86 (-300.00 - 78.57)	-40.78 (-339.58 - 43.33)	47.24 (-316.31 - 88.63)	0.19
Δ $V_{0.2}/V_{0.2}$				
Median	11.75 (-25.26 - 29.57)	13.04 (-28.19 - 29.61)	1.93 (-35.15 – 27.46)	0.90
Max	8.30 (-9.45 - 23.41)	12.07 (-9.49 - 35.24)	3.74 (-28.11 - 19.48)	0.38
Δ $V_{0.2}/V_1$				
Median	23.81 (-14.20 - 36.40)	25.27 (-17.16 - 50.83)	23.16 (-6.83 - 31.49)	0.75
Max	14.71 (-61.37 - 38.88)	-37.07 (-93.39 - 39.27)	22.60 (-4.52 - 38.89)	0.28
Δ $V_{0.5}/V_{0.5}$				
Median	-2.32 (33.23)	2.35 (31.14)	-9.58 (36.92)	0.43
Max	14.50 (-9.01 - 23.38)	0.92 (-26.48 - 33.19)	17.27 (1.09 - 20.36)	0.80
Δ $V_{0.5}/V_1$				
Median	17.77 (-16.35 - 35.48)	8.05 (-34.34 - 49.62)	20.71 (-3.82 – 31.78)	0.61
Max	1.76 (-84.32 - 39.86)	-3.88 (--125.93 - 42.63)	25.77 (-14.21 - 37.68)	0.61

Values are given in numbers (%), medians (interquartile ranges), or mean (standard deviations).

It was also investigated whether there were significant differences in the secondary parameters for the MAD successful and non-successful group based on both definitions of MAD success. Besides the medium and maximum delay in retracted position, there were no significant differences between the MAD successful and non-successful group based on the first definition of MAD success. The exact values of this analysis can be found in Table A.20 in chapter 8 (Appendices 'Subchapter D – Additional results'). Based on the second definition of MAD success, two parameters were significant different between the successful and non-successful group, the max of the $V_{0.2}/V_1$ and the max of the $V_{0.5}/V_1$ with the mandible in retracted position for the successful MAD group (0.69 (0.28 8.74) and 1.63 (0.79 18.20) respectively) were significantly higher compared to the non-successful MAD (0.25 (0.19 0.43) and 0.76 (0.52 1.21) respectively). For these parameters, ROC-curves were made, which are shown in Figure 24. An overview of the results of this analysis can be found in Table A.21 in chapter 8 (Appendices 'Subchapter D – Additional results').

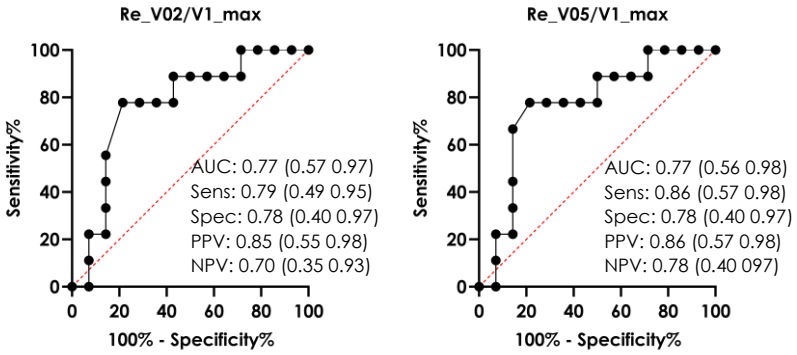


Figure 24 – Receiver Operating Characteristic (ROC)-curves of the NEP parameters. The ROC-curves are shown from the parameters which were significantly different between MAD successful and MAD non-successful group based on the second definition of MAD success. V02/V1 = relationship between the volume after NEP for the first 0.2 seconds and the mean volume of the previous three expiration during the first second of expiration, V05/V1 = relationship between the volume after NEP for the first 0.5 seconds and the mean volume of the previous three expiration during the first second of expiration,, AUC = area under the curve, Spec = specificity, Sens = sensitivity, PPV = positive predictive value, NPV = negative predictive value with the 95% confidence interval. ** These parameters predict MAD failure instead of success.

Subchapter 4F – Experiences

The patients' experiences were obtained through a questionnaire. The results of the analysis for the first definition of MAD success are shown in Table 8. There were no significant differences in scores between the MAD successful and non-successful group based on both definitions of MAD success. Four patients noted in the comments field some negative points of the adjustable mouthpiece (e.g. the material was too solid, painful, or the lips were stuck at the inlet or the screw). The results for the second definition of MAD success are presented in Table A.22 in chapter 8 (Appendices 'Subchapter D – Additional results').

Table 8 – Questionnaire outcomes and duration of the measurements of the successful MAD therapy group versus the non-successful MAD therapy group based on the first definition of MAD success

	All included patients (n=25)	Successful MAD therapy (n=14)	Non-successful MAD therapy (n=9)	P-value
Q1: Time NEP	8 (7-9)	8 (7-9)	7.8 (1.6)	0.62
Q2: Comfortable NEP	7.7 (1.4)	7.8 (1.4)	7.7 (1.4)	0.89
Q3: Time FOT	7.9 (1.5)	7.9 (1.7)	7.8 (1.4)	0.82
Q4: Comfortable FOT	8 (7-8)	7.8 (1.6)	7.8 (1.3)	0.85
Q5: Time Spirometry	7.5 (1.8)	7.5 (2.1)	7.7 (1.3)	0.78
Q6: Comfortable Spirometry	8 (6-9)	7.5 (5.3-9.0)	7.6 (1.7)	0.80
Q7: Comfortable adjustable mouthpiece	7.2 (1.5)	7.4 (1.6)	7.0 (6-8)	0.54
NEP duration (min)	10 (10-12)	10 (10-12.3)	9.7 (2.2)	0.27
FOT duration (min)	25 (20-25)	25 (20-25)	24.4 (3.6)	0.54
Spirometry duration (min)	15 (10-15)	14.5 (4.1)	13.7 (6.2)	0.73

Values are given in numbers (%), medians (interquartile ranges), or mean (standard deviations), the duration of the measurements is based on the total duration, including multiple repetitions and different mandible positions. The scores range from 0-10 and a high score on the questionnaire corresponds to very satisfied or comfortable.

Chapter 5 – Discussion

The primary objective of this study was: "*to predict the success of MAD therapy in OSAS patients by using resistance and flow parameters obtained by spirometry, FOT, and NEP both in protrusion and retraction of the mandible.*" Secondly, the experience of subjects per measurement and the time it took to perform the different measurements was investigated. In this chapter, the outcomes of this study will be discussed, they are linked to previous studies and recommendations for the future are given.
The results of this study showed that the parameters of the spirometry are not suitable as predictors for MAD success. Two parameters of the NEP could be used as predictors for MAD success and multiple parameters of the FOT could be suitable as predictors for MAD success. the first subchapter, the population of the study is discussed. In the second subchapter, the different measurements and the patients' experiences are discussed and in the third subchapter, the future recommendations of this study are given.

Subchapter 5A – Population

In this study, 67% of the OSAS patients had a successful MAD therapy based on both of the used definitions for successful MAD therapy (definition 1: >50% reduction in AHI and AHI < 20, definition 2: AHI < 10). This is in accordance with the results described by Attali et al. and Marklund et al. Attali et al. described a reduction in the AHI of more than 50% in 67% of the patients wearing a MAD for three till six months[63]. Marklund et al. described in 72% an AHI of < 10 in patients wearing a MAD starting with an AHI of ≥10 without the MAD[64].
A strength of the current study is the limited exclusion criteria used, which makes it a realistic representation of the OSA population. Patients with other pulmonary disorders were not excluded from this study since it is also relevant for these patients to be able to predict the outcome of MAD therapy. Three of the patients in this study were familiar with an obstructive airway disease (chronic obstructive pulmonary disease or asthma). As the main outcome parameters were relative (the difference between protruded and retracted position of the mandible), it is assumed that pulmonary disorders would not have influenced the results.
A disadvantage of the current method to determine MAD success is the limited time between the initial and control polygraphy. All patients in this study had a maximum delay of 15 months between the initial polygraphy and the control polygraphy. For some patients, the titration of the MAD continues after the control polygraphy. Therefore, it is possible that the MAD becomes successful after the control polygraphy, which is not measured and taken into account in the current study. Another possible disadvantage is the patient inclusion. In the present study, only patients with an initial AHI ≥ 15 were included, since these patients will receive a control polygraphy based on usual care. This inclusion criterion leads to a study population which is not a representation of the total population having MAD therapy. Lee et al. investigated the effect of MAD therapy for OSA patients with different severity levels[65]. Patients with mild, moderate, and severe OSA had a respective success rate of MAD therapy of 43%, 82%, and 75%. So it is possible that patients with an AHI < 15 had a lower chance of success for MAD therapy.

Subchapter 5B – Measurement

In this study, three different measurements were performed in a supine position with the mandible both in protrusion and retracted position. This is the first study using lung function measurements with the mandible in a retracted and protruded position for the prediction of MAD success. One of the strengths of this study is the choice of measurements equipment. The adjustable mouthpiece is designed in such a way that it could be used for all patients, which results in low costs. The spirometry and FOT are regularly used lung function tests and all three measurements can be performed when the patient is awake. The measurements could be incorporated with ease in the current healthcare for the prediction of MAD therapy

success, which makes it simply clinically applicable. For this study, only a maximal protruded and retracted position was chosen for the sake of time for the patient. It was supposed that this would result in maximal differences in outcome. However, it could be debated whether a maximal retracted position corresponds to the situation during the night in these patients. A maximal retracted position forces the mandible in an unnatural position, which could have influenced the upper airway muscle tone and therefore the results. In the present study, twenty-three patients were included, whereas the target was twenty-five. This results in a wider confidence interval around the diagnostic accuracy parameters. It should be noted that it is a small study group and lots of parameters were tested for significant differences between the MAD successful and non-successful group. Some of the significant differences could, therefore, be a coincidence instead of a possible predictor of MAD success. Additionally, due to the small study group, some significantly different parameters could have been missed.

Section 5B.1 – Spirometry

This study showed no significant differences between the relative or absolute differences of the mandible in protruded and retracted position for the MAD successful and non-successful group. These results are in contradiction with the results of Zeng et al. who investigated the flow-volume curves of patients with successful and not successful MAD therapy[41]. They found a significantly higher MEF50:MIF50 and a lower MIF50 in patients with successful MAD therapy compared to those without a successful MAD therapy both in supine and sitting position. In the present study, there were no significant differences in the MEF50:MIF50 ratio and MIF50 between responders and non-responders. A possible explanation of this difference could be due to changes in the bronchomotor tone. A first effect that could have influenced the bronchomotor tone is breathing through the adjustable mouthpiece. The adjustable mouthpiece forces the mandible in an unnatural position, which could cause some tension or traction on the upper airway. This could influence the bronchomotor tone and therefore, the collapsibility of the upper airways. Another effect that influences the bronchomotor tone is the performance of maximal fast in- and expiration manoeuvres. Before the spirometry measurements were executed, the patients have performed multiple maximal fast in- and expiration manoeuvres during the FOT measurements. These manoeuvres result in a higher bronchomotor tone and therefore lower compliance. This leads to a less collapsible airway. This effect could be present during the FOT measurements, which makes the bronchomotor tone of the airways far from the situation during sleep. The increased bronchomotor tone prevents the airway from (partially) collapse, which results in less compliant and stiffer airways. This could be the reason that there were no significant differences in the present study in the MEF50:MIF50 and the MIF50 between the MAD successful and non-successful group. Another reason could be a possible air leakage during the measurements. During the maximal fast in- and expirations, the patients were breathing forcefully through the adjustable mouthpiece. This could have affected the connection of the adjustable mouthpiece to the used filter and leakage could occur. It was visually checked whether the adjustable mouthpiece was connected properly, however it could not be excluded that an air leak was absent. To prevent an air leak in the future, a ring is designed and 3D-printed which fits airtight on the filter and increases the interface between the filter and the adjustable mouthpiece. A 3D-image and picture of the ring are shown in chapter 8 (Appendices 'Subchapter E – 3D-image of the ring'). Another possible reason for the lack of significantly different parameters between the successful and non-successful MAD group could be the small study group. The relative difference in MIF50 was not significantly different between these groups based on the first definition of MAD success, however, there was a trend present. By including more patients, this trend could turn out to be a significant difference. A strength of the spirometry measurement is that it is a standard lung function test and reference values are available and clinically accepted. Therefore, the measurements with the mandible in protruded and retracted position could be examined in comparison with the "normal" measurements. This

gives more insight into the effect of the adjustable mouthpiece and supine position on the measurement parameters. On top of that, since spirometry is a standardised method, reproducibility criteria are present to assess the quality of the measurement. This makes it easier to determine the reproducibility of the measurements.
During the measurements, the patient had to perform a maximal fast in- and expiration manoeuvre at least three times (mandible in protruded and retracted position and without the adjustable mouthpiece). Some of the patients experienced a cough reflex during the measurements with the adjustable mouthpiece, especially with the mandible in a retracted position. This cough could persist during the measurement without the mandible. This was one of the reasons why it was impossible to accomplish reproducible measurements for all patients. In three patients, one of the measurements was not reproducible. On top of that, the patients had to perform the measurement with the maximal fast in- and expiration manoeuvre at least three times. In the worst case, this could result in performing this manoeuvre around fifteen to twenty times. This was exhausting for the patients. It is possible that for this reason the maximum is not achieved during the last measurement (without adjustable mouthpiece). On the other hand, the frequent repetition of the maximal fast in- and expiration measurement could have resulted in a learning curve of the patients. Therefore, the results of the last measurement could be better compared to the first measurements. The measurements were also performed in a specific order. The first measurement was in a supine position with the mandible in a retracted position, the second measurement was also in a supine position but with the mandible in protruded position and the last measurement was in sitting position without the adjustable mouthpiece. So based on the learning curve, the sitting and the measurement with the mandible in protruded position could be better performed compared to the measurement with the mandible in a retracted position. Based on the exhaustion hypothesis, this effect could be the other way around.

Section 5B.2 – Forced Oscillation Technique

This study did not found significant differences in the main outcome parameters between the MAD successful and the MAD non-successful group. In the secondary parameters of the FOT measurements, some significant differences between the MAD successful and non-successful group were found. During normal breathing, the resistance at 5 Hz and the difference in resistance between 5 and 20 Hz were higher with the mandible in a retracted position for the successful group compared to the non-successful group. This result may be partly explained by the fact that the worse the beginning state of the patient is, the better the effect could be. With a high resistance in the retracted position, some improvement might be good enough to obtain a successful therapy. The differences in R5 between the successful and non-successful group could also be an expression of the different OSA phenotypes. High resistance in the retracted position could be a manifestation of the anatomy phenotype, for instance, a small pharyngeal airway. A small pharyngeal airway leads to higher resistance (following Poiseuille's law) and also a higher P_{crit}. In this phenotype, when the narrowing is present at the level of the tongue base, the MAD should hypothetically be a successful treatment, since it improves the airway patency. In the non-successful group, it is possible that another OSA phenotype is dominant, which could be the reason that MAD therapy is not successful. This hypothesis is in accordance with the study of Bamagoos et al. who suggested that the main mechanism of MAD success is the decrease in P_{crit} which represents an improvement in passive pharyngeal anatomy[37, 66]. Following this hypothesis, it is expected that protrusion of the mandible reduces P_{crit} and resistance and therefore, the airway will collapse less easily. This effect is investigated by several studies. Lorino et al. investigated the effect of mandibular advancement on the respiratory resistance in healthy subjects both with passive and active mandibular advancement. Passive advancement was achieved by a wax bite and active by voluntary mandibular advancement. The resistance at 0 Hz and 16 Hz decreased significantly with passive advancement of the mandible whereas it did not change with voluntary advancement. Choi et al. also investigated the airway resistance in

OSA patients by using plethysmography[48]. They found a decrease in airway resistance by mandibular protrusion. With higher resistances in patients with OSA compared to control subjects. The results of the present study are in accordance with the results of Lorino et al. and Choi et al. The mean resistance in the protruded position is lower compared to the resistance in a retracted position.
The difference in resistance between 20 and 5 Hz was bigger in the successful group compared to the non-successful group. This corresponds with the higher resistances at 5 Hz, which results in bigger differences. However, it was expected that the difference would be around zero. When a central obstruction would be present, not only the 5 Hz resistance would be increased but the resistance at 20 Hz would also be increased, resulting in a difference between these two around zero. A higher difference indicates a peripheral obstruction. Since there are no indications for a peripheral obstruction and the differences are around 1 kPa/s*L, this finding could be a coincidence and not be a sign of peripheral obstruction.
During the maximal slow in- and expiration, some other parameters were significantly different between the two groups. The y-intercept of the linear approximation of the correlation between R5 and R20 and the inspiratory volume was significantly different between the groups, with higher values for both y-interceptions (R5 and R20) in the successful group compared to the non-successful group. So at the lowest inspiratory volume, the R5 and R20 were significantly higher in the successful group compared to the non-successful group. This could also be an effect of the differences in OSA phenotype, as explained above. With the anatomy playing a possibly more important role in the successful group, whereas other mechanisms could have more influence in the non-successful group.
For the maximal fast in- and expirations, there were multiple parameters significantly different between the MAD successful and non-successful group. An interesting finding is the significant difference of almost all linear approximation lines of the specific parameter against the inspiratory volume between the MAD successful and non-successful group. The y-interceptions for the linear approximation of the resonance frequency is significantly higher in the successful group whereas the y-intercept for the reactance at 5 Hz and the area under the reactance curve are lower in the successful group. This is in accordance with each other. A higher y-intercept of the resonance frequency at a low inspiratory volume indicates a right shift of the reactance curve. This is a sign of a decrease in elasticity (or increase of the compliance) of the airways, which is a physiologically finding. At a low inspiratory volume, there is almost no traction on the pharyngeal airways, which make them more compliant. So, in the successful group, the lungs are more compliant at a low inspiratory volume compared to the non-successful group. High compliance indicates a more collapsible airway and this result corresponds to the earlier described higher resistances found in the successful MAD therapy group.
The coefficients of the linear approximation lines of the resonance frequency, area under the reactance curve and the x5 were also significantly different between the MAD successful and non-successful group. The coefficients were positive for the area under the reactance curve and the X5 and negative for the resonance frequency. This corresponds to a left shift of the reactance curve, so less compliant airways by increasing inspiratory volumes. This left shift is more present in the successful MAD group compared to the non-successful group. Apparently, in the successful MAD group, an increase in inspiratory volume causes more traction on the pharyngeal airways which results in less collapsible airways (lower compliance) compared to the non-successful group. An explanation for this difference could not be found.
The y-interceptions of R5 and R5-20 were also higher in the successful group versus the non-successful group, whereas the coefficient of R5 and R5-20 were more negative in the successful group compared to the non-successful group (in protruded and retracted position of the mandible). This indicates higher R5 at low inspiratory volume in the successful MAD group, which could be explained by the differences in OSA phenotypes as described above.

The coefficients of R5 and R5-20 were more negative in the successful group compared to the non-successful group. So in the successful group, the resistance decreases faster as a function of the inspiratory volume compared to the non-successful group. An explanation for this could be the differences in the beginning values. In the successful MAD group, the R5 is higher compared to the non-successful group. This indicates a smaller cross-sectional area at lower inspiratory volume compared to the non-successful group. When the airway is completely open, the resistance is lower (and the cross-sectional area is maximal). It could be that the difference in cross-sectional area is bigger in the successful group (due to the initial condition) compared to the non-successful group, which results in a higher coefficient.
All the significantly different FOT parameters between the MAD successful and non-successful groups had an AUC of approximately 0.7-0.8. This indicates a fair ability to discriminate between MAD success or no success. By itself, none of these parameters are good enough to predict with certainty whether MAD therapy will be successful. However, by adding these parameters in a multivariate model, the diagnostic accuracy could be good enough to predict MAD success.
It stands out that the highest number of significantly different parameters was found between the MAD successful and non-successful group for the measurement with maximal fast in- and expiration and the least for normal breathing. This could be due to the high flow that is present during the maximal fast in- and expiration measurements, which results in more negative pressures in the airways. Differences in airway collapsibility will result in differences in cross-sectional area and therefore, in the resistance differences. Contributing to this is the effect of maximal in- and expiration. At the lowest or highest inspiratory volumes differences in traction on the pharyngeal airways and compliance of the airways become more pronounced. This strengthens the differences between the MAD successful and non-successful group.
For the FOT analysis, some additional parameters were taken into consideration. For example, the standard deviation, coefficient of variation and coherence could also be calculated. However, these parameters mainly say something about the reliability and the dispersion of the signals. Since the main objective of this study was to investigate predictive parameters for MAD success, these parameters were not included in the analysis.
During the FOT measurements, three different manoeuvres were performed. When the results of the three different manoeuvres are compared, it stands out that the reactance at 5 Hz decreases with the intensity of the manoeuvre, and the resonance frequency increases. This corresponds to a left-shift of the reactance curve. A possible explanation for this could be differences that are present in the inertance during an increased flow. Oostveen et al. described a decreased inertance by an increased flow[67]. During the maximal fast in- and expirations, the flow is considerably larger compared to normal breathing which could result in a lower inertance. However, the reactance is a sum of the inertance and the capacitance. It is expected that the capacitance will be decreased during fast maximal in- and expiration, due to a higher bronchomotor tone. This leads to a less collapsible airway and a right-shift of the capacitance curve. On top of that, during maximal in- and expiration the patients tried to reach residual volume and breathed in till total lung capacity. At the minimum and maximum volumes, as shown in Figure 25, the compliance of the airways is low, which corresponds to stiffer airways. This also results in a right-shift of the reactance curve, which causes lower X5 values and higher resonance frequencies. However, a left-shift of the reactance curve is present when comparing the normal breathing manoeuvre and the maximal in- and expiration manoeuvre. Probably the influence of increased flow on the inertance is larger than the influence of bronchomotor tone and inspiratory volume on the reactance curve, which results in a left-shift of the reactance curve.

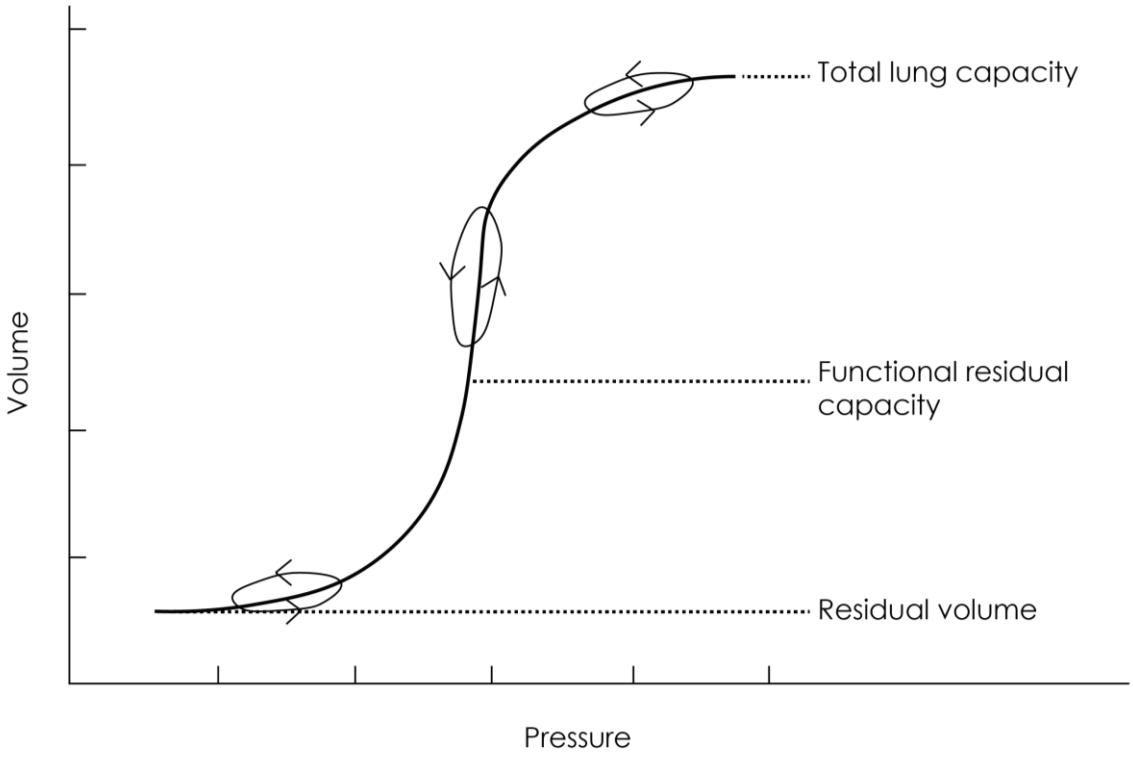


Figure 25 – Volume-pressure curve of the lungs, with the slope representing the compliance, adapted from[68].

A strength of the FOT measurement is the relative ease to perform the measurement. The patient only had to breathe through the mouthpiece to obtain the data. On top of that, in one single measurement of thirty seconds, lots of data is obtained. Around 450 different impedance spectra were obtained per measurement, and from every impedance spectra, the resistance and reactance could be determined. By taking the mean of all these signals, the FOT can be considered as a reliable measurement.
During a maximal fast in- and expiration, most of the curves were excluded since one of the reliability criteria was not met. In the worst case, only ten pulses were accepted and analysed. This was mostly due to the criteria of the maximum coefficient of the resistance and the minimum coefficient of the reactance. It is doubtable whether it was permitted to remove the curves. The choice to add the resistance and reactance coefficient criteria was based on visual inspection of the data. Improbable bumps were believed to be a consequence of measurement errors and therefore it was chosen to remove them. However, it is possible that the improbable bumps were an actual representation of what happened in the airways. To evaluate this, a sensitivity analysis of the FOT data was also performed without the coefficient of the resistance and reactance criteria. The results of this analysis revealed one significant parameter for the first definition of MAD success between the successful and non-successful groups (The Re_Fit_fR_coef), which was not found in the previous analysis. For the second definition, three parameters differed significantly, whereof two were not found in the previous analysis (Re_fres_total_mean and Pr_impulses_accepted). Since most of the significantly different parameters disappeared by removing the reliability criteria of the coefficient of the resistance and reactance, we believe no crucial information is lost by adding these criteria to the analysis.

Section 5B.3 – Negative Expiratory Pressure

The present study did not show a significant difference in any of the absolute and relative differences in NEP parameters between the MAD successful and not successful group. A possible explanation for this could be that it was the first measurement for the patients. Some

of the patients were nervous for the measurements and most of the patients were focussed on their breathing during the NEP measurement. This nervousness and focus on breathing could influence the muscle tension of the upper airway, making it less collapsible and therefore influencing the measurements. Another explanation could be the used pressure. In this study a negative pressure of -5 cmH_2O was applied, which might not be enough to make differences in outcome visible between the two groups. A last possible explanation could be due to the pressure setting. The pressure was set by turning a screw and a visual check for the right pressure. So an exact pressure of -5 cmH_2O could not be established. This inaccuracy could have led to changes between the patients. Since the amount of pressure affects some of the NEP parameters, a possible difference between the MAD successful and the not successful group could have been missed.
There was a significant difference in the maximum and mean delay of the application of NEP for the MAD successful and not successful group for the mandible in a retracted position. The difference in mean delay for the mandible in protruded and a retracted position was also significantly different for the MAD successful and not successful group. The latter is probably due to the first significant difference. However, there is not an explanation found for the differences in mean and maximum delay for the mandible in retracted position between the MAD successful and not successful group. We have tried to correct for these differences in delays by taking the delays also into account for the determination of the mean of the expiration before the NEP. So by taking the ratio between the NEP and the expiration before the NEP, the effect of the delay should have filtered out when there is a linear correlation between the expiration before the NEP and the expiration in which the NEP was applied. When the expiration of the NEP is different compared to the previous expirations, the delay influenced the results of the study. The measuring method must be optimized to prevent these differences in the future so a reliable analysis method can be performed.
The max of the $V_{0.2}/V_1$ and the max of the $V_{0.5}/V_1$ with the mandible in retracted position were significantly higher in the successful MAD group compared to the non-successful MAD group. Higher values indicate a less collapsible airway, due to a higher flow after NEP application. This is a surprising result, since it is expected that patients in whom MAD therapy is successful have a more collapsible airway in the retracted position of the mandible. A possible explanation for this could be the unnatural retracted position of the mandible, this could have influenced the bronchomotor tone of the upper airway muscles and therefore the results of this measurement. The AUC of these two significantly different parameters was 0.77, which indicates a fair ability to discriminate between the successful and non-successful MAD groups. This is not good enough to predict with certainty the outcome of MAD therapy. It should be investigated whether the NEP measurements could be improved to obtain more parameters, or to improve the diagnostic accuracy of the parameters that are found in the present study.
A strength of the NEP measurements is the relative ease with which the measurement can be performed. The patient only had to breathe through the mouthpiece and the instructor applied the NEP at the specified moments. There is no need for maximal fast in- and expirations and the measurement is therefore easy to perform. Patients are also not getting exhausted by the performance of this measurement and when no unnatural position of the mandible is used, the (upper) airway muscle tone remains unchanged.
A disadvantage of the NEP measurement was the way some parameters were defined. Some of the parameters were compared to the three breaths before the breath in which the NEP was applied. Visually it was checked whether the breaths were “normal” and after three “normal” breaths the NEP was applied. These checks included especially signs of coughing or clearing the throat. When these signs were not present, a NEP was applied. However, it was

possible that one of the breaths before NEP had a remarkably larger volume compared to the other two, which influenced the mean of the three breaths. Therefore, the parameters in which the mean of the three breaths are taken into account are also changed. A possible solution for this could be to determine the percentual difference or the coefficient of variation between the inspirations before the NEP as well as the percentual difference or coefficient of variation between the expiration before the NEP. The percental difference or the coefficient of variation should be within 10% for example, otherwise, the measurement results of the NEP manoeuvre has to be removed.

Section 5B.4 – Questionnaire

The results of the questionnaire did not show any differences in patients' experience between the MAD successful and non-successful group based on both definitions of MAD success. The duration of the measurements did also not differ between these two groups. Altogether, the patients noted the lowest scores for the comfort of the adjustable mouthpiece and the highest scores for the time of the NEP and the comfort of the FOT and spirometry. Four patients noted some negative points of the adjustable mouthpiece, which is probably reflected in the lower score on the questionnaire. The NEP had the shortest duration, which could be the reason for the high score on the questionnaire. The FOT duration was more than twice as long, this is also reflected in the questionnaire with a lower score. It is doubtable whether the questionnaire was a suitable way to measure the user experiences since some patients indicated that they did not have an opinion about it and filled in the same score for every question. However, it is expected that it would have been reflected in the scores when a measurement was experienced considerably different. Since this is not the case in the present study, it could be concluded that there were no big differences in patients' experience between the different measurements.

Subchapter 5D – Future recommendations

The most promising test for the prediction of MAD success seems to be the FOT. The best combination of sensitivity and specificity found was around 0.86 and 0.78 respectively. With an AUC of 0.81, this indicates a good ability to discriminate between successful and non-successful MAD therapy. It is advised to further develop the FOT method to investigate whether it is a suitable clinically accepted method to predict MAD success. The first step is to include more patients to be able to develop a multivariate model of different FOT parameters. This multivariate model could be used to increase the AUC, sensitivity, specificity, PPV, and NPV. With higher diagnostic accuracy parameters, the multivariate model should be able to determine with certainty whether MAD therapy would be successful or not for a specific patient. It should also be investigated whether it is possible to build a more powerful FOT. With a more powerful FOT, the power of the impulses is larger and therefore, an impulse could be separated more easily and more reliable from the underlying respiration. This results in more pulses that can be included in the analysis and therefore, a more reliable analysis. Besides a more powerful FOT, it should be investigated whether it is possible to optimise the used script for the FOT analysis. The script corrects for the improbable bumps present in the resistance and reactance spectra, however, it is unclear what causes these bumps. An example of an impedance spectra including some graphs with these bumps is shown in Figure 26.

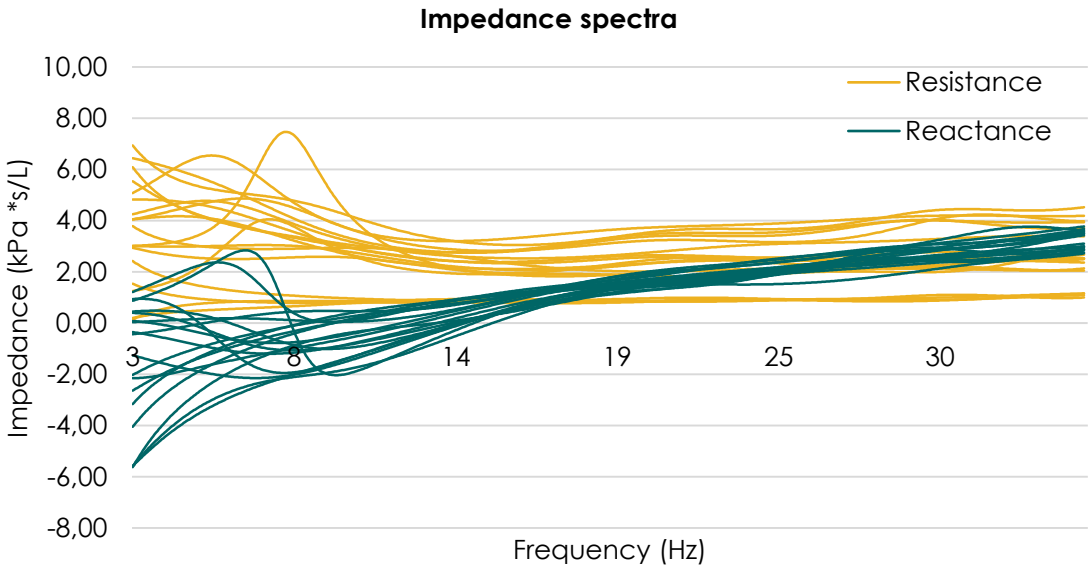


Figure 26 – Example of an impedance spectra including some graphs with the improbable bumps.

A possible explanation for these bumps could be a temporary (partial) closure of the adjustable mouthpiece by the tongue. When such a possible explanation is figured out, it should be studied what the effect on the resistance and reactance curve is. And the script should correct for these specific effects instead of just removing curves with a too low or high coefficient. This reduces the change of removing important data and improves the reliability of the signals. A disadvantage of the current FOT method is the lack of understanding of what exactly happens in the pharyngeal airways when the mandible stands in protruded and retracted position and during a maximal inspiration and expiration. A method to visualise what is happening during these tests is to use an intraoral 3D scanner. With such a scanner it might be possible to get an overview of the upper airways. Based on that image, the cross-sectional area could be determined in the different positions of the mandible and different inspiratory volumes. This gives more understanding of the physiological mechanisms underlying the results of the FOT analysis. Another disadvantage that appears during the FOT measurements is the effect of maximal fast in- and expirations on the bronchomotor tone of the upper airway muscles. This effect makes the situation far from the situation during sleep. To investigate the effect of high flows on a relaxed upper airway, the NEP could be incorporated in the FOT. By applying a more negative pressure than used in the current study, there is a larger increase in flow and the effect on the FOT parameters could be determined. By this, a more comparable situation to sleep state can be made. A new device should be made to apply a negative pressure during FOT. Dellaca et al. showed that it is possible to build such a device and to apply NEP during a FOT measurement[69].
Something that must be investigated is the effect of the retracted position of the mandible on the outcomes of the different measurements. The retracted position of the mandible was chosen to have a large difference in parameters (between protruded and retracted). However, the forced retracted position of the mandible could have influenced the upper airway muscle tone, since it is an unnatural position. It is necessary to investigate whether there are more (or other) significantly differences between the MAD successful and non-successful group when a neutral position of the mandible is used instead of a retracted position.
For the spirometry, it stands out that there were no significant differences found in the present study between the MAD successful and non-successful group. This could have been due to the changes in the bronchomotor tone of the upper airway muscles by the maximal fast in- and expiration manoeuvres performed before the spirometry. To investigate whether there

are significant differences between the MAD successful and non-successful group, this effect should be as small as possible. This could be done by training patients in performing a maximal fast in- and expiration manoeuvre on another moment than the real measurements are performed. By this, the patients only have to perform the manoeuvre three or four times, instead of a maximum eight times. Besides, the spirometry should be performed without performing any other maximal fast in- and expiration manoeuvre before this measurement. These two activities should reduce the effect of maximal fast in- and expiration on the bronchomotor tone of the upper airway muscles.
During the NEP application, most of the parameters did not change significantly between the MAD successful and non-successful group. This could be due to the significant differences in delay between these two groups. The NEP should be applied instantly after the beginning of the expiration. To achieve this, the script for the Arduino should be optimised. Besides, patients were a bit anxious for the measurements, this could have influenced there breathing. To reduce this effect, it is necessary to let the patients settle down. This can be done by giving the patient more time to get used with the devices and the breathing through the adjustable mouthpiece. Also, the NEP should be applied multiple times before the real measurement is performed. By this, the patient is more used to the measurement is probably less anxious and conscious of its breathing.
Four patients indicated negative points of the adjustable mouthpiece. The material was solid which makes it uncomfortable in the mouth. To improve this, it could be investigated whether it is possible to 3D print the inlets for the teeth with a softer material. A screw was used to fixate the slider and some patients indicated that their lips were suffered by this. The design of the adjustable mouthpiece should be optimised to avoid this. A simple solution for this is by placing the screw further away from the mouth opening, so the lips will not touch the screw.

Chapter 6 – Conclusion

The primary objective of this study was: "*to predict the success of MAD therapy in OSAS patients by using resistance and flow parameters obtained by spirometry, FOT, and NEP both in protrusion and retraction of the mandible.*" Secondly, the experience of subjects per measurement and the time it took to perform the different measurements was investigated. This study showed that the parameters of the spirometry are not suitable as predictors for MAD success. Two parameters of the NEP differed significantly between the MAD successful and non-successful group and could possibly in the future be used to predict MAD success. Multiple parameters of the FOT differed significantly between the two groups and could have potential to be used as predictors for MAD success. Further research should in the first place focus on the FOT as a possible screening method for MAD success. More patients must be included to be able to build a multivariate model for the prediction of MAD success and the physiological background of the changes in FOT parameters should be investigated for example by use of an intraoral 3D scanner.

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Chapter 8 – Appendices

In this chapter, all supplementary material of this study can be found. In the first subchapter, the measurement protocol of this study can be found. The second subchapter contains the VAS-questionnaire to investigate the user's experience with the different measurements and the adjustable mouthpiece. The third subchapter shows the 3D-images of the adjustable mouthpiece made in SolidWorks 2016. In subchapter D the additional results of the measurements are described. In section 1 of this subchapter the baseline characteristics for the second definition of MAD success are presented, in section 2 the additional results of the spirometry are discussed, in section 3 the results of the different FOT analysis, in section 4 the results of the NEP analysis, and in section 5 the results for the questionnaire. Subchapter E contains the 3D-images of the ring that was designed and printed to prevent air leakage during the spirometry measurements.

Subchapter A – Measurement Protocol

Benodigdheden

- Meetlint
- Antibacterieel filter
- Onderzoeksbank
- Kalibratiespuit
- weegschaal

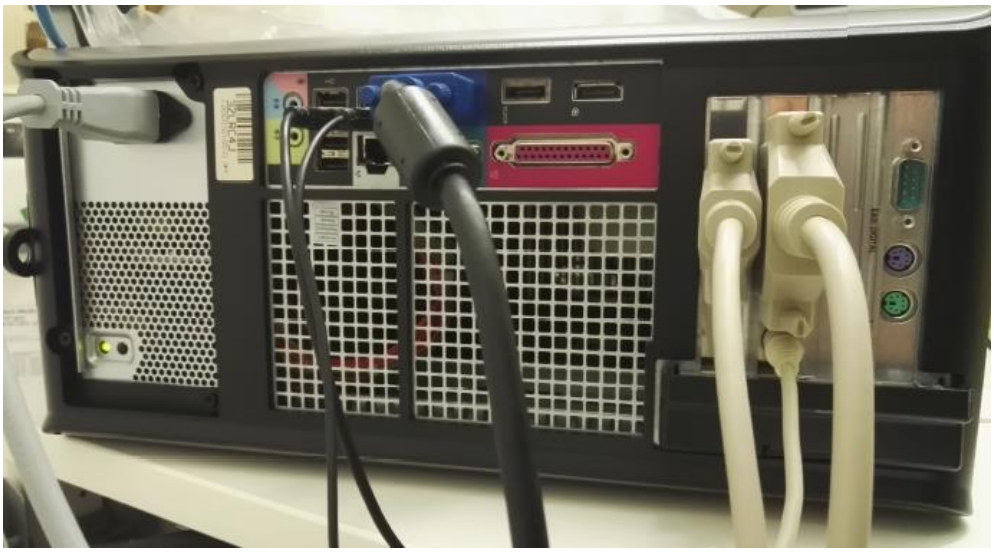
Voorafgaand aan meting

FOT

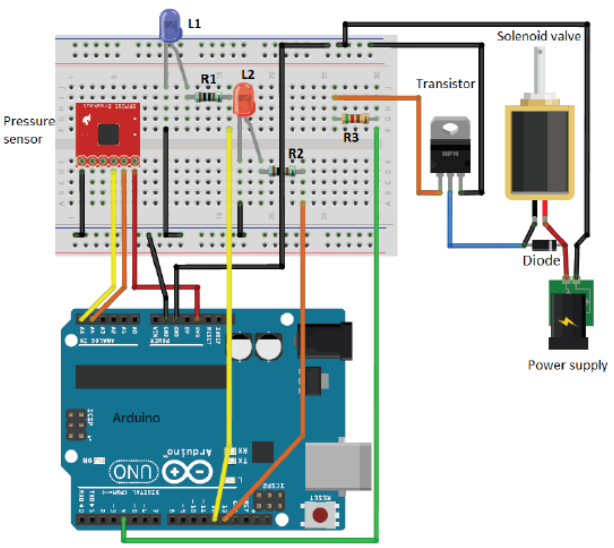
1. FOT aansluiten op laptop
2. Laptop en FOT opstarten
3. Start JLab op (systeem opwarmen = 5 minuten)
4. Zet bij Options - Settings de 'Bacterial filter in use' uit.
5. Start Ambient Conditions op en vul hier de waarden in die gemeten zijn via een computer met een Ambient Unit (Via LabManager en Ambient Conditions). Klik op Exit.
6. Zet het klepje aan de achterkant van de FOT open.
7. Doe een volume kalibratie met de kalibratiespuit. Klik op F1 om de kalibratie te starten (daarna pas de spuit erop). Klik op F12 om op te slaan en de kalibratie af te sluiten.
8. Doe het klepje aan de achterkant van de FOT weer dicht.

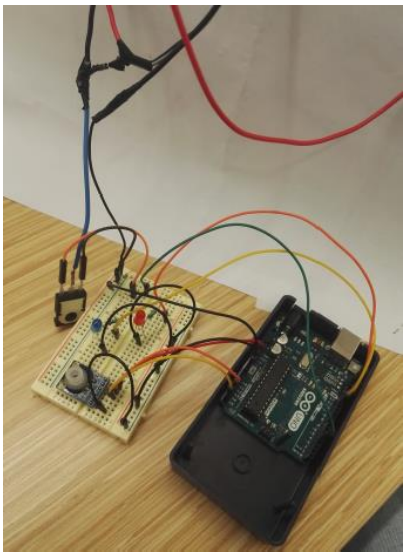
NEP

1. Zorg ervoor dat de apparatuur aangesloten is op de oude computer (alles behalve de internetkabel en de kabel rechtsonder moet overgezet worden), hiervoor eerst de spanning eraf halen.

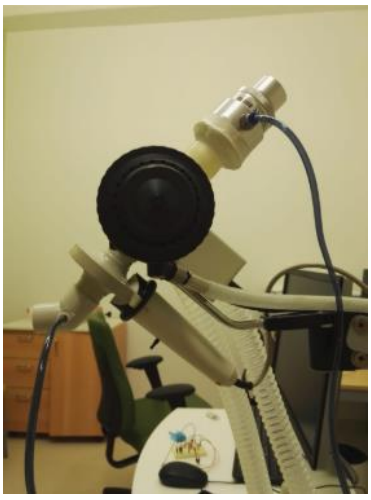


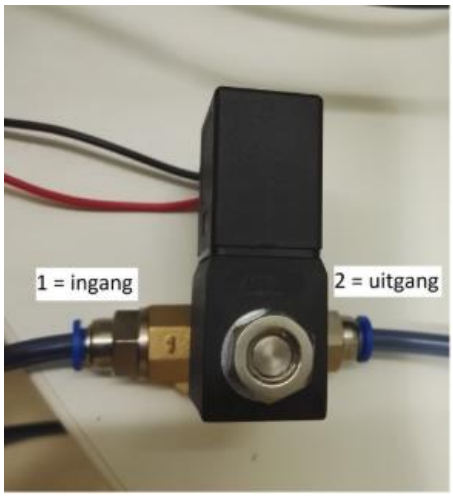
2. Start de computer op (Login: LF 7)
3. Start “Start JLab” op, hij warmt op en dat duurt ongeveer een kwartier
4. Zet de arduino klaar en zorg dat de bedrading aangesloten is zoals in deze foto’s





5. Plaats de luchtversterker op de pneumotach en verbindt hem met de solenoid klep (2=uitgang). Zorg dat de luchtversterker rechtop staat, zoals in onderstaande figuur, laat de aansluiting naar de perslucht nog leeg.





6. Plaats de opzetstukken op de pneumotach voor de liggende opstelling.
7. Sluit de gasfles aan op de solenoid klep.
8. JLab: Start Ambient Conditions op, wacht tot de nieuwe waarden gevonden zijn en klik op exit (F12).
9. Ga naar kalibratiehulpmiddelen, volume kalibratie met kalibratiespuit (niet automatisch) Klik op F12. Houdt tijdens de kalibratie de druksensor uitgang dicht.
10. Sluit de druksensoruitgang aan op de druksensor.
11. Stop de NEP USB stick in de computer, ga naar Arduino-1.8.7 en open arduino.exe.
12. Ga in het Arduino programma naar Tools, Port en selecteer de COM poort waar Arduino achter staat.
13. Klik in het Arduino programma op het pijltje naar boven en open NEP.
14. Klik in het Arduino programma op het pijltje naar rechts, hiermee wordt de NEP sketch geupload.
15. Open het Serial Monitor programma door in het Arduino programma op Tools – Serial Monitor te klikken.
16. Klik op Shortcut to Jscope32
17. Open Test_Douwe
18. Open Channel - Settings en zet bij default settings de sample rate op 5 ms dus 200 Hz.
19. JScope: klik op F1, je ziet nu de meetdata lopen.
20. Draai de kleine draaiknop op de drukfles dicht (meer schroefdraad zichtbaar/geen weerstand voelen). Grote draaiknop opendraaien, het wijzertje van de rechter drukmeter geeft dan de druk aan. Controleer of er voldoende druk in de fles zit (minimaal 30 bar) Draai de kleine draaidop open, zodat je minder schroefdraad ziet, zet de druk (linker wijzertje) op 4-5 bar.
21. Arduino commando scherm: Open de klep even (o), kijk wat voor druk er is. Sluit met je hand het mondstuk af en lees het drukverschil af. Stel de perslucht zo bij dat het juiste drukverschil (=500 Pa) bereikt wordt. Sluit de klep (c).
22. Sluit de meting af

<u>Spirometrie</u>

1. Wordt omgebouwd na de NEP meting.

Ontvangst proefpersoon

1. Uitleg onderzoek + 'Zijn er nog vragen over het onderzoek' + ondertekenen informed consent
2. Vragen/meten van de onderwerpen op het case report form.
3. Uitleg onderdelen van de metingen

Start meting

<u>Bepalen stand aanpasbare mondstuk</u>

1. Bepaal de maximale comfortabele positie in de kaak naar achteren, schrijf stand op, laat de patiënt nogmaals proberen of dit goed zit.
2. Bepaalde maximale comfortabele positie in de kaak naar voren, schrijf stand op, laat de patiënt nogmaals proberen of dit goed zit.
3. Zet een van de aanpasbare mondstukken in de maximaal naar achteren stand en een ander mondstuk in de maximaal naar voren stand.

<u>NEP</u>

1. Zet het aanpasbare mondstuk in maximaal naar achteren stand op de NEP opstelling.
2. Open JScope.
3. Laat de patiënt even ervaren wat het is door in de Serial monitor van de Aruino even (t) te doen tijdens uitademing, klep gaat dan 1 seconde open.
4. Zet het programma van de Arduino in Serial monitor
5. Neusklem op en mondstuk in en geef instructies
6. JScope: Start de meting door op F2 te drukken.
7. Open Serial monitor: Laat de patiënt rustig in en uitademen. Na 30 seconden geademd te hebben, klik je tijdens een inademing (rode lampje brand) op g en druk je op enter (blauwe lampje gaat branden). De NEP gaat dan aan bij de volgende uitademing.
8. Herhaal bovenstaande tot je 5 goede metingen hebt.
9. Laat de patiënt het mondstuk uit de mond nemen en laat ten minste nog 15 seconden meten om de offset eruit te halen.
10. Stop de meting met F3 op in JScope
11. Sla de meting op met F5 onder PxxReNEPx.
12. Zet het aanpasbare mondstuk in maximaal naar voren stand op de NEP opstelling.
13. Neusklem op en mondstuk in en geef instructies
14. JScope: Start de meting door op F2 te drukken.
15. Open Serial monitor: Laat de patiënt rustig in en uitademen. Na 30 seconden geademd te hebben, klik je tijdens een inademing (rode lampje brand) op g en druk je op enter (blauwe lampje gaat branden). De NEP gaat dan aan bij de volgende uitademing.
16. Herhaal bovenstaande tot je 5 goede metingen.
17. Laat de patiënt het mondstuk uit de mond nemen en laat ten minste nog 15 seconden meten om de offset eruit te halen.
18. Stop de meting met F3 op in JScope
19. Sla de meting op met F5 onder PxxProNEPx.

<u>Ombouw van NEP naar spirometrie</u>

1. Draai de grote draaiknop van de perslucht dicht.
2. Open de solenoid klep kort (o) zodat de druk eraf gaat en sluit weer (c).
3. Haal de luchtversterker eraf.
4. Klik in de Arduino software op het pijltje omhoog en klik op Leeg.
5. Klik in de Arduino software op het pijltje naar rechts.
6. Haal de Arduino uit de computer.

<u>FOT</u>

1. Klik op Patient Data en vul de gegevens van de proefpersoon in. Klik op exit.
2. Zet het aanpasbare mondstuk in maximaal naar achteren stand op de FOT opstelling.
3. Neusklem op en handen op de wangen vertel de patiënt om gewoon rustig in en uit te ademen. En de tong zoveel mogelijk naar beneden te houden.
4. Start Impulse Oscillometry op en klik op F2 om de meting op te nemen
5. Klik aan het eind van de meting op F4 en dan external om de data op te slaan. Sla op als PxxRNx.
6. Klik op F9 om de meting te herhalen. Herhaal nog 2x
7. Zet het aanpasbare mondstuk in maximaal naar voren stand op de FOT opstelling.
8. Neusklem op en handen op de wangen vertel de patiënt om gewoon rustig in en uit te ademen. En de tong zoveel mogelijk naar beneden te houden.
9. Start Impulse Oscillometry op en klik op F2 om de meting op te nemen

10. Klik aan het eind van de meting op F4 en dan external om de data op te slaan. Sla op als PxxPNx.
11. Klik op F9 om de meting te herhalen. Herhaal nog 2x
12. Neusklem op en handen op de wangen en vertel de patiënt nu om langzaam helemaal in en helemaal uit te ademen. En de tong zoveel mogelijk naar beneden te houden.
13. Start Impulse Oscillometry op en klik op F2 om de meting op te nemen
14. Klik aan het eind van de meting op F4 en dan external om de data op te slaan. Sla op als PxxPSx.
15. Klik op F9 om de meting te herhalen. Herhaal nog 2x
16. Zet het aanpasbare mondstuk in maximaal naar achteren stand op de FOT opstelling.
17. Neusklem op en handen op de wangen en vertel de patiënt nu om langzaam helemaal in en helemaal uit te ademen. En de tong zoveel mogelijk naar beneden te houden.
18. Start Impulse Oscillometry op en klik op F2 om de meting op te nemen
19. Klik aan het eind van de meting op F4 en dan external om de data op te slaan. Sla op als PxxRSx.
20. Klik op F9 om de meting te herhalen. Herhaal nog 2x
21. Neusklem op en handen op de wangen en vertel de patiënt nu zo snel mogelijk helemaal in en helemaal uit te ademen. En de tong zoveel mogelijk naar beneden te houden.
22. Start Impulse Oscillometry op en klik op F2 om de meting op te nemen
23. Klik aan het eind van de meting op F4 en dan external om de data op te slaan. Sla op als PxxRFx.
24. Klik op F9 om de meting te herhalen. Herhaal nog 2x waarbij telkens 1,5 minuut pauze wordt gehouden tussen de metingen.
25. Zet het aanpasbare mondstuk in maximaal naar voren stand op de FOT Opstelling.
26. Neusklem op en handen op de wangen en vertel de patiënt nu zo snel mogelijk helemaal in en helemaal uit te ademen. En de tong zoveel mogelijk naar beneden te houden.
27. Start Impulse Oscillometry op en klik op F2 om de meting op te nemen. Zorg dat er minimaal 5 goede ademhalingen zijn en stop dan de meting.
28. Klik aan het eind van de meting op F4 en dan external om de data op te slaan. Sla op als PxxPFx.
29. Klik op F9 om de meting te herhalen. Herhaal nog 2x waarbij telkens 1,5 minuut pauze wordt gehouden tussen de metingen.

<u>Spirometrie Liggend</u>

1. Zet het aanpasbare mondstuk in maximaal naar achteren stand op de spirometer
2. Open JLab
3. Ga naar Patient Data, maak een subject aan met Pxx, klik op F12
4. Klik op ‘Spirometry Flow-Volume’
5. Instructies + neusklem
6. Open JScope met lay-out ‘PUMA spiro’
7. Start meting in Jscope door op F2 te drukken.
8. Klik op F3 om Forced vital capacity meting te starten, klik na een meting op F7 om resultaten te berekenen, herhaal tenminste 3x waarvan 2 metingen reproduceerbaar moeten zijn.
9. Stop meting in JLab door op F12 te drukken
10. Stop Jscope, druk op F3 sluit Jscope af
11. Opslaan Jscope data (F5) als PxxReSpirox.ACS sluit Jscope af

12. Zet het aanpasbare mondstuk in maximaal naar voren stand op de spirometer
13. Instructies + neusklem
14. Klik in JLab op Spirometry Flow-Volume
15. Open Jscope met lay-out 'PUMA spiro'.
16. Start meting in Jscope door op F2 te drukken.
17. Klik op F3 om Forced vital capacity meting te starten, klik na een meting op F7 om resultaten te berekenen, herhaal tenminste 3x waarvan 2 metingen reproduceerbaar moeten zijn.
18. Stop meting in Jlab door op F12 te drukken
19. Stop Jscope, druk op F3 sluit Jscope af
20. Opslaan Jscope data als PxxProSpirox.ACS

Spirometrie zittend

1. Zet de spirometer in de juiste positie
2. Instructies + neusklem
3. Klik in JLab op Spirometry Flow-Volume
4. Open Jscope met lay-out 'PUMA spiro'
5. Start meting in Jscope door op F2 te drukken.
6. Begin met slow vital capacity (VC) F2, klik na een meting op F7 om resultaten te berekenen, herhaal tenminste 3x waarvan 2 metingen reproduceerbaar moeten zijn.
7. Stop meting in Jlab door op F12 te drukken.
8. Stop meting in Jscope, druk op F3. Sluit Jscope af
9. Opslaan data Jscope als PxxSpiroSlowx
10. Klik in JLab op Spirometry Flow-Volume
11. Open Jscope met lay-out 'PUMA spiro'
12. Start meting in Jscope door op F2 te drukken.
13. Klik op forced spirometry F3, klik na een meting op F7 om resultaten te berekenen, herhaal tenminste 3x waarvan 2 metingen reproduceerbaar moeten zijn.
14. Stop meting in Jlab door op F12 te drukken.
15. Stop meting in Jscope, druk op F3.
16. Opslaan data Jscope als PxxSpiroForcedx

Vragenlijst

1. Laat de patiënt de vragenlijst invullen.

Na meting

1. Maak de aanpasbare MRA schoon met 70% alcohol
2. Gooi de filters weg
3. Haal de data van de FOT laptop en zet het op een beveiligde harde schijf
4. Haal de data van de NEP en spirometrie van de computer en zet op een beveiligde harde schijf

5. Schakel de computer weer om naar de nieuwe kast.

Subchapter B – VAS-questionnaire

Vragenlijst naar tevredenheid van de metingen met verschillende opstellingen (Versie 3, 01-04-2019)

Deelnemer nummer (in te vullen door onderzoeker): .....

Datum vragenlijst ingevuld:

.....

Omcirkel het cijfer naar keuze

1. **Hoe tevreden bent u over de tijdsduur van de eerste meting (NEP)?**

1	2	3	4	5	6	7	8	9	10

Helemaal niet tevreden — Neutraal — Heel tevreden

1. **Hoe vond u de eerste meting (NEP)?**

1	2	3	4	5	6	7	8	9	10

Heel onprettig — Neutraal — Heel comfortabel

2. **Hoe tevreden bent u over de tijdsduur van de tweede meting (FOT)?**

1	2	3	4	5	6	7	8	9	10

Helemaal niet tevreden — Neutraal — Heel tevreden

3. **Hoe vond u de tweede meting (FOT)?**

1	2	3	4	5	6	7	8	9	10

Heel onprettig — Neutraal — Heel comfortabel

4. **Hoe tevreden bent u over de tijdsduur van de derde meting (spirometrie)?**

1	2	3	4	5	6	7	8	9	10

Helemaal niet tevreden — Neutraal — Heel tevreden

5. **Hoe vond u de derde meting (spirometrie)?**

1	2	3	4	5	6	7	8	9	10

Heel onprettig — Neutraal — Heel comfortabel

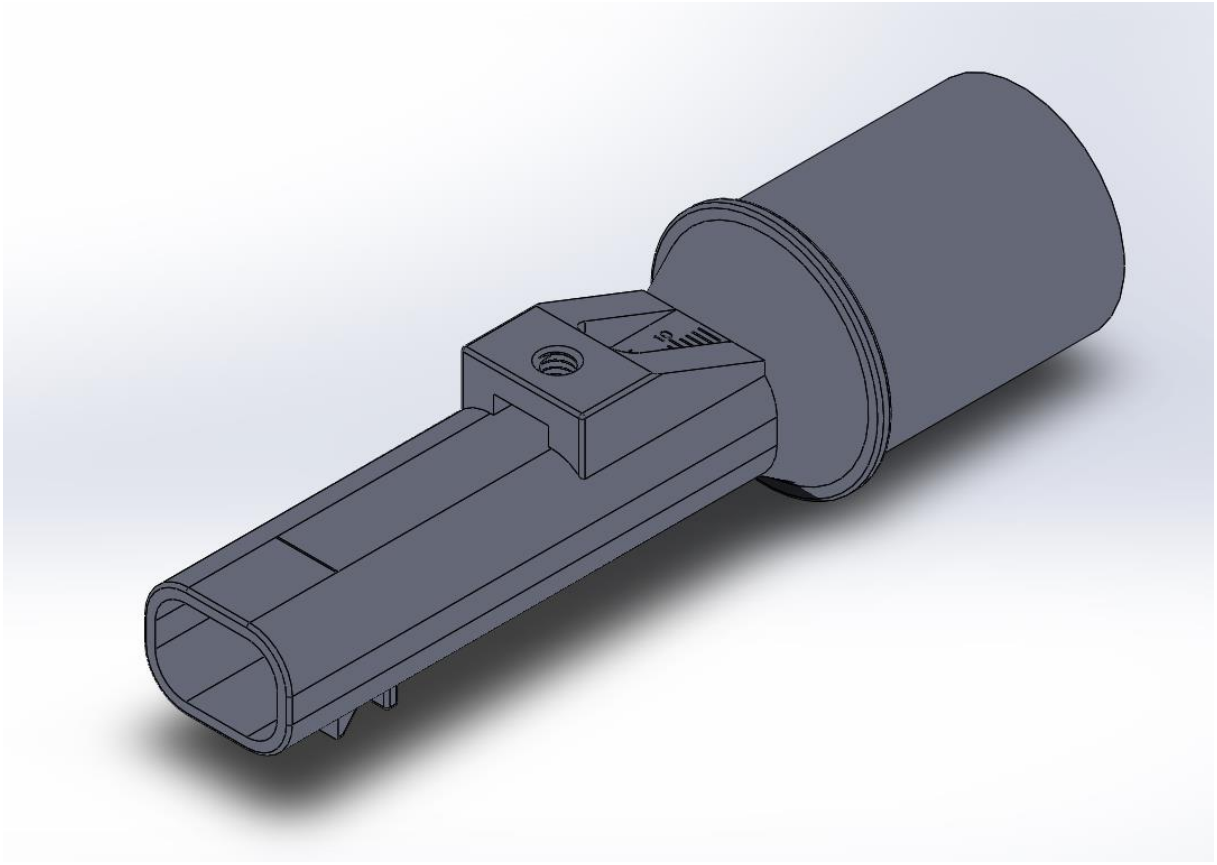
6. **Hoe vond u het dragen van het aanpasbare 'bitje' in uw mond tijdens de metingen?**

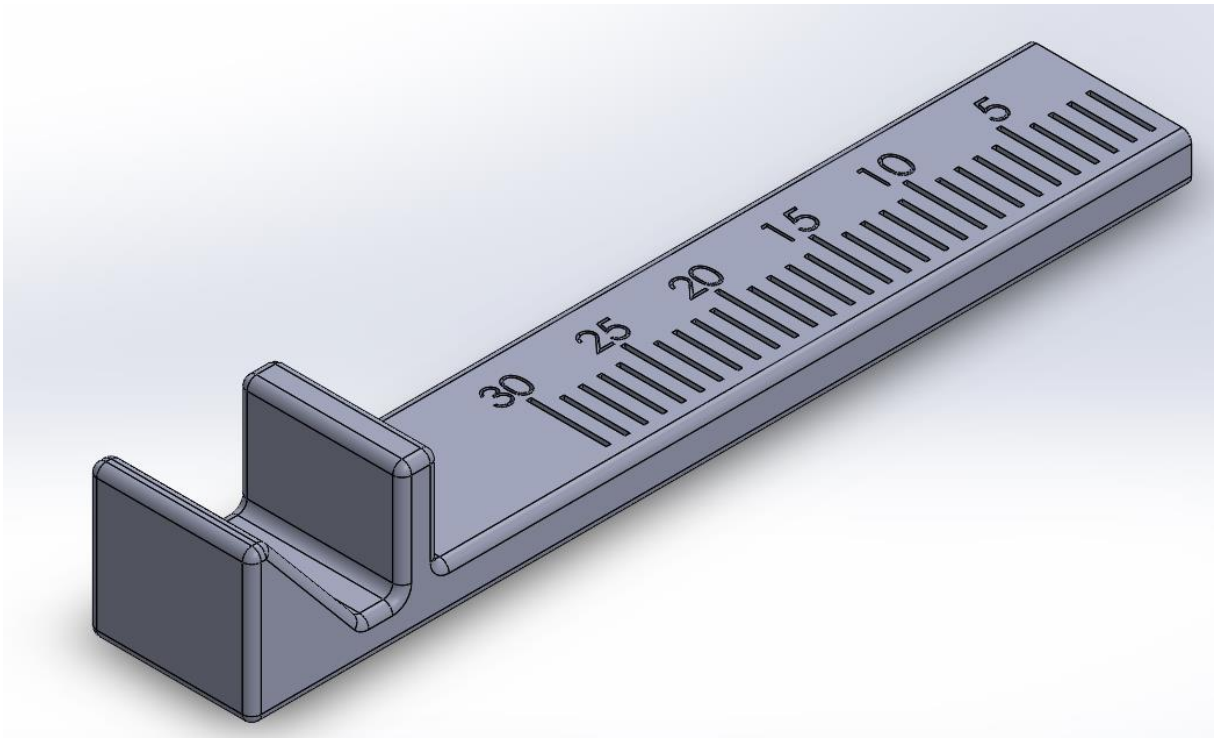
1	2	3	4	5	6	7	8	9	10

Heel onprettig — Neutraal — Heel comfortabel

Als u nog opmerkingen heeft, dan kunt u die hieronder opschrijven.

Subchapter C – 3D-images adjustable mouthpiece





Subchapter D – Additional results

Section D.1 – Baseline characteristics

Table A.1 – Baseline characteristics of the successful MAD therapy group versus the non-successful MAD therapy group based on the second definition of MAD success

	All included patients (n=23)	Successful MAD therapy (n=14)	Non-successful MAD therapy (n=9)	P-value
Age (yrs)	53.8 (9.7)	55.6 (8.7)	51.3 (11.2)	0.38
Male gender (n)	20 (87)	11 (78.6)	9 (100)	0.25
BMI (kg/m^2)	28.2 (3.0)	27.2 (25.9 – 29.3)	28.4 (26.0 – 32.2)	0.41
Baseline AHI Total	17.7 (15.9 - 25.9)	17.3 (15.1 – 28.2)	17.9 (17.2 – 23.5)	0.51
Control AHI Total	8.6 (4.1)	5.9 (4.0 – 7.9)	11.8 (11.1 – 13.7)	<0.01
Neck circumference (cm)	41.2 (2.3)	41.0 (2.5)	41.6 (1.9)	0.49
Retrognathia (n)	5 (21.7)	4 (28.6)	1 (11.1)	0.61
Mallampati Score				0.25
I	2 (8.7)	1 (7.1)	1 (11.1)	
II	13 (56.5)	6 (42.9)	7 (77.8)	
III	7 (30.4)	6 (42.9)	1 (11.1)	
IV	1 (4.3)	1 (7.1)	0 (0)	
Nasal obstruction	6 (26.1)	5 (35.7)	1 (11.1)	0.34
Weight gain (n)	1 (4.4)	1 (7.1)	0 (0)	0.61
Weight loss (n)	3 (13)	1 (7.1)	2 (22.2)	0.54
Smoking (n)	1 (4.3)	1 (7.1)	0 (0)	1.00
Packyears (yrs)	1.8 (0 - 8)	4.1 (0.0 – 12.8)	0.0 (0.0 – 4.0)	0.10
Medical history				
Cardiovascular (n)	2 (8.7)	1 (7.1)	1 (11.1)	1.00
COPD (n)	1 (4.3)	1 (7.1)	0 (0)	1.00
Asthma (n)	2 (8.7)	0 (0)	2 (22.2)	0.14
Tonsillectomy (n)	6 (26.1)	3 (21.4)	3 (33.3)	0.64
Position difference of adjustable mouthpiece (mm)	9.4 (4.2)	7.0 (5.0 – 13.8)	10.0 (7.5 – 11.5)	0.78

Values are given in numbers (%), medians (interquartile ranges), or mean (standard deviations), yrs = years, n = number of patients, BMI = Body Mass Index, AHI = Apnoea-hypopnoea index, COPD = chronic obstructive pulmonary disease

Section D.2 – Spirometry

In the table below the absolute differences between the parameters were taken for the mandible in protruded and retracted position (protruded minus retracted) for both definitions of MAD success.

Table A.2 – Absolute differences in spirometry parameters for both definitions of MAD success for the successful MAD therapy group versus the non-successful MAD therapy group.

	All included patients (n=25)	Successful MAD therapy (n=14)		Non-successful MAD therapy (n=9)		P-value	
		Def 1	Def 2	Def 1	Def 2	Def 1	Def 2
Δ FVC (L)	0.00 (0.13)	-0.01 (0.15)	-0.01 (0.15)	0.02 (0.17)	0.03 (0.11)	0.65	0.47
Δ FEV1 (L)	0.02 (-0.04 - 0.04)	0.01 (0.08)	0.00 (0.06)	0.00 (0.06)	0.01 (0.08)	0.94	0.71
Δ FEV1/IVC	-0.10 (-1.34 - 1.64)	0.30 (2.97)	0.45 (3.09)	0.13 (2.22)	-0.10 (1.88)	0.88	0.60
Δ FIV1 (L)	0.00 (-0.11 - 0.27)	0.04 (-0.14 - 0.38)	-0.01 (-0.14 - 0.37)	0.05 (-0.11 – 0.12)	0.00 (-0.08 – 0.16)	0.36	0.88
Δ FIVC (L)	0.02 (0.17)	0.03 (0.18)	0.01 (0.19)	0.02 (0.15)	0.04 (0.14)	0.95	0.68
Δ MIF50 (L/s)	0.19 (0.75)	0.33 (0.90)	0.21 (0.85)	-0.04 (0.37)	0.15 (0.61)	0.19	0.83
Δ MEF50 (L/s)	0.04 (0.41)	0.05 (0.31)	0.02 (0.29)	0.04 (0.57)	0.08 (0.58)	0.95	0.79
Δ MEF50/MIF50	-0.01 (0.12)	-0.04 (0.12)	-0.02 (0.12)	0.02 (0.11)	-0.00 (0.13)	0.27	0.73

Values are given in numbers (%), medians (interquartile ranges), or mean (standard deviations). Def 1 = first definition of MAD success, Def 2 = second definition of MAD success

Table A.3 – Relative differences in spirometry parameters for the second definition of MAD success for the successful MAD therapy group versus the non-successful MAD therapy group.

	All included patients (n=25)	Successful MAD therapy (n=14)	Non-successful MAD therapy (n=9)	P-value
		Def 2	Def 2	Def 2
Δ FVC (%)	0.84 (-1.13 - 1.74)	0.90 (-1.89 - 1.77)	-0.19 (-0.77 – 1.64)	0.95
Δ FEV1 (%)	0.55 (-1.04 - 1.50)	0.36 (2.09)	0.36 (1.70)	1.00
Δ FEV1/IVC (%)	-0.13 (-1.85 - 2.00)	0.77 (4.57)	-0.21 (2.65)	0.52
Δ FIV1 (%)	0.00 (-2.25 - 5.90)	1.03 (11.9)	0.80 (4.16)	0.95
Δ FIVC (%)	0.27 (3.39)	0.03 (3.98)	0.65 (2.34)	0.64
Δ MIF50 (%)	3.53 (-3.59 - 7.93)	5.41 (-4.86 - 7.99)	1.29 (-3.47 – 6.06)	0.45
Δ MEF50 (%)	0.75 (-3.70 - 6.67)	3.96 (15.1)	1.83 (11.3)	0.70
Δ MEF50/MIF50 (%)	-2.90 (17.50)	-3.58 (19.4)	-1.85 (15.1)	0.81

Values are given in numbers (%), medians (interquartile ranges), or mean (standard deviations). Def 2 = second definition of MAD success.

Table A.4 – Secondary parameters for both definitions of MAD success for the successful MAD therapy group versus the non-successful MAD therapy group for the mandible in retracted position.

	All included patients (n=25)	Successful MAD therapy (n=14)		Non-successful MAD therapy (n=9)		P-value	
		Def 1	Def 2	Def 1	Def 2	Def 1	Def 2
Saw toothing insp	1 (4.3)	1 (7.1)	1 (7.1)	0 (0)	0 (0)	0.61	0.61
Saw toothing exp	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	-	-
FEV1 (L)	3.37 (0.94)	3.32 (0.90)	3.37 (2.28 - 4.05)	3.44 (1.05)	3.94 (3.33 – 4.40)	0.77	0.17
FEV1 (% of normal)	88.8 (84.6 - 91.4)	89.5 (84.8 - 92.5)	91.4 (9.91)	88.1 (83.4 – 89.8)	87.0 (3.83)	0.31	0.15
FEV1/IVC	72.1 (66.7 - 76.2)	72.1 (6.46)	72.4 (65.8 - 76.1)	68.1 (9.90)	70.7 (67.4 - 76.4)	0.30	0.85
FEV1/IVC (% of normal)	96.3 (92.8 - 98.2)	96.2 (92.9 - 98.3)	98.8 (11.4)	96.3 (90.9 – 98.2)	94.4 (4.23)	0.75	0.27
FIV1 (L)	4.43 (1.08)	4.25 (1.11)	4.21 (3.10 - 5.17)	4.72 (1.02)	4.74 (4.38 – 5.29)	0.31	0.19
FIV1 (% of normal)	92.2 (89.2 - 97.5)	92.0 (84.9 - 99.9)	98.9 (25.2)	92.2 (89.4 – 97.2)	93.3 (7.95)	0.71	0.10
IVC (L)	4.74 (1.23)	4.59 (1.27)	4.45 (1.31)	4.97 (1.20)	5.20 (0.99)	0.48	0.14
IVC (% of normal)	94.6 (5.28)	95.5 (4.85)	95.3 (4.99)	93.2 (5.91)	93.5 (5.84)	0.36	0.48
MIF50 (L/s)	5.74 (1.33)	5.45 (1.31)	5.35 (4.00 - 6.54)	6.18 (1.30)	6.46 (5.26 – 7.11)	0.36	0.17
MIF50 (% of normal)	97.8 (77.5 - 107)	96.0 (74.1 - 104)	99.9 (35.9)	99.7 (78.9 – 110)	91.6 (21.1)	0.61	0.49
MEF50 (L/s)	3.24 (1.29)	3.32 (1.22)	3.22 (1.80 - 4.02)	3.12 (1.46)	3.54 (2.81 – 4.29)	0.79	0.40
MEF50 (% of normal)	78.9 (71.7 - 88.8)	83.4 (74.9 - 93.7)	105 (82.4)	78.6 (67.3 – 87.8)	76.9 (9.00)	0.26	0.23
MEF50/MIF50	0.58 (0.27)	0.64 (0.28)	0.50 (0.33 - 0.84)	0.50 (0.23)	0.48 (0.40 - 0.78)	0.20	0.90
MEF50/MIF50 (% of normal)	85.5 (74.6 - 111)	91.9 (73.5 - 133)	101 (33.56)	78.8 (70.0 - 103)	89.1 (28.3)	0.31	0.38
FVC (L)	4.62 (1.20)	4.48 (1.22)	4.32 (1.27)	4.83 (1.20)	5.08 (0.95)	0.50	0.11
FVC (% of normal)	91.0 (4.36)	91.0 (4.89)	91.2 (4.99)	90.9 (3.64)	90.6 (3.40)	0.96	0.76

Table A.5 – Secondary parameters for both definitions of MAD success for the successful MAD therapy group versus the non-successful MAD therapy group for the mandible in protruded position.

	All included patients (n=25)	Successful MAD therapy (n=14)		Non-successful MAD therapy (n=9)		P-value	
		Def 1	Def 2	Def 1	Def 2	Def 1	Def 2
Saw toothing insp	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	-	-
Saw toothing exp	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	-	-
FEV1 (L)	3.37 (0.92)	3.32 (0.89)	3.14 (0.98)	3.45 (1.02)	3.74 (0.73)	0.78	0.11
FEV1 (% of normal)	89.1 (84.9 - 92.5)	90.4 (85.6 - 92.8)	91.6 (85.6 - 93.0)	88.7 (84.0 – 90.9)	88.7 (84.0 - 90.3)	0.38	0.17
FEV1/IVC	70.8 (7.51)	72.4 (6.17)	70.3 (8.46)	68.2 (9.01)	71.4 (6.15)	0.24	0.73
FEV1/IVC (% of normal)	95.6 (93.45 - 98.51)	95.6 (93.8 - 101)	95.9 (93.8 - 102)	97.6 (90.9 – 98.1)	95.6 (90.9 – 97.8)	0.80	0.38
FIV1 (L)	4.45 (1.14)	4.28 (1.18)	4.14 (1.20)	4.70 (1.09)	4.92 (0.88)	0.40	0.09
FIV1 (% of normal)	91.0 (89.4 - 97.9)	90.9 (89.7 - 99.0)	90.9 (88.6 - 99.0)	95.2 (88.6 – 96.5)	95.2 (90.1 – 96.5)	0.75	0.75
IVC (L)	4.76 (1.27)	4.62 (1.30)	4.46 (1.35)	4.99 (1.24)	5.24 (1.01)	0.49	0.13
IVC (% of normal)	94.9 (5.21)	95.8 (4.97)	95.3 (5.45)	93.4 (5.52)	94.2 (5.06)	0.30	0.63
MIF50 (L/s)	5.92 (1.40)	5.78 (1.48)	5.65 (1.56)	6.14 (1.34)	6.35 (1.06)	0.56	0.21
MIF50 (% of normal)	93.7 (81.5 - 107)	92.3 (79.6 - 106)	92.3 (80.6 - 106)	97.3 (80.0 – 109)	97.3 (78.0 - 109)	0.71	0.90
MEF50 (L/s)	101.55 (48.46)	3.67 (1.27)	3.07 (1.38)	3.15 (1.49)	3.61 (1.25)	0.73	0.34
MEF50 (% of normal)	3.24 (2.02 - 4.43)	0.61 (0.40 - 0.81)	92.3 (80.6 - 106)	0.43 (0.33 0.74)	97.3 (78.0 - 109)	0.19	0.13
MEF50/MIF50	0.57 (0.25)	0.60 (0.24)	0.56 (0.25)	0.52 (0.28)	0.59 (0.26)	0.45	0.77
MEF50/MIF50 (% of normal)	93.4 (24.0)	97.2 (24.5)	97.3 (24.7)	87.5 (23.4)	87.3 (23.0)	0.36	0.34
FVC (L)	4.62 (1.22)	4.47 (1.24)	4.31 (1.28)	4.85 (1.22)	5.11 (0.98)	0.48	0.10
FVC (% of normal)	90.9 (3.18)	90.7 (3.25)	91.0 (88.0 – 93.4)	91.2 (3.23)	91.6 (87.4 - 93.9)	0.70	0.82

Section D.3 – Forced Oscillation Technique

The absolute differences between the values in protruded and retracted position are calculated (protruded – retracted). The results are presented in the table below (Table 2).

For the analysis of the FOT parameters, the relative differences between the mandible in protruded and retracted position is determined, where the values for the mandible in protruded position are taken as 100%. The results of this analysis are presented in the table below (Table 3).

Table A.6 – Absolute differences in FOT parameters for normal (N), maximal slow in- and exhalation (S) and maximal fast in- and exhalation (F) manoeuvres for successful MAD therapy group versus the non-successful MAD therapy group based on the first definition of MAD success

	All included patients (n=23)			Successful MAD therapy (n=14)			Non-successful MAD therapy (n=9)			P-value		
	N	S	F	N	S	F	N	S	F	N	S	F
Δ Fres	0.27 (1.13)	-0.22 (1.24)	1.22 (3.55)	0.20 (-0.14 - 0.58)	-0.20 (1.40)	0.97 (4.35)	0.53 (-0.64 – 1.21)	-0.25 (1.00)	1.60 (1.94)	0.57	0.92	0.64
Δ AX	-0.18 (-2.56 - 0.79)	-0.14 (-2.54 - 3.57)	-7.54 (15.66)	-0.03 (-2.54 - -0.94)	-0.39 (5.50)	-6.40 (16.85)	-0.75 (-3.86 - 0.47)	-0.50 (6.02)	-9.31 (14.39)	0.57	0.97	0.66
Δ R5	-0.31 (0.64)	-0.48 (0.76)	-0.13 (0.71)	-0.41 (0.46)	-0.38 (0.83)	-0.12 (0.81)	-0.16 (0.85)	-0.64 (0.65)	-0.16 (0.56)	0.45	0.41	0.88
Δ X5	-0.09 (-0.36 0.12)	-0.03 (0.68)	-0.16 (-1.41 0.90)	-0.16 (-0.30 – 0.12)	0.01 (0.24)	-0.17 (-1.94 – 1.08)	-0.09 (-0.68 - 0.14)	-0.04 (0.68)	-0.16 (-1.21 - 0.38)	0.50	0.96	0.71
Δ R20	-0.39 (0.60)	-0.41 (0.59)	-0.26 (0.42)	-0.44 (0.54)	-0.29 (0.59)	-0.32 (0.43)	-0.31 (0.73)	-0.59 (0.56)	-0.16 (0.41)	0.66	0.23	0.38
Δ R5-R20	0.07 (0.30)	-0.07 (0.31)	-0.14 (-0.23 - 0.45)	0.03 (0.32)	-0.09 (0.38)	0.20 (0.81)	0.15 (0.26)	-0.04 (0.17)	0.00 (0.46)	0.34	0.97	0.45
Δ Imp. accept	31.8 (28.3)	21.17 (45.52)	-11.83 (26.86)	23.50 (12.75 - 41.25)	15.21 (49.04)	-17.57 (29.12)	39.00 (4.00 – 75.50)	30.44 (40.40)	-2.89 (21.42)	0.73	0.48	0.18
Δ Fit fR start	0.39 (1.87)	-0.22 (-1.20 - 0.70)	0.42 (-0.60)	0.48 (1.76)	-0.29 (-1.13 - 0.52)	0.30 (7.28)	0.26 (2.14)	0.24 (-1.94 - 1.04)	0.62 (4.00)	0.20	0.85	0.66
Δ Fit fR coef	0.10E-3 (-1.3E-3 - 0.50E-3)	0.30E-3 (-0.20E-3 - -0.60E-3)	0.30E-3 (-0.60E-3 - 2.10E-3)	0.00E-3 (-1.50E-3 - 0.40E-3)	0.30E-3 (0.13E-3)	0.90E-3 (-1.10E-3 – 2.60E-3)	0.30E-3 (-1.00E-3 – 0.80E-3)	0.40E-3 (0.11E-3)	-0.30E-3 (-0.50E-3 - 0.80E-3)	0.26	0.74	0.76
Δ Fit AX start	-0.38 (-4.79 - 0.71)	-0.66 (-4.06 - 1.63)	-5.02 (34.1)	-0.03 (-5.75 - 0.72)	-1.54 (-3.42 - 2.23)	-2.53 (40.0)	-0.57 (-4.41 - 1.02)	0.83 (-7.35 - 6.43)	-8.90 (23.9)	0.95	0.66	0.41
Δ Fit AX coef	0.30E-3 (-0.60E-3 - 1.70E-3)	0.00E-3 (-2.50E-3 - 1.30E-3)	0.40E-3 (-5.80E-3 - 6.40E-3)	0.60E-3 (-0.30E-3 - 2.10E-3)	0.40E-3 (-0.23E-3 - 0.14E-3)	-0.20E-3 (-6.70E-3 – 9.40E-3)	-0.20E-3 (-0.80E-3 - 2.29E-3)	-0.30E-3 (-3.20E-3 – 2.70E-3)	0.40E-3 (-2.90E-3 6.20E-3)	0.35	0.80	0.90
Δ Fit X5 start	-0.17 (-7.00 - 0.12)	0.02 (-0.33 - 0.76)	-0.51 (4.36)	-1.57 (-0.72 0.06)	-0.07 (1.61)	0.46 (-5.00 – 3.29)	-0.36 (0.63)	-0.17 (1.68)	0.08 (-0.84 - 2.07)	0.75	0.94	0.89
Δ Fit X5 coef	0.10E-3 (0.00E-3 - 0.40E-3)	0.00E-3 (0.65E-3)	0.00E-3 (-0.90E-3 - 0.50E-3)	0.10E-3 (0.00E-3 - 0.40E-3)	0.00E-3 (-0.80E-3 - 0.20E-3)	-0.20E-3 (1.47E-3)	0.00E-3 (-0.20E-3 - 0.40E-3)	0.00E-3 (-0.40E-3 – 0.30E-3)	-0.20E-3 (0.97E-3)	0.13	0.85	0.75
Δ Fit R5 start	-0.31 (0.83)	-0.64 (1.28)	-0.33 (1.48)	-0.33 (0.79)	-0.38 (1.37)	-0.16 (1.73)	-0.28 (0.95)	-1.04 (1.08)	-0.60 (1.01)	0.89	0.21	0.45
Δ Fit R5 coef	0.10E-3 (-0.20E-3 - 0.30E-3)	0.10E-3 (0.43E-3)	0.20E-3 (0.43E-3)	0.00E-3 (-0.40E-3 - 0.40E-3)	0.00E-3 (-0.20E-3 – 0.30E-3)	0.10E-3 (0.52E-3)	0.10E-3 (-0.10E-3 – 0.40E-3)	0.10E-3 (0.10E-3 - 0.30E-3)	0.20E-3 (0.26E-3)	0.61	0.08	0.66
Δ Fit R20 start	-0.36 (0.75)	-0.48 (0.77)	-0.49 (0.63)	-0.36 (0.79)	-0.29 (0.79)	-0.55 (0.49)	-0.36 (0.74)	-0.78 (0.68)	-0.41 (0.83)	0.98	0.14	0.66
Δ Fit R20 coef	0.00E-3 (0.30E-3)	0.10E-3 (0.17E-3)	0.20E-3 (0.23E-3)	-0.10E-3 (0.35E-3)	0.00E-3 (0.19E-3)	0.20E-3 (0.24E-3)	0.10E-3 (0.17E-3)	0.10E-3 (0.14E-3)	0.10E-3 (0.22E-3)	0.13	0.48	0.74
Δ Fit R520 start	0.05 (0.46)	-0.15 (0.75)	-0.01 (-0.86 0.86)	0.03 (0.55)	-0.08 (0.81)	0.20 (-0.86 1.02)	0.08 (0.30)	0.01 (-0.49 0.12)	-0.19 (0.87)	0.80	0.57	0.53
Δ Fit R520 coef	0.10E-3 (-0.10E-3 - 0.20E-3)	0.00E-3 (-0.10E-3 - 0.20E-3)	0.00E-3 (0.34E-3)	0.10E-3 (-0.10E-3 - 0.20E-3)	0.00E-3 (-0.20E-3 - 0.10E-3)	-0.10E-3 (-0.40E-3 – 0.20E-3)	0.00E-3 (-0.10E-3 - 0.10E-3)	0.10E-3 (0.00E-3 - 0.20E-3)	0.20E-3 (-0.10E-3 - 0.20E-3)	0.41	0.13	0.23

Values are given in numbers (%), medians (interquartile ranges), or mean (standard deviations). Imp = impulses

Table A.7 – Absolute differences in FOT parameters for normal (N), maximal slow in- and exhalation (S) and maximal fast in- and exhalation (F) manoeuvres for successful MAD therapy group versus the non-successful MAD therapy group based on the second definition of MAD success

	All included patients (n=23)			Successful MAD therapy (n=14)			Non-successful MAD therapy (n=9)			P-value		
	N	S	F	N	S	F	N	S	F	N	S	F
Δ Fres	0.27 (1.13)	-0.22 (1.24)	1.22 (3.55)	0.20 (-0.14 - 0.58)	-0.38 (1.48)	1.59 (3.87)	0.53 (-0.64 – 1.16)	0.03 (0.73)	0.63 (3.13)	0.66	0.39	0.52
Δ AX	-0.18 (-2.56 - 0.79)	-0.14 (-2.54 - 3.57)	-7.54 (15.66)	-0.03 (-2.90 - 0.94)	0.01 (5.64)	-8.86 (16.00)	-0.75 (-3.21 – 0.47)	-1.12 (5.74)	-5.48 (15.83)	0.80	0.65	0.63
Δ R5	-0.31 (0.64)	-0.48 (0.76)	-0.13 (0.71)	-0.31 (-0.70 - -0.08)	-4.1 (0.83)	-0.03 (0.72)	-0.10 (-0.67 - 0.11)	-0.60 (0.66)	-0.30 (0.70)	0.53	0.55	0.39
Δ X5	-0.09 (-0.36 - 0.12)	-0.03 (0.68)	-0.16 (-1.41 - 0.90)	-0.16 (-0.38 - 0.12)	-0.03 (0.70)	-0.51 (-1.94 – 0.92)	-0.09 (-0.51 0.14)	-0.04 (0.68)	-0.07 (-1.17 - 0.95)	0.95	0.96	0.66
Δ R20	-0.39 (0.60)	-0.41 (0.59)	-0.26 (0.42)	-0.34 (0.62)	-0.29 (-0.60 – 0.12)	-0.30 (0.42)	-0.46 (0.60)	-0.22 (-1.19 -- 0.14)	-0.19 (0.43)	0.65	0.57	0.64
Δ R5-R20	0.07 (0.30)	-0.07 (0.31)	-0.14 (-0.23 - 0.45)	0.04 (0.34)	-0.09 (0.38)	0.27 (0.76)	0.13 (0.22)	-0.04 (0.17)	-0.11 (0.52)	0.45	0.67	0.53
Δ Imp. accept	31.8 (28.3)	21.17 (45.52)	-11.83 (26.86)	26.57 (22.63)	13.36 (49.01)	-18.93 (28.60)	40.00 (35.34)	33.33 (39.01)	-6.22 (23.27)	0.33	0.29	0.16
Δ Fit fR start	0.39 (1.87)	-0.22 (-1.20 - 0.70)	0.42 (-0.60)	0.56 (1.89)	-0.49 (-2.10 - 0.51)	1.15 (6.64)	0.14 (1.94)	0.70 (-0.97 – 1.10)	-0.71 (5.32)	0.61	0.67	0.26
Δ Fit fR coef	0.10E-3 (-1.3E-3 - 0.50E-3)	0.30E-3 (-0.20E-3 - -0.60E-3)	0.30E-3 (-0.60E-3 - 2.10E-3)	0.00E-3 (-2.00E-3 - 0.40E-3)	0.50E-3 (1.52E-3)	0.40E-3 (-1.10E-3 – 2.30E-3)	0.30E-3 (-0.60E-3 – 0.80E-3)	0.10E-3 (0.56E-3)	-0.30E-3 (-0.50E-3 - 1.70E-3)	0.23	0.37	1.00
Δ Fit AX start	-0.38 (-4.79 - 0.71)	-0.66 (-4.06 - 1.63)	-5.02 (34.11)	-0.03 (-6.56 - 0.72)	-1.00 (-3.07 – 5.47)	-5.85 (39.52)	-0.57 (-4.41 – 1.02)	0.09 (-7.35 - 1.01)	-3.73 (25.69)	0.80	0.57	0.88
Δ Fit AX coef	0.30E-3 (-0.60E-3 - 1.70E-3)	0.00E-3 (-2.50E-3 - 1.30E-3)	0.40E-3 (-5.80E-3 - 6.40E-3)	0.60E-3 (-0.30E-3 - 3.60E-3)	-0.70E-3 (6.10E-3)	0.70E-3 (-6.20E-3 – 9.40E-3)	-0.20E-3 (0.80E-3 - 2.20E-3)	0.40E-3 (3.03E-3)	0.20E-3 (-5.20E-3 - 6.20E-3)	0.28	0.57	0.75
Δ Fit X5 start	-0.17 (-7.00 - 0.12)	0.02 (-0.33 - 0.76)	-0.51 (4.36)	-0.16 (-0.88 - 0.06)	0.07 (-0.29 - 1.66)	0.46 (4.96 – 2.68)	-0.17 (-0.68 – 0.16)	-0.03 (-1.27 – 0.59)	0.08 (-0.84 2.50)	0.57	0.38	0.90
Δ Fit X5 coef	0.10E-3 (0.00E-3 - 0.40E-3)	0.00E-3 (0.65E-3)	0.00E-3 (-0.90E-3 - 0.50E-3)	0.10E-3 (0.00E-3 - 0.40E-3)	0.00E-3 (-0.80E-3 - 0.20E-3)	-0.20E-3 (1.50E-3)	0.10E-3 (-0.20E-3 - 0.50E-3)	0.00E-3 (-0.40E-3 – 0.40E-3)	-0.10E-3 (0.91E-3)	0.53	0.45	0.91
Δ Fit R5 start	-0.31 (0.83)	-0.64 (1.28)	-0.33 (1.48)	-0.18 (-0.90 – 0.45)	-0.18 (-1.86 – 0.62)	-0.07 (1.63)	0.01 (-1.09 0.20)	-0.27 (-1.51 -0.06)	-0.74 (1.19)	0.95	0.57	0.26
Δ Fit R5 coef	0.10E-3 (-0.20E-3 - 0.30E-3)	0.10E-3 (0.43E-3)	0.20E-3 (0.43E-3)	0.10E-3 (-0.40E-3 - 0.40E-3)	0.10E-3 (0.55E-3)	0.10E-3 (0.51E-3)	-0.10E-3 (-0.10E-3 – 0.40E-3)	0.10E-3 (0.16E-3)	0.20E-3 (0.28E-3)	0.71	0.86	0.54
Δ Fit R20 start	-0.36 (0.75)	-0.48 (0.77)	-0.49 (0.63)	-0.27 (0.81)	-0.39 (0.82)	-0.55 (0.50)	-0.50 (0.66)	-0.63 (0.72)	-0.40 (0.82)	0.48	0.46	0.62
Δ Fit R20 coef	0.00E-3 (0.30E-3)	0.10E-3 (0.17E-3)	0.20E-3 (0.23E-3)	-0.10E-3 (0.35E-3)	0.10E-3 (0.19E-3)	0.20E-3 (0.25E-3)	0.10E-3 (0.17E-3)	0.10E-3 (0.14E-3)	0.10E-3 (0.20E-3)	0.12	0.86	0.46
Δ Fit R520 start	0.05 (0.46)	-0.15 (0.75)	-0.01 (-0.86 - 0.86)	0.01 (0.52)	-0.21 (0.94)	-.20 (-0.51 - 1.02)	0.11 (0.36)	-0.06 (0.32)	-0.34 (0.96)	0.58	0.60	0.13
Δ Fit R520 coef	0.10E-3 (-0.10E-3 - 0.20E-3)	0.00E-3 (-0.10E-3 - 0.20E-3)	0.00E-3 (0.34E-3)	0.10E-3 (0.00E-3 - 0.20E-3)	0.10E-3 (0.41E-3)	-0.10E-3 (0.38E-3)	0.00E-3 (-0.20E-3 - 0.10E-3)	0.10E-3 (0.11E-3)	0.10E-3 (0.27E-3)	0.26	0.90	0.21

*Values are given in numbers (%), medians (*interquartile *ranges), or mean (standard deviations). Imp = impulses*

Table A.8 – Relative differences in FOT parameters for normal (N), maximal slow in- and exhalation (S) and maximal fast in- and exhalation (F) manoeuvres for successful MAD therapy group versus the non-successful MAD therapy group based on the first definition of MAD success

	All included patients (n=23)			Successful MAD therapy (n=14)			Non-successful MAD therapy (n=9)			P-value		
	N	S	F	N	S	F	N	S	F	N	S	F
Δ Fres	0.90 (9.24)	-1.63 (8.29)	6.89 (-4.06 - 16.77)	2.47 (-3.37 – 6.36)	-1.73 (9.44)	1.73 (30.03)	4.23 (-5.60 – 7.87)	-1.49 (6.66)	9.88 (11.56)	0.45	0.16	0.37
Δ AX	2.85 (-22.44 - 20.54)	-3.00 (26.76)	31.70 (-14.55 - 44.19)	-0.49 (-23.48 – 23.46)	-2.91 (28.95)	11.00 (-23.93 - 37.41)	12.47 (-44.77 - 22.91)	-3.14 (24.65)	33.21 (-22.30 – 50.26)	0.95	0.98	0.85
Δ R5	-7.64 (-19.32 - 0.31)	-12.54 (17.30)	-3.00 (-14.24 - 7.60)	-11.46 (13.95)	-9.36 (17.05)	-0.15 (-15.53 – 9.33)	-8.05 (23.68)	-17.48 (17.50)	-3.55 (-24.53 - 4.49)	0.70	0.29	0.75
Δ X5	5.49 (20.97)	-2.43 (21.78)	2.61 (-19.97 - 23.87)	6.58 (16.61)	-3.52 (21.97)	2.60 (-26.53 - 28.53)	3.80 (27.49)	-0.74 (22.69)	2.61 (-23.07 – 23.85)	0.79	0.78	0.90
Δ R20	-8.56 (-23.11 - -0.23)	-14.48 (19.66)	-10.59 (14.99)	-16.63 (20.31)	-9.75 (17.69)	-11.51 (14.43)	-12.76 (26.08)	-21.83 (21.32)	-9.15 (16.61)	0.71	0.18	0.73
Δ R5-R20	4.10 (-36.46 - 29.97)	-17.71 (-26.66 - 6.97)	14.85 (-35.57 - 31.20)	1.63 (-21.15 - 27.45)	-21.85 (-30.74 – 16.36)	19.18 (-41.31 - 30.75)	18.16 (-53.83 - 26.25)	-5.69 (-21.94 - 2.59)	14.85 (-19.03 - 42.24)	0.85	0.71	0.66
Δ Imp. accept	9.00 (8.01)	7.18 (18.30)	-20.53 (46.11)	8.34 (5.45)	5.89 (21.68)	-28.53 (53.39)	10.02 (11.25)	9.18 (12.24)	-8.10 (30.48)	0.68	0.65	0.26
Δ Fit fR start	0.10 (13.6)	-2.40 (-1.61)	-4.70 (37.5)	1.04 (11.1)	-1.16 (12.3)	-7.45 (42.9)	-1.37 (17.4)	-4.32 (15.3)	-0.44 (29.1)	0.72	0.61	0.65
Δ Fit fR coef	-2.55 (-22.8 - 26.3)	-5.78 (-37.4 - 23.9)	14.2 (-55.8 - 94.01)	-0.36 (-19.3 - 29.2)	-11.35 (-40.16 – 14.68)	17.8 (-99.8 - 72.3)	-10.1 (-210 - 41.7)	4.95 (-40.9 - 74.3)	14.2 (-23.6 – 123)	0.66	0.45	0.38
Δ Fit AX start	1.18 (-23.3 - 20.1)	-3.95 (37.6)	-17.5 (-91.7 - 48.0)	0.50 (33.90)	1.81 (33.2)	-18.5 (-93.7 - 45.1)	-19.3 (65.0)	-12.9 (44.2)	14.9 (-108 – 61.2)	0.42	0.41	0.80
Δ Fit AX coef	4.67 (-45.9 - 42.1)	4.20 (-59.8 - 30.5)	31.0 (-52.7 - 88.8)	10.5 (-12.1 - 69.7)	5.00 (-62.7 - 24.1)	34.1 (-133 – 82.2)	1.62 (-380 - 29.1)	-4.38 (-64.3 - 44.0)	31.0 (-36.2 - 118)	0.23	0.95	0.80
Δ Fit X5 start	5.81 (-9.85 - 21.9)	-0.46 (-14.1 - 16.1)	-3.76 (-38.9 - 36.6)	4.89 (-5.73 – 27.15)	-4.71 (41.8)	-9.61 (-60.8 - 37.8)	13.7 (-26.5 - 21.1)	-0.47 (28.2)	-3.76 (-18.7 - 26.6)	0.71	0.77	0.71
Δ Fit X5 coef	9.31 (-3.75 - 44.1)	0.75 (-53.5 - 44.0)	7.78 (-57.7 - 58.5)	8.63 (-0.61 - 43.7)	12.6 (-53.9 - 52.8)	4.19 (-127 - 39.3)	12.49 (-40.90 – 87.36)	-7.17 (-58.04 – 37.46)	58.1 (-42.3 - 201)	0.90	0.41	0.23
Δ Fit R5 start	-1.31 (-18.6 - 5.41)	-9.99 (17.9)	-14.28 (-28.8 - 7.89)	-4.16 (-18.31 – 2.68)	-5.68 (19.1)	-7.86 (-29.0 – 9.09)	0.91 (-24.5 - 8.56)	-16.7 (14.4)	-16.1 (-28.2 - 1.92)	0.61	0.13	0.66
Δ Fit R5 coef	8.04 (-36.7 - 30.7)	-10.49 (-25.1 12.1)	-1.82 (-118 - 23.7)	10.6 (-27.2 - 38.0)	3.68 (-27.5 - 27.6)	4.04 (-156 - 30.8)	-4.43 (-56.96 – 18.79)	-13.2 (-36.1 - 8.70)	-32.9 (-250 - 16.6)	0.41	0.12	0.61
Δ Fit R20 start	-13.5 (23.7)	-12.0 (19.1)	-16.6 (20.5)	-8.39 (-26.89 – 4.08)	-6.54 (18.3)	-16.7 (14.6)	-4.21 (-28.5 - 4.68)	-20.4 (18.1)	-16.3 (28.5)	0.71	0.09	0.97
Δ Fit R20 coef	1.53 (-39.1 - 30.4)	-11.9 (-36.5 - 16.5)	-64.8 (136)	23.1 (-42.4 - 62.1)	-9.41 (-35.1 - 25.7)	-74.0 (166)	-4.55 (-41.36 – 8.20)	-21.9 (-43.6 - 0.31)	-50.4 (72.1)	0.31	0.49	0.65
Δ Fit R520 start	-6.53 (-39.7 - 16.8)	-10.0 (37.3)	21.9 (-10.0 - 56.1)	-8.83 (-28.8 - 20.9)	-8.93 (40.5)	16.4 (-56.0 - 44.5)	36.3 (-27.7 - 182)	-11.7 (34.0)	43.2 (-3.30 - 365)	0.90	0.86	0.15
Δ Fit R520 coef	0.55 (-34.0 - 85.6)	-2.29 (-67.3 - 17.7)	58.4 (23.1 - 181)	-2.95 (-45.0 - 46.3)	7.68 (-38.6 - 26.1)	49.5 (22.0 - 140)	36.30 (-27.70 – 181.64)	-17.70 (-112.13 – 2.10)	89.5 (12.4 - 215)	0.15	0.10	0.49

Values are given in numbers (%), medians (interquartile ranges), or mean (standard deviations). Imp = impulses

Table A.9 – Relative differences in FOT parameters for normal (N), maximal slow in- and exhalation (S) and maximal fast in- and exhalation (F) manoeuvres for successful MAD therapy group versus the non-successful MAD therapy group based on the second definition of MAD success

	All included patients (n=23)			Successful MAD therapy (n=14)			Non-successful MAD therapy (n=9)			P-value		
	N	S	F	N	S	F	N	S	F	N	S	F
Δ Fres	0.90 (9.24)	-1.63 (8.29)	6.89 (-4.06 - 16.77)	2.47 (-3.37 - 6.36)	-2.87 (9.71)	6.52 (-5.22 - 28.63)	4.23 (-5.60 – 7.87)	0.30 (5.39)	9.21 (-4.74 - 16.63)	0.80	0.33	0.75
Δ AX	2.85 (-22.44 - 20.54)	-3.00 (26.76)	31.70 (-14.55 - 44.19)	-0.49 (-23.48 – 23.46)	-5.13 (28.26)	22.98 (-4.56 – 37.41)	12.47 (-44.77 - 22.91)	0.32 (25.53)	33.21 (-35.77 - 50.26)	0.90	0.64	0.39
Δ R5	-7.64 (-19.32 - 0.31)	-12.54 (17.30)	-3.00 (-14.24 - 7.60)	-9.77 (16.37)	-9.56 (17.05)	-0.14 (-14.00 - 9.33)	-2.37 (-17.30)	-17.17 (17.65)	-5.11 (-43.25 - 4.49)	0.91	0.32	0.38
Δ X5	5.49 (20.97)	-2.43 (21.78)	2.61 (-19.97 - 23.87)	7.48 (17.76)	-4.12 (21.66)	4.76 (34.75)	2.40 (26.06)	0.19 (23.02)	-18.68 (67.80)	0.62	0.66	0.36
Δ R20	-8.56 (-23.11 - -0.23)	-14.48 (19.66)	-10.59 (14.99)	-13.97 (22.11)	-9.87 (-16.70 – 3.10)	-10.71 (14.07)	-16.89 (23.67)	-7.50 (-44.22 - 5.36)	-10.40 (17.22)	0.77	0.41	0.96
Δ R5-R20	4.10 (-36.46 - 29.97)	-17.71 (-26.66 - 6.97)	14.85 (-35.57 - 31.20)	1.63 (-21.15 - 27.45)	-21.85 (-30.74 – 16.36)	19.26 (-11.58 - 30.75)	18.16 (-53.83 - 26.25)	-10.28 (-21.94 - 10.59)	5.96 (-41.69 - 42.24)	0.75	0.75	0.80
Δ Imp. accept	9.00 (8.01)	7.18 (18.30)	-20.53 (46.11)	7.47 (7.01)	5.45 (21.69)	-28.39 (49.28)	11.38 (9.29)	9.87 (11.96)	-19.03 (43.33)	0.30	0.55	0.64
Δ Fit fR start	0.10 (13.56)	-2.40 (-1.61)	-4.70 (37.51)	0.99 (10.99)	-2.84 (-13.19 – 2.27)	1.25 (29.22)	-1.29 (17.49)	5.48 (-9.32 - 8.03)	-13.97 (48.20)	0.73	0.13	0.41
Δ Fit fR coef	-2.55 (-22.81 - 26.30)	-5.78 (-37.40 - 23.90)	14.24 (-55.77 - 94.01)	-0.36 (-19.28 - 26.78)	-17.84 (-49.20 - 13.49)	0.400.80 (-99.76 - 45.01)	-10.07 (-209.85 - 43.35)	6.85 (-18.07 74.27)	94.01 (-15.75 - 185.74)	0.65	0.12	0.09
Δ Fit AX start	1.18 (-23.26 - 20.13)	-3.95 (37.62)	-17.48 (-91.69 - 47.99)	0.16 (33.52)	-2.24 (33.32)	-1.27 (-48.33 – 45.08)	-18.77 (65.50)	-6.60 (45.56)	-21.43 (-167.16 - 61.18)	0.44	0.89	0.61
Δ Fit AX coef	4.67 (-45.85 - 42.14)	4.20 (-59.80 - 30.49)	30.98 (-52.69 - 88.83)	10.54 (-12.08 - 69.69)	-4.79 (-62.70 19.83)	21.78 (-133.43 – 53.05)	1.62 (-379.60 - 34.63)	5.69 (64.34 - 43.96)	49.26 (-36.20 - 133.72)	0.28	0.53	0.26
Δ Fit X5 start	5.81 (-9.85 - 21.91)	-0.46 (-14.06 - 16.09)	-3.76 (-38.85 - 36.61)	4.89 (-5.73 – 27.15)	-7.48 (40.99)	-5.74 (-42.83 – 37.77)	13.67 (-26.49 - 24.69)	3.84 (28.79)	-3.76 (-95.43 - 26.58)	0.90	0.45	0.80
Δ Fit X5 coef	9.31 (-3.75 - 44.13)	0.750 (-53.52 - 44.01)	7.78 (-57.68 - 58.46)	6.15 (-2.12 - 37.74)	7.55 (-53.90 - 41.44)	-2.29 (-126.75 - 32.21)	19.64 (-40.90 - 87.36)	-1.38 (-58.04 – 45.15)	58.46 (-27.87 - 271.40)	0.61	0.85	0.032*
Δ Fit R5 start	-1.31 (-18.63 - 5.41)	-9.99 (17.91)	-14.28 (-28.83 - 7.89)	-4.16 (-18.31 – 2.68)	-8.16 (20.24)	-7.15 (23.02)	0.11 (-24.52 - 4.50)	-12.83 (14.18)	-30.48 (43.78)	0.95	0.52	0.17
Δ Fit R5 coef	8.04 (-36.66 - 30.75)	-10.49 (-25.08 - 12.05)	-1.82 (-117.98 - 23.71)	4.95 (-27.19 - 37.98)	2.15 (-50.96 - 27.59)	-11.94 (-155.64 - 24.79)	-4.43 (-56.96 – 18.79)	-11.99 (20.41 - 2.57)	8.02 (-249.83 - 263.65)	0.49	0.49	0.80
Δ Fit R20 start	-13.45 (23.72)	-11.97 (19.07)	-16.56 (20.54)	-12.32 (25.88)	-8.42 (18.50)	-15.71 (13.44)	-15.21 (21.27)	-17.50 (19.69)	-17.88 (29.40)	0.77	0.29	0.84
Δ Fit R20 coef	1.53 (-39.12 - 30.40)	-11.92 (-36.52 - 16.52)	-64.76 (135.67)	23.07 (-32.66 - 62.07)	-16.55 (-35.11 - 18.01)	-63.81 (162.48)	-4.55 (-41.36 – 8.20)	-8.81 (-43.58 - 18.72)	-66.24 (87.80)	0.19	1.00	0.96
Δ Fit R520 start	-6.53 (-39.74 - 16.81)	-10.01 (37.30)	21.92 (-10.01 - 56.06)	-8.83 (-28.81 - 14.78)	-12.16 (41.64)	13.26 (-55.98 – 30.49)	10.58 (-85.93 - 28.72)	-6.67 (31.41)	48.76 (17.45 - 962.67)	0.66	0.72	0.017*
Δ Fit R520 coef	0.55 (-33.98 - 85.58)	-2.29 (-67.28 - 17.72)	58.37 (23.07 - 180.96)	-2.95 (-44.99 - 46.26)	7.68 (-68.80 - 26.13)	37.62 (10.38 - 96.30)	36.30 (-27.70 – 181.64)	-13.68 (-112.13 - 8.42)	125.36 (51.16 - 215.25)	0.10	0.21	0.12

*Values are given in numbers (%), medians (interquartile ranges), or mean (standard deviations). Imp = impulses, * indicates significant differences*

Table A.10 –FOT parameters for normal (N), maximal slow in- and exhalation (S) and maximal fast in- and exhalation (F) manoeuvres with the mandible in protruded position for successful MAD therapy group versus the non-successful MAD therapy group based on the first definition of MAD success

	All included patients (n=23)			Successful MAD therapy (n=14)			Non-successful MAD therapy (n=9)			P-value		
	N	S	F	N	S	F	N	S	F	N	S	F
Fres	12.05 (3.73)	13.13 (3.00)	15.97 (3.54)	12.37 (3.33)	13.35 (2.82)	16.50 (3.45)	11.56 (4.44)	12.79 (3.42)	15.14 (3.72)	0.65	0.69	0.39
AX	-6.03 (-18.58 - 2.16)	-17.01 (12.82)	-31.81 (19.26)	-6.10 (-19.84 - - 3.54)	-16.15 (-22.06 - - 5.37)	-31.84 (15.02)	-4.75 (-18.29 - - 1.78)	-14.25 (-35.01 - - 6.36)	-31.76 (25.56)	0.45	0.75	0.99
R5	4.21 (1.20)	4.28 (1.07)	4.07 (1.18)	4.39 (1.19)	4.47 (0.98)	4.29 (1.17)	3.93 (1.24)	3.98 (1.19)	3.71 (1.17)	0.38	0.32	0.26
X5	-1.40 (-3.17 - - 1.02)	-2.84 (1.78)	-5.29 (3.26)	-1.37 (-3.20 - - 1.04)	-2.87 (-3.37 - - 1.23)	-5.27 (-7.27 - - 2.97)	-1.40 (-3.08 - - 0.70)	-2.43 (-4.90 - - 1.45)	-2.50 (-8.64 - - 1.98)	0.85	0.71	0.57
R20	3.18 (0.82)	3.12 (0.76)	2.93 (0.69)	3.25 (0.88)	3.25 (0.81)	2.93 (0.55)	3.06 (0.75)	2.91 (0.68)	2.93 (0.90)	0.58	0.30	0.98
R5-R20	1.03 (0.64)	1.16 (0.51)	1.14 (0.78)	1.14 (0.63)	1.22 (0.44)	1.36 (0.82)	0.88 (0.65)	1.07 (0.61)	0.79 (0.58)	0.34	0.53	0.06
Imp. accept	335.00 (295.00 - 388.00)	265.09 (70.63)	60.65 (33.90)	338.57 (45.22)	264.43 (58.58)	63.79 (34.41)	323.67 (81.88)	266.11 (90.22)	55.78 (34.54)	0.63	0.96	0.59
Fit fR start	12.9 (8.59 20.9)	18.1 (5.68)	19.8 (7.12)	15.3 (6.42)	18.1 (5.02)	20.9 (5.98)	13.8 (6.84)	18.1 (6.90)	18.1 (8.71)	0.61	0.99	0.41
Fit fR coef	-2.50E-3 (-8.50E-3 - -0.20E-3)	-1.30E-3 (-3.20E-3 - 0.00E-3)	-2.16E-3 (-3.26E-3 - -0.26E-3)	-3.60E-3 (-8.90E-3 - -0.20E-3)	-0.80E-3 (-3.10E-3 - 0.00E-3)	-2.33E-3 (1.80E-3)	-1.80E-3 (-6.00E-3 - -0.20E-3)	-2.60E-3 (-4.60E-3 - -0.10E-3)	-1.08E-3 (4.19E-2)	0.45	0.37	0.38
Fit AX start	-8.38 (-32.5 -2.25)	-32.7 (-54.0 -- 10.2)	-50.7 (39.5)	-8.98 (-37.2 -- 3.70)	-31.3 (25.1)	-51.8 (32.6)	-7.98 (-37.2 -1.60)	-44.6 (35.8)	-49.07 (50.57)	0.61	0.35	0.89
Fit AX coef	3.40E-3 (0.10E-3 - 29.3E-3)	1.00E-3 (0.90E-3 - 17.3E-3)	9.91E-3 (14.1E-3)	4.40E-3 (0.10E-3 - 3.32E-3)	1.00E-3 (0.90E-3 - 1.33E-3)	11.4E-3 (10.86E-3)	2.20E-3 (0.10E-3 - 1.88E-3)	10.0E-3 (1.90E-3 – 25.2E-3)	7.54E-3 (18.65E-3)	0.53	0.61	0.53
Fit X5 start	-1.81 (-4.83 - - 0.77)	-5.27 (3.99)	-6.07 (-9.62 -3.14)	-1.67 (-5.19 - - 0.89)	-4.21 (-6.57 -1.65)	-6.43 (-10.96 - - 4.67)	-1.81 (-5.30 - - 0.62)	-5.16 (-11.18 - - 1.90)	-3.14 (-12.21 - - 2.09)	0.75	0.53	0.38
Fit X5 coef	0.40E-3 (-0.10E-3 - 2.90E-3)	0.40E-3 (0.00E-3 - 1.70E-3)	0.96E-3 (0.18E-3 - 2.00E-3)	0.60E-3 (-0.10E-3 - 3.90E-3)	0.00E-3 (0.00E-3 - 1.40E-3)	1.18E-3 (0.75E-3 - 2.30E-3)	0.30E-3 (-0.10E-3 - 2.00E-3)	0.98E-3 (0.00E-3 – 3.07E-3)	0.57E-3 (-0.04E-3 - 2.31E-3)	0.90	0.31	0.23
Fit R5 start	5.18 (3.87 6.01)	6.23 (1.55)	4.79 (3.49 6.33)	5.44 (1.93)	6.43 (1.45)	5.10 (3.76 - 7.24)	4.83 (1.57)	5.91 (1.73)	4.46 (3.02 – 6.70)	0.42	0.38	0.26
Fit R5 coef	-1.00E-3 (-2.40E-3 - -0.60E-3)	-0.60E-3 (-1.30E-3 - 0.00E-3)	-0.44E-3 (-1.17E-3 - -0.09E-3)	-1.00E-3 (-3.20E-3 - -0.60E-3)	-0.60E-3 (-1.30E-3 - 0.00E-3)	-0.77E-3 (0.72E-3)	-0.80E-3 (-2.20E-3 – -0.50E-3)	-1.00E-3 (-1.40E-3 – 0.20E-3)	-0.55E-3 (0.60E-3)	0.49	0.66	0.38
Fit R20 start	3.68 (1.07)	4.07 (0.85)	3.65 (1.04)	3.72 (1.20)	4.22 (0.91)	3.61 (0.91)	3.61 (0.88)	3.83 (0.74)	3.70 (1.28)	0.80	0.29	0.86
Fit R20 coef	-0.70E-3 (-0.90E-3 - -0.30E-3)	-0.40E-3 (-0.60E-3 - 0.00E-3)	-0.36E-3 (0.28E-3)	-0.60E-3 (-1.10E-3 - -0.30E-3)	-0.40E-3 (0.35E-3)	-0.35E-3 (0.32E-3)	-0.70E-3 (-0.90E-3 - -0.30E-3)	-0.40E-3 (0.38E-3)	-0.38E-3 (0.22E-3)	0.80	0.70	0.57
Fit R520 start	1.52 (1.14)	2.16 (0.96)	1.41 (0.57 2.46)	1.71 (1.23)	2.22 (0.89)	1.56 (0.98 - 3.04)	1.22 (0.98)	2.07 (1.12)	0.63 (-0.16 - 2.18)	0.30	0.75	0.10
Fit R520 coef	-0.50E-3 (-1.40E-3 - -0.10E-3)	-0.30E-3 (-0.70E-3 - 0.00E-3)	-0.24E-3 (-0.48E-3 - 0.02E-3)	-0.60E-3 (-2.00E-3 - -0.10E-3)	-0.20E-3 (-0.70E-3 - 0.00E-3)	-0.42E-3 (0.49E-3)	-0.20E-3 (-1.00E-3 - 0.00E-3)	-0.50E-3 (0.80E-3 - -0.10E-3)	-0.17E-3 (0.41E-3)	0.41	0.61	0.13

Values are given in numbers (%), medians (interquartile ranges), or mean (standard deviations). Imp = impulses

Table A.11 –FOT parameters for normal (N), maximal slow in- and exhalation (S) and maximal fast in- and exhalation (F) manoeuvres with the mandible in protruded position for successful MAD therapy group versus the non-successful MAD therapy group based on the second definition of MAD success

	All included patients (n=23)			Successful MAD therapy (n=14)			Non-successful MAD therapy (n=9)			P-value		
	N	S	F	N	S	F	N	S	F	N	S	F
Fres	12.05 (3.73)	13.13 (3.00)	15.97 (3.54)	12.95 (3.99)	13.75 (2.93)	18.77 (14.65 - 19.24)	10.66 (2.97)	12.16 (3.02)	12.90 (10.86 – 17.08)	0.13	0.23	0.044*
AX	-6.03 (-18.58 - 2.16)	-17.01 (12.82)	-31.81 (19.26)	-6.10 (-23.67 - - 3.54)	-17.95 (13.06)	-36.09 (14.43)	-4.76 (-10.55 - - 1.78)	-15.55 (13.08)	-25.15 (24.49)	0.23	0.67	0.25
R5	4.21 (1.20)	4.28 (1.07)	4.07 (1.18)	4.56 (1.33)	4.65 (0.99)	4.44 (1.13)	3.66 (0.72)	3.71 (0.97)	3.48 (1.05)	0.047*	0.039*	0.05
X5	-1.40 (-3.17 - - 1.02)	-2.84 (1.78)	-5.29 (3.26)	-1.37 (-3.33 - - 1.04)	-3.00 (1.89)	-5.45 (-7.84 - - 4.34)	-1.40 (-1.85 - - 0.70)	-2.59 (1.68)	-2.30 (-7.08 - - 1.65)	0.53	0.59	0.08
R20	3.18 (0.82)	3.12 (0.76)	2.93 (0.69)	3.38 (0.94)	3.35 (0.79)	2.99 (0.58)	2.86 (0.46)	2.75 (0.59)	2.84 (0.86)	0.10	0.05	0.65
R5-R20	1.03 (0.64)	1.16 (0.51)	1.14 (0.78)	1.19 (0.67)	1.29 (0.48)	1.45 (0.75)	0.79 (0.53)	0.96 (0.51)	0.64 (0.53)	0.14	0.13	0.006*
Imp. accept	335.00 (295.00 - 388.00)	265.09 (70.63)	60.65 (33.90)	324.71 (69.78)	247.29 (69.76)	66.50 (34.40)	345.22 (44.48)	292.78 (66.28)	51.56 (32.95)	0.40	0.13	0.31
Fit fR start	12.9 (8.59 - 20.9)	18.1 (5.68)	19.8 (7.12)	13.8 (9.95 - 24.3)	19.0 (5.49)	21.92 (18.67 – 25.60)	12.37 (8.05 – 16.50)	16.7 (6.00)	11.4 (10.5 - 22.7)	0.28	0.37	0.023*
Fit fR coef	-2.50E-3 (-8.50E-3 - -0.20E-3)	-1.30E-3 (-3.20E-3 - 0.00E-3)	-2.16E-3 (-3.26E-3 - -0.26E-3)	-3.60E-3 (-9.00E-3 - -0.20E-3)	-0.80E-3 (-3.40E-3 - 0.00E-3)	-2.73E-3 (-3.71E-3 - -1.72E-3)	-1.80E-3 (-4.00E-3 - -0.20E-3)	-1.80E-3 (-3.20E-3 - -0.10E-3)	-0.59E-3 (-2.64E-3 - 0.45E-3)	0.45	0.70	0.038*
Fit AX start	-8.38 (-32.5 - - 2.25)	-32.7 (-54.0 - - 10.2)	-50.7 (39.5)	-8.98 (-51.7 - - 3.70)	-37.4 (29.7)	-47.3 (-91.5 - - 30.4)	-7.98 (-18.6 -1.60)	-35.1 (31.46)	-11.62 (-74.80 - - 5.97)	0.31	0.87	0.05
Fit AX coef	3.40E-3 (0.10E-3 - 29.3E-3)	1.00E-3 (0.90E-3 - 17.3E-3)	9.91E-3 (14.1E-3)	4.40E-3 (0.10E-3 – 33.2E-3)	10.0E-3 (0.90E-3 - 15.30E-3)	14.64E-3 (1.30E-3)	2.20E-3 (0.10E-3 - 8.00E-3)	7.90E-3 (1.30E-3 17.4E-3)	2.56E-3 (13.18E-3)	0.61	0.66	0.046*
Fit X5 start	-1.81 (-4.83 - - 0.77)	-5.27 (3.99)	-6.07 (-9.62 - - 3.14)	-1.67 (-.644 - - 0.89)	-5.43 (-6.77 - - 1.65)	-6.93 (-16.80 - - 5.49)	-1.81 (-2.90 - - 0.62)	-4.28 (-9.51 - - 1.31)	-2.57 (-9.21 - - 1.86)	0.66	0.80	0.032*
Fit X5 coef	0.40E-3 (-0.10E-3 - 2.90E-3)	0.40E-3 (0.00E-3 - 1.70E-3)	0.96E-3 (0.18E-3 - 2.00E-3)	0.60E-3 (-0.10E-3 - 3.90E-3)	0.00E-3 (0.00E-3 - 1.60E-3)	1.35E-3 (0.92E-3 - 3.64E-3)	0.30E-3 (-0.10E-3 - 1.00E-3)	0.60E-3 (0.00E-3 - 2.20E-3)	0.18E-3 (-0.20E-3 – 1.34E-3)	0.66	0.66	0.014*
Fit R5 start	5.18 (3.87 - 6.01)	6.23 (1.55)	4.79 (3.49 - 6.33)	5.63 (2.05)	6.75 (1.52)	5.46 (4.18 - 8.90)	4.52 (1.05)	5.42 (1.27)	3.77 (2.83 – 5.07)	0.10	0.035*	0.027*
Fit R5 coef	-1.00E-3 (-2.40E-3 - -0.60E-3)	-0.60E-3 (-1.30E-3 - 0.00E-3)	-0.44E-3 (-1.17E-3 - -0.09E-3)	-1.70E-3 (1.40E-3)	-0.60E-3 (-1.40E-3 - 0.00E-3)	-0.90E-3 (0.72E-3)	-1.10E-3 (0.73E-3)	-0.60E-3 (-1.10E-3 - -0.20E-3)	-0.33E-3 (0.41E-3)	0.15	0.85	0.024*
Fit R20 start	3.68 (1.07)	4.07 (0.85)	3.65 (1.04)	3.87 (1.25)	4.37 (0.89)	3.76 (0.96)	3.39 (0.67)	3.60 (0.55)	3.47 (1.19)	0.25	0.018*	0.54
Fit R20 coef	-0.70E-3 (-0.90E-3 - -0.30E-3)	-0.40E-3 (-0.60E-3 - 0.00E-3)	-0.36E-3 (0.28E-3)	-0.80E-3 (0.66E-3)	-0.40E-3 (0.37E-3)	-0.40E-3 (0.33E-3)	-0.60E-3 (0.44E-3)	-0.30E-3 (0.22E-3)	-0.31E-3 (-0.17E-3)	0.51	0.62	0.41
Fit R520 start	1.52 (1.14)	2.16 (0.96)	1.41 (0.57 - 2.46)	1.77 (1.27)	2.38 (0.98)	1.85 (1.32 - 3.78)	1.14 (0.84)	1.82 (0.89)	0.57 (-0.16 – 1.65)	0.17	0.17	0.008*
Fit R520 coef	-0.50E-3 (-1.40E-3 - -0.10E-3)	-0.30E-3 (-0.70E-3 - 0.00E-3)	-0.24E-3 (-0.48E-3 - 0.02E-3)	-0.90E-3 (0.96E-3)	-0.20E-3 (-0.80E-3 - 0.00E-3)	-0.36E-3 (1.05E-3 - 0.20E-3)	-0.40E-3 (0.52E-3)	-0.30E-3 (-0.50E-3 – 0.10E-3)	0.02E-3 (-0.24E-3 – 0.18E-3)	0.12	1.00	0.008*

*Values are given in numbers (%), medians (interquartile ranges), or mean (standard deviations). Imp = impulses, * indicates significant differences*

Table A.12 –FOT parameters for normal (N), maximal slow in- and exhalation (S) and maximal fast in- and exhalation (F) manoeuvres with the mandible in retracted position for successful MAD therapy group versus the non-successful MAD therapy group based on the first definition of MAD success

	All included patients (n=23)			Successful MAD therapy (n=14)			Non-successful MAD therapy (n=9)			P-value		
	N	S	F	N	S	F	N	S	F	N	S	F
Fres	11.19 (8.88 - 15.46)	13.35 (3.32)	14.75 (3.41)	12.20 (9.41 – 15.61)	12.33 (11.01 - 16.41)	15.53 (3.38)	9.55 (8.74 - 13.58)	12.55 (9.87 - 16.13)	13.54 (3.28)	0.21	1.00	0.18
AX	-5.27 (-14.70 - - 2.58)	-16.58 (12.28)	-24.27 (13.46)	-5.75 (-15.26 - - 3.30)	-11.32 (-22.70 - - 5.24)	-25.44 (10.54)	-3.99 (-14.43 - - 1.92)	-19.94 (-28.56 - - 4.94)	-22.45 (17.65)	0.45	0.61	0.66
R5	4.52 (1.02)	4.76 (1.18)	4.20 (0.81)	4.37 (4.12 - 5.65)	4.85 (1.15)	4.41 (0.75)	4.32 (3.45 – 4.72)	4.62 (1.28)	3.87 (0.84)	0.15	0.66	0.14
X5	-1.33 (-2.17 - - 0.87)	-2.81 (1.64)	-4.53 (2.08)	-1.26 (-2.33 - - 1.01)	-2.52 (-3.55 - - 1.22)	-4.83 (1.81)	-1.33 (-2.50 - - 0.69)	-3.39 (-4.57 - - 1.20)	-4.06 (2.48)	0.90	0.80	0.44
R20	3.56 (0.72)	3.53 (0.85)	3.19 (0.64)	3.69 (0.74)	3.54 (0.93)	3.25 (0.67)	3.37 (0.69)	3.51 (0.77)	3.09 (0.62)	0.30	0.93	0.55
R5-R20	0.96 (0.53)	1.24 (0.55)	1.01 (0.44)	1.11 (0.55)	1.31 (0.43)	1.16 (0.46)	0.72 (0.42)	1.11 (0.69)	0.79 (0.31)	0.07	0.45	0.032*
Imp. accept	300.91 (55.40)	243.91 (71.57)	74.61 (43.23)	310.29 (44.93)	249.21 (76.12)	82.79 (45.27)	286.33 (69.04)	235.67 (67.41)	61.89 (38.87)	0.37	0.66	0.25
Fit fR start	12.9 (9.42 - 20.5)	18.6 (6.84)	19.4 (6.36)	13.90 (9.84 – 20.62)	18.3 (5.51)	20.6 (4.89)	10.2 (8.92 - 18.7)	19.1 (8.90)	17.5 (8.11)	0.57	0.82	0.32
Fit fR coef	-1.40E-3 (-6.70E-3 - -0.50E-3)	-1.60E-3 (-2.90E-3 - 0.00E-3)	-2.55E-3 (2.27E-3)	-2.50E-3 (-8.50E-3 - -0.40E-3)	-1.40E-3 (-3.1E-3 - 0.00E-3)	-2.14E-3 (-4.43E-3 - -1.39E-3)	-1.40E-3 (-5.00E-3 - -0.30E-3)	-2.20E-3 (-5.90E-3 - -0.10E-3)	-1.55E-3 (-3.19E-3 – 0.12E-3)	0.66	0.57	0.21
Fit AX start	-7.97 (-22.2 - - 3.01)	-32.1 (-54.7 - - 8.79)	-35.5 (-59.6 -14.6)	-8.60 (-24.7 - - 3.56)	-21.8 (-47.4 -8.59)	-48.8 (-58.9 - - 26.7)	-4.68 (-27.4 - - 2.47)	-38.7 (-67.1 - - 9.53)	-33.2(-70.4 - - 7.41)	0.57	0.53	0.28
Fit AX coef	2.60E-3 (0.50E-3 - 14.3E-3)	8.70E-3 (0.20E-3 - 0.30E-3)	7.17E-3 (3.11E-3 13.26E-3)	3.50E-3 (0.40E-3 - 18.4E-3)	6.50E-3 (1.90E-3 - 15.5E-3)	7.92E-3 (4.33E-3 - 16.16E-3)	1.00E-3 (0.20E-3 - 13.6E-3)	9.80E-3 (1.90E-3 - 25.0E-3)	6.45E-3 (-0.47E-3 - 12.20E-3)	0.80	0.57	0.26
Fit X5 start	-1.46 (-2.77 - - 0.73)	-5.19 (3.96)	-6.15 (-10.90 - 2.92)	-1.53 (-3.24 - - 0.84)	-4.57 (3.37)	-7.17 (-12.1 - - 5.06)	-1.39 (-4.29 -0.65)	-6.15 (4.80)	-4.62 (-9.94 - - 2.27)	1.00	0.41	0.23
Fit X5 coef	0.20E-3 (-0.20E-3 - 1.10E-3)	0.30E-3 (0.00E-3 - 1.40E-3)	1.00E-3 (0.42E-3 2.75E-3)	0.20E-3 (-0.20E-3 - 1.70E-3)	0.30E_3 (0.00E-3 - 1.20E_3)	1.04E-3 (0.73E-3 - 2.97E-3)	0.20E-3 (-0.20E-3 - 1.90E-3)	0.20E-3 (0.00E-3 - 1.50E-3)	0.75E-3 (0.05E-3 - 1.78E-3)	0.85	0.95	0.19
Fit R5 start	5.51 (1.56)	6.86 (2.16)	5.72 (1.67)	5.13 (4.53 - 6.75)	6.81 (2.00)	5.96 (1.50)	5.19 (4.10 – 6.22)	6.95 (2.51)	5.35 (1.94)	0.31	0.89	0.44
Fit R5 coef	-1.00E-3 (-2.40E-3 - -0.60E-3)	-0.70E-3 (-1.30E-3 - 0.00E-3)	-5.72E-3 (-1.00E-3 -0.44E-3)	-1.0E-3 (-2.60E-3 - -0.60E-3)	-0.80E-3 (-1.40E-3 - 0.00E-3)	-0.61E-3 (-1.31E-3 - -0.51E-3)	-1.00E-3 (-2.60E-3 - -0.60E-3)	-0.70E-3 (-1.10E-3 - 0.00E-3)	-0.48E-3 (-0.92E-3 - -0.32E-3)	0.85	0.57	0.21
Fit R20 start	4.04 (0.90)	4.55 (1.19)	4.14 (0.98)	4.09 (0.92)	4.51 (1.29)	4.16 (0.87)	3.97 (0.91)	4.61 (1.08)	4.11 (1.18)	0.77	0.83	0.92
Fit R20 coef	-0.50E-3 (-1.00E-3 - -0.40E-3)	-0.40E-3 (-0.80E-3 - 0.00E-3)	-0.43E-3 (-0.63E-3 - -0.34E-3)	-0.50E-3 (-0.70E-3 -0.30E-3)	-0.40E-3 (-0.80E-3 - 0.00E-3)	-0.53E-3 (0.24E-3)	-0.80E-3 (-1.10E-3 - -0.40E-3)	-0.40E-3 (-0.70E-3 - 0.00E-3)	-0.53E-3 (0.36E-3)	0.41	0.75	1.00
Fit R520 start	1.47 (1.00)	2.31 (1.21)	1.35 (0.96 - 1.85)	1.68 (1.05)	2.30 (0.98)	1.39 (1.14 2.14)	1.14 (0.88)	2.34 (1.57)	0.98 (0.73 - 1.46)	0.20	0.95	0.06
Fit R520 coef	-0.30E-3 (-1.40E-3 - -0.10E-3)	-0.30E-3 (-0.60E-3 - 0.00E-3)	-0.21E-3 (-0.33E-3 - -0.10E-3)	-0.50E-3 (-1.70E-3 -0.30E-3)	-0.30E-3 (-0.70E-3 - 0.00E-3)	-0.27E-3 (-0.47E-3 - -0.15E-3)	-0.10E-3 (-1.00E-3 - 0.00E-3)	-0.40E-3 (-0.50E-3 - 0.00E-3)	-0.14E-3 (-0.25E-3 - -0.03E-3)	0.13	0.66	0.13

Values are given in numbers (%), medians (interquartile ranges), or mean (standard deviations). Imp = impulses

Table A.13 –FOT parameters for normal (N), maximal slow in- and exhalation (S) and maximal fast in- and exhalation (F) manoeuvres with the mandible in retracted position for successful MAD therapy group versus the non-successful MAD therapy group based on the second definition of MAD success

	All included patients (n=23)			Successful MAD therapy (n=14)			Non-successful MAD therapy (n=9)			P-value		
	N	S	F	N	S	F	N	S	F	N	S	F
Fres	11.19 (8.88 - 15.46)	13.35 (3.32)	14.75 (3.41)	12.70 (3.36)	14.13 (3.29)	15.66 (3.39)	10.35 (2.44)	12.13 (3.15)	13.35 (3.11)	0.07	0.16	0.11
AX	-5.27 (-14.70 - - 2.58)	-16.58 (12.28)	-24.27 (13.46)	-6.18 (-17.65 - - 3.30)	-17.96 (13.16)	-27.23 (11.14)	-3.99 (-7.34 - - 1.92)	-14.44 (11.18)	-19.67 (16.05)	0.19	0.50	0.24
R5	4.52 (1.02)	4.76 (1.18)	4.20 (0.81)	4.87 (1.05)	5.05 (1.17)	4.47 (0.79)	3.99 (0.75)	4.31 (1.10)	3.77 (0.68)	0.029*	0.14	0.036*
X5	-1.33 (-2.17 - - 0.87)	-2.81 (1.64)	-4.53 (2.08)	-1.26 (-2.83 - -1.01)	-2.98 (1.68)	-5.28 (1.98)	-1.33 (-1.44 - - 0.69)	-2.55 (1.63)	-3.35 (1.72)	0.53	0.56	0.023*
R20	3.56 (0.72)	3.53 (0.85)	3.19 (0.64)	3.72 (0.74)	3.67 (0.91)	3.29 (0.70)	3.32 (0.66)	3.31 (0.75)	3.02 (0.54)	0.20	0.32	0.31
R5-R20	0.96 (0.53)	1.24 (0.55)	1.01 (0.44)	1.15 (0.55)	1.39 0.48)	1.20 (0.86 – 1.39)	0.67 (0.35)	1.00 (0.59)	0.82 (0.52 - 0.94)	0.018*	0.12	0.017*
Imp. accept	300.91 (55.40)	243.91 (71.57)	74.61 (43.23)	298.14 (61.45)	233.93 (84.25)	91.50 (44.50 – 125.75)	305.22 (47.63)	259.44 (45.90)	40.00 (31.50 - 90.50)	0.76	0.36	0.16
Fit fR start	12.9 (9.42 - 20.5)	18.6 (6.84)	19.4 (6.36)	14.4 (9.84 – 21.2)	19.9 (7.28)	21.7 (5.91)	10.2 (8.92 - 14.8)	16.5 (5.88)	15.9 (5.64)	0.35	0.23	0.031*
Fit fR coef	-1.40E-3 (-6.70E-3 - -0.50E-3)	-1.60E-3 (-2.90E-3 - 0.00E-3)	-2.55E-3 (2.27E-3)	--2.50E-3 (-8.50E-3 - -0.40E-3)	-1.50E-3 (-4.50E-3 - -0.40E-3)	-3.32E-3 (2.38E-3)	-1.40E-3 (-3.40E-3 - -0.30E-3)	-1.80E-3 (-2.60E-3 - 0.00E-3)	-1.35E-3 (1.53E-3)	0.53	0.59	0.025*
Fit AX start	-7.97 (-22.2 - - 3.01)	-32.1 (-54.7 - - 8.79)	-35.5 (-59.6 - - 14.6)	-8.93 (-33.3 - -3.56)	-33.3 (-57.6 - - 8.84)	-53.2 (-62.9 - - 33.4)	-4.68 (-13.6 - - 2.47)	-31.9 (-52.3 - - 5.07)	-24.9 (-50.2 - - 7.41)	0.35	0.61	0.044*
Fit AX coef	2.60E-3 (0.50E-3 - 14.3E-3)	8.70E-3 (0.20E-3 - 0.30E-3)	7.17E-3 (3.11E-3 - 13.26E-3)	3.80E-3 (0.40E-3 - 22.8E-3)	9.40E-3 (2.10E-3 - 21.4E-3)	10.32E-3 (5.18E-3 - 18.76E-3)	1.00E-3 (0.20E-3 - 5.70E-3)	7.60E-3 (0.10E-3 – 15.9E-3)	4.73E-3 (-0.47E-3 – 10.24E-3)	0.57	0.51	0.044*
Fit X5 start	-1.46 (-2.77 - - 0.73)	-5.19 (3.96)	-6.15 (-10.9 - - 2.92)	-1.53 (-4.94 - -0.84)	-5.48 (4.13)	-9.61 (5.77)	-1.39 (-2.26 - - 0.65)	-4.74 (3.87)	-4.78 (3.29)	0.71	0.67	0.019*
Fit X5 coef	0.20E-3 (-0.20E-3 - 1.10E-3)	0.30E-3 (0.00E-3 - 1.40E-3)	1.00E-3 (0.42E-3 - 2.75E-3)	0.20E-3 (-0.20E-2 - 3.00E-3)	0.40E-3 (0.00E-3 - 1.80E-3)	1.53E-3 (0.84E-3 - 3.53E-3)	0.20E-3 (-0.20E-3 - 0.80E-3)	0.00E-3 (0.00E-3 - 1.20E-3)	0.72E-3 (0.05E-3 1.46E-3)	0.95	0.28	0.020*
Fit R5 start	5.51 (1.56)	6.86 (2.16)	5.72 (1.67)	5.44 (4.53 - 7.39)	7.34 (2.35)	6.27 (1.80)	5.19 (4.10 – 5.53)	6.11 (1.68)	4.87 (1.03)	0.28	0.16	0.027*
Fit R5 coef	-1.00E-3 (-2.40E-3 - -0.60E-3)	-0.70E-3 (-1.30E-3 - 0.00E-3)	-5.72E-3 (-1.00E-3 - -0.44E-3)	-1.10E-3 (-2.60E-3 - - 0.60E-3)	-1.10E-3 (0.95E-3)	-0.75E-3 (-1.45E-3 - -0.51E-3)	-1.00E-3 (-1.40E-3 - -0.60E-3)	-0.50E-3 (0.49E-3)	-0.48E-3 (-0.83E-3 - -0.32E-3)	0.57	0.037*	0.038*
Fit R20 start	4.04 (0.90)	4.55 (1.19)	4.14 (0.98)	4.14 (0.93)	4.75 (1.31)	4.31 (1.04)	3.88 (0.88)	4.23 (0.95)	3.86 (0.86)	0.51	0.28	0.28
Fit R20 coef	-0.50E-3 (-1.00E-3 - -0.40E-3)	-0.40E-3 (-0.80E-3 - 0.00E-3)	-0.43E-3 (-0.63E-3 - -0.34E-3)	-0.60E-3 (-1.00E-3 - -0.30E-3)	-0.50E-3 (0.43E-3)	-0.59E-3 (0.30E-3)	-0.40E-3 (-1.10E-3 - -0.40E-3)	-0.30E-3 (0.29E-3)	-0.43E-3 (0.24E-3)	0.75	0.08	0.17
Fit R520 start	1.47 (1.00)	2.31 (1.21)	1.35 (0.96 - 1.85)	1.76 (1.07)	2.59 (1.32)	1.56 (1.14 - 2.72)	1.02 (0.74)	1.88 (0.94)	0.98 (0.73 – 1.40)	0.06	0.15	0.017*
Fit R520 coef	-0.30E-3 (-1.40E-3 - -0.10E-3)	-0.30E-3 (-0.60E-3 - 0.00E-3)	-0.21E-3 (-0.33E-3 - -0.10E-3)	-0.50E-3 (-1.70E-3 - -0.30E-3)	-0.40E-3 (-0.90E-3 - -0.10E-3)	-0.28E-3 (-0.62E-3 - -0.15E-3)	-0.10E-3 (-0.60E-3 - 0.00E-3)	-0.10E-3 (-0.40E-3 - 0.00E-3)	-0.14E-3 (-0.21E-3 – 0.03E-3)	0.08	0.10	0.032*

*Values are given in numbers (%), medians (interquartile ranges), or mean (standard deviations). Imp = impulses, * indicates significant differences*

Table A.14 – Secondary FOT parameters for the successful MAD therapy group versus the non-successful MAD therapy group during normal breathing.

	All included patients (n=23)	Successful MAD therapy (n=14)	Non-successful MAD therapy (n=9)	P-value	AUC (95% CI)	Sens (95% CI)	Spec (95% CI)	PPV (95% CI)	NPV (95% CI)
Second definition of MAD success									
Re_R5_mean	4.52 (4.36)	4.87 (1.05)	3.99 (0.75)	0.029	0.71 (0.50 0.93)	0.50 (0.23 0.77)	0.89 (0.52 1.00)	0.88 (0.47 1.00)	0.53 (0.27 0.79)
Pr_R5_mean	4.21 (1.20)	4.56 (1.33)	3.66 (0.72)	0.047	0.69 (0.47 0.91)	0.50 (0.23 0.77)	1.00 (0.66 1.00)	1.00 (0.59 1.00)	0.56 (0.29 0.80)
Re_R520_mean	0.96 (0.53)	1.15 (0.55)	0.67 (0.35)	0.018	0.77 (0.57 0.97)	0.71 (0.42 0.92)	0.89 (0.52 1.00)	0.91 (0.59 1.00)	0.67 (0.35 0.90)

Values are given in medians (interquartile ranges), or mean (standard deviations). Re = retracted position of the mandible, Pr = protruded position of the mandible, R5 = resistance at 5 Hz, R520 = resistance at 5 Hz minus the resistance at 20 Hz, AUC = area under the curve, *Spec = specificity, Sens = sensitivity, PPV = positive predictive value, NPV = negative predictive value with the 95% confidence interval.*

Table A.15 – Secondary FOT parameters for the successful MAD therapy group versus the non-successful MAD therapy group for maximal slow in- and expiration

	All included patients (n=23)	Successful MAD therapy (n=14)	Non-successful MAD therapy (n=9)	P-value	AUC (95% CI)	Sens (95% CI)	Spec (95% CI)	PPV (95% CI)	NPV (95% CI)
Second definition of MAD success									
Pr_R5_total_mean	4.28 (1.07)	4.65 (0.99)	3.71 (0.97)	0.039	0.75 (0.55 0.96)	0.71 (0.42 0.92)	0.78 (0.40 0.92)	0.83 (0.52 0.98)	0.64 (0.31 0.89)
Pr_Fit_R5_start	6.23 (1.55)	6.75 (1.52)	5.42 (1.27)	0.035	0.73 (0.53 0.94	0.43 (0.35 0.87)	1.00 (0.66 1.00)	1.00 (0.54 1.00)	0.53 (0.28 0.77)
Pr_Fit_R20_start	4.07 (0.85)	4.37 (0.89)	3.60 (0.55)	0.018	0.76 (0.56 0.96)	0.79 (0.49 0.95)	0.78 (0.40 0.97)	0.85 (0.55 0.98)	0.70 (0.35 0.93)
Re_Fit_R5_coef	-0.70E-3 (-1.30E-3 0.00E-3)	-1.10E-3 (0.95E-3)	-0.50E-3 (0.49E-3)	0.037	0.72 [0.51 0.93]	1.00 [0.77 1.00]	0.44 [0.14 0.79]	0.74 [0.49 0.91]	1.00 [0.40 1.00]

Values are given in medians (interquartile ranges), or mean (standard deviations), Pr = mandible in protruded position, R5 = resistance at 5 Hz, R20 = resistance at 20 Hz, Fit = the linear approximation of the relationship between the parameter and the volume during breathing, start gives the y-intercept of this linear approximation and coef the coefficient, AUC = area under the curve, *Spec = specificity, Sens = sensitivity, PPV = positive predictive value, NPV = negative predictive value with the 95% confidence interval.*

Table A.16 – Secondary significant FOT parameters for the successful MAD therapy group versus the non-successful MAD therapy group for maximal fast in- and expiration for the mandible in protruded position

	All included patients (n=23)	Successful MAD therapy Def 2 (n=14)	Non-successful MAD therapy Def 1 (n=9)	P-value	AUC (95% CI)	Sens (95% CI)	Spec (95% CI)	PPV (95% CI)	NPV (95% CI)
fres_total_mean	16.0 (3.54)	18.8 (14.7 - 19.2)	12.9 (10.9 – 17.1)	0.044	0.75 (0.53 0.98)	0.93 (0.66 1.00)	0.56 (0.21 0.86)	0.76 (0.50 0.93)	0.83 (0.36 1.00)
R520_total_mean	1.14 (0.78)	1.45 (0.75)	0.64 (0.53)	0.006	0.83 (0.67 1.00)	0.79 (0.49 0.95)	0.78 (0.40 0.97)	0.85 (0.55 098)	0.70 (0.35 0.93)
Fit_fR_start	19.8 (7.12)	21.9 (18.7 – 25.6)	11.4 (10.5 - 22.7)	0.023	0.79 (0.57 1.00)	0.93 (0.66 1.00)	0.67 (0.30 0.93)	0.81 (0.54 0.96)	0.86 (0.42 1.00)
Fit_fR_coef	-2.20E-3 (-3.30E-3 -0.30E-3)	-2.73E-3 (-3.71E-3 - -1.72E-3)	-0.60E-3 (-2.60E-3 0.50E-3)	0.038	0.76 (0.54 0.99)	0.79 (0.49 0.95)	0.76 (0.40 0.97)	0.85 (0.55 0.98)	0.70 (0.35 0.93)
Fit_AX_coef	0.01 (0.01)	0.01 (0.01)	0.00 (0.01)	0.046	0.74 (0.52 0.96)	0.93 (0.66 1.00)	0.56 (0.21 0.86)	0.76 (0.50 0.93)	0.83 (0.36 1.00)
Fit_X5_start	-6.07 (-9.62 - -3.14)	-6.93 (-16.80 - -5.49)	-2.26 (-9.21 - -1.86)	0.032	0.78 (0.57 0.98)	0.64 (0.35 0.87)	1.00 (0.66 1.00)	1.00 (0.59 1.00)	0.64 (0.35 0.87)
Fit_X5_coef	0.96E-3 (0.18E-3 - 0.20E-3)	1.35E-3 (0.92E-3 - 03.64E-3)	0.18E-3 (-0.20E-3 – 1.34E-3)	0.014	0.81 (0.61 1.00)	0.86 (0.57 0.98)	0.78 (0.40 0.97)	0.86 (0.57 0.98)	0.78 (0.40 0.97)
Fit_R5_start	4.79 (3.49 - 6.33)	5.46 (4.18 - 8.90)	4.12 (1.76)	0.027	0.78 (0.58 0.97)	0.71 (0.42 0.92)	0.76 (0.40 0.97)	0.83 (0.52 0.98)	0.64 (0.31 0.89)
Fit_R5_coef	-0.44E-3 (-1.17E-3 - -0.09E-3)	-0.90E-3 (0.72E-3)	-0.33E-3 (0.41E-3)	0.024	0.77 (0.57 0.97)	0.79 (0.49 0.95)	0.67 (0.30 0.93)	0.79 (0.49 0.95)	0.67 (0.30 0.93)
Fit_R520_start	1.41 (0.57 - 2.46)	1.85 (1.32 - 3.78)	0.57 (-0.16 – 1.65)	0.008	0.83 (0.66 1.00)	0.93 (0.66 1.00)	0.67 (0.30 0.93)	0.81 (0.54 1.00)	0.86 (0.42 1.00)
Fit_R520_coef	-0.24E-3 (-0.48E-3 - 0.02E-3)	-0.36E-3 (-1.05E-3- -0.20E-3)	0.02E-3 (-0.24E-3 – 0.18E-3)	0.008	0.83 (0.65 1.00)	0.79 (0.49 0.95)	0.78 (0.40 0.97)	0.85 (0.55 0.98)	0.70 (0.35 0.93)

Values are given in medians (interquartile ranges), or mean (standard deviations), Pr = mandible in protruded position, R5 = resistance at 5 Hz, R20 = resistance at 20 Hz, Fit = the linear approximation of the relationship between the parameter and the volume during breathing, start gives the y-intercept of this linear approximation and coef the coefficient, AUC = area under the curve, *Spec = specificity, Sens = sensitivity, PPV = positive predictive value, NPV = negative predictive value with the 95% confidence interval. ** These parameters predict MAD failure instead of success.*

Table A.17 – Secondary significant FOT parameters for the successful MAD therapy group versus the non-successful MAD therapy group for maximal fast in- and expiration for the mandible in retracted position

	All included patients (n=23)	Successful MAD therapy (n=14)	Non-successful MAD therapy (n=9)	P-value	AUC (95% CI)	Sens (95% CI)	Spec (95% CI)	PPV (95% CI)	NPV (95% CI)
First definition of MAD success									
R520_total_mean	1.01 (0.44)	1.16 (0.46)	0.79 (0.31)	0.032	0.76 (0.56 0.96)	0.64 (0.35 0.87)	0.89 (0.53 1.00)	0.90 (0.55 1.00)	0.62 (0.32 0.86)
Second definition of MAD success									
R5_total_mean	4.20 (0.81)	4.47 (0.79)	3.77 (0.68)	0.036	0.72 (0.51 0.93)	0.64 (0.35 0.87)	0.78 (0.40 0.97)	0.82 (0.48 0.98)	0.58 (0.28 0.85)
R520_total_mean	1.01 (0.44)	1.20 (0.86 – 1.39)	0.82 (0.52 - 0.94)	0.023	0.80 (0.62 0.98)	0.64 (0.35 0.87)	1.00 (0.66 1.00)	1.00 (0.66 1.00)	0.64 (0.35 0.87)
X5_total_mean	-4.53 (2.08)	-5.28 (1.98)	-3.35 (1.72)	0.017	0.75 (0.52 0.97)	0.79 (0.49 0.97)	0.78 (0.40 0.97)	0.85 (0.55 0.98)	0.70 (0.35 0.93)
Fit_fR_start	19.4 (6.36)	21.7 (5.91)	15.9 (5.64)	0.031	0.76 (0.56 0.97)	0.71 (0.42 0.92)	0.78 (0.40 0.97)	0.83 (0.52 0.98)	0.64 (0.31 0.89)
Fit_fR_coef	-2.50E-3 (2.27E-3)	-3.30E-3 (2.38E-3)	-1.30E-3 (1.53E-3)	0.025	0.73 (0.52 0.95)	1.00 (0.77 1.00)	0.44 (0.14 0.79)	0.74 (0.49 0.91)	1.00 (0.40 1.00)
Fit_AX_start	-35.5 (-59.6 - -14.6)	-53.2 (-62.9 - -33.4)	-24.9 (-50.2 - -7.41)	0.044	0.75 (0.52 0.98)	0.79 (0.49 0.95)	0.78 (0.40 0.97)	0.85 (0.55 0.98)	0.70 (0.35 0.93)
Fit_AX_coef	7.20E-3 (3.10E-3 - 13.3E-3)	10.3E-3 (5.2E-3 - 18.8E-3)	4.73E-3 (-0.47E-3 – 10.24E-3)	0.044	0.75 (0.55 0.96)	0.50 (0.23 0.77)	0.89 (0.52 1.00)	0.88 (0.47 1.00)	0.53 (0.27 0.79)
Fit_X5_start	-6.15 (-10.90 - -2.92)	-9.61 (5.77)	-4.78 (3.29)	0.019	0.78 (0.58 0.98)	0.64 (0.35 0.87)	0.89 (0.52 1.00)	0.90 (0.55 1.00)	0.62 (0.32 0.86)
Fit_X5_coef	1.00E-3 (0.40E-3 - 2.80E-3)	1.50E-3 (0.80E-3 - 3.50E-3)	0.72E-3 (0.05E-3 1.46E-3)	0.020	0.79 (0.61 0.98)	0.50 (0.23 0.77)	1.00 (0.66 1.00)	1.00 (0.59 1.00)	0.56 (0.30 0.80)
Fit_R5_start	5.72 (1.67)	6.27 (1.80)	4.89 (1.03)	0.027	0.73 (0.53 0.94)	0.43 (0.18 0.71)	1.00 (0.66 1.00)	1.00 (0.54 1.00)	0.53 (0.28 0.77)
Fit_R5_coef	-0.60E-3 (-1.00E-3 - -0.40E-3)	-0.80E-3 (-1.50E-3 - -0.50E-3)	-0.48E-3 (-0.83E-3 - -0.32E-3)	0.038	0.76 (0.56 0.96)	0.57 (0.29 0.82)	0.89 (0.52 1.00)	0.89 (0.52 1.00)	0.57 (0.29 0.82)
Fit_R520_start	1.34 (0.96 - 1.85)	1.96 (1.08)	1.00 (0.39)	0.017	0.80 (0.62 0.99)	0.50 (0.23 0.77)	1.00 (0.66 1.00)	1.00 (0.59 1.00)	0.56 (0.30 0.80)
Fit_R520_coef	-0.20E-3 (-0.30E-3 - -0.10E-3)	-0.30E-3 (-0.60E-3 - -0.20E-3)	-0.14E-3 (-0.21E-3 – 0.03E-3)	0.032	0.77 (0.58 0.96)	0.86 (0.57 0.98)	0.67 (0.30 0.93)	0.80 (0.52 0.96)	0.75 (0.35 0.97)

Values are given in medians (interquartile ranges), or mean (standard deviations), R5 = resistance at 5 Hz, R520 = difference in resistance between 5 and 20 Hz (5Hz – 20Hz), X5 = reactance at 5 Hz, AX = area under the reactance curve, fR = resonance frequency, Fit = the linear approximation of the relationship between the parameter and the volume during breathing, start gives the y-intercept of this linear approximation and coef the coefficient, AUC = area under the curve, *Spec = specificity, Sens = sensitivity, PPV = positive predictive value, NPV = negative predictive value with the 95% confidence interval. ** These parameters predict MAD failure instead of success.*

Table A.18 – Secondary significant FOT parameters for the successful MAD therapy group versus the non-successful MAD therapy group for maximal fast in- and expiration for the difference in mandible position (protruded – retracted)

	All included patients (n=23)	Successful MAD therapy (n=14)	Non-successful MAD therapy (n=9)	P-value	AUC (95% CI)	Sens (95% CI)	Spec (95% CI)	PPV (95% CI)	NPV (95% CI)
Second definition of MAD success									
Δ Fit_X5_coef_rel	7.78 (-57.7 - 58.5)	-2.29 (-127 - 32.3)	58.5 (-27.9 - 271)	0.032	0.77 (0.55 0.99)	0.64 (0.35 0.87)	0.89 (0.52 1.00)	0.90 (0.55 1.00)	0.62 (0.32 0.86)
Δ Fit_R520_start_rel	21.9 (-10.0 - 56.1)	36.3 (-27.7 - 182)	48.8 (17.5 - 963)	0.017	0.80 (0.60 1.00)	0.79 (0.49 0.95)	0.89 (0.52 1.00)	0.92 (0.62 1.00)	0.73 (0.39 0.94)

Values are given in medians (interquartile ranges), or mean (standard deviations, R520 = difference in resistance between 5 and 20 Hz (5Hz – 20Hz), X5 = reactance at 5 Hz, Fit = the linear approximation of the relationship between the parameter and the volume during breathing, start gives the y-intercept of this linear approximation and coef the coefficient, AUC = area under the curve, *Spec = specificity, Sens = sensitivity, PPV = positive predictive value, NPV = negative predictive value with the 95% confidence interval. ** These parameters predict MAD failure instead of success.*

Section D.4 – Negative Expiratory Pressure

Table A.19 – Absolute differences in NEP parameters for the MAD successful and MAD non-successful group, based on the first definition of MAD success

	All included patients (n=23)	Successful MAD therapy (n=14)	Non-successful MAD therapy (n=9)	P-value
Δ Flow drop				
Median	-0.03 (-0.17 - 0.03)	-0.03 (-0.17 - 0.05)	-0.01 (-0.23 - 0.03)	1.00
Max	0.00 (-0.02 - 0.03)	-0.05 (-1.22 - 0.04)	0.00 (-0.01 - 0.03)	0.66
Δ Percentage below				
Median	0.50 (-0.50 - 12.44)	0.00 (-0.87 - 13.93)	1.49 (-0.37 - 11.19)	0.51
Max	-2.92 (37.27)	-4.48 (-23.13 – 11.57)	11.94 (-23.38 - 34.58)	0.19
Δ $V_{0.2}/V_{0.2}$				
Median	0.00 (0.01)	0.00 (-0.01 – 0.01)	0.00 (-0.01 - 0.01)	0,85
Max	0.01 (0.05)	0.01 (0.05)	-0.00 (0.06)	0.57
Δ $V_{0.2}/V_{1}$				
Median	0.04 (-0.04 - 0.11)	0.00 (-0.10 - 0.11)	0.05 (-0.00 – 0.16)	0.41
Max	0.04 (-0.22 - 0.28)	0.04 (-0.37 - 0.17)	0.07 (-0.01 - 0.33)	0.35
Δ $V_{0.5}/V_{0.5}$				
Median	0.01 (0.04)	0.02 (0.04)	-0.00 (0.04)	0.37
Max	0.05 (-0.03 - 0.09)	0.00 (-0.06 – 0.14)	0.05 (-0.00 - 0.08)	0.75
Δ $V_{0.5}/V_{1}$				
Median	0.06 (-0.17 - 0.36)	-0.08 (-0.35 - 0.27)	0.17 (-0.02 – 0.36)	0.21
Max	0.01 (-0.58 - 0.57)	-0.03 (-1.55 - 0.66)	0.29 (-0.09 - 0.64)	0.61

Values are given in numbers (%), medians (interquartile ranges), or mean (standard deviations).

Table A.20 – NEP parameters for the mandible in retracted position for both definitions of MAD success

	All included patients (n=23)	Successful MAD therapy (n=14)		Non-successful MAD therapy (n=9)		P-value	
		Def 1	Def 2	Def 1	Def 2	Def 1	Def 2
N measurements	5.00 (5.00 - 5.00)	5.00 (5.00 - 5.00)	5.00 (5.00 - 5.00)	5.00 (4.00 - 5.00	5.00 (4.00 - 5.00)	0.22	0.033*
Flow drop							
Median	0.86 (0.59 - 0.95)	0.78 (0.59 - 0.94)	0.70 (0.59 – 0.92)	0.86 (0.61 – 0.95)	0.87 (0.66 - 0.95)	0.56	0.21
Max	0.94 (0.76 - 0.99)	0.93 (0.74 - 0.99)	0.90 (0.74 - 0.97)	0.94 (0.87 – 0.98)	0.95 (0.87 - 0.99)	0.57	0.21
Percentage below							
Median	1.00 (0.50 - 14.93)	0.50 (0.44 - 16.79)	0.75 (0.50 - 16.79)	1.00 (1.00 - 13.18)	1.00 (0.87 - 10.45)	0.13	0.57
Max	30.85 (1.49 - 41.79)	30.88 (30.09)	25.73 (22.58)	26.92 (26.06)	34.94 (35.70)	0.74	0.50
$V_{0.2}/V_{0.2}$							
Median	0.04 (0.01)	0.04 (0.01)	0.04 (0.01)	0.05 (0.02)	0.05 (0.02)	0.44	0.26
Max	0.12 (0.05)	0.12 (0.05)	0.12 (0.05)	0.13 (0.05)	0.13 (0.05)	0.46	0.53
$V_{0.2}/V_1$							
Median	0.24 (0.18 - 0.76)	0.24 (0.21 - 1.06)	0.27 (0.22 - 1.12)	0.21 (0.16 - 0.64)	0.21 (0.16 - 0.34)	0.28	0.09
Max	0.37 (0.24 - 1.05)	0.52 (0.25 - 1.31)	0.69 (0.28 - 8.74)	0.26 (0.19 - 1.06)	0.25 (0.19 - 0.43)	0.23	0.032*
$V_{0.5}/V_{0.5}$							
Median	0.12 (0.04)	0.11 (0.04)	0.11 (0.03)	0.13 (0.05)	0.13 (0.05)	0.31	0.17
Max	0.29 (0.22 - 0.41)	0.32 (0.11)	0.31 (0.12)	0.36 (0.17)	0.37 (0.17)	0.47	0.37
$V_{0.5}/V_1$							
Median	0.73 (0.54 - 1.89)	0.77 (0.67 - 2.45)	0.91 (0.67 - 3.19)	0.64 (0.43 - 1.92)	0.64 (0.43 - 0.85)	0.17	0.05
Max	0.81 (0.75 - 2.82)	1.15 (0.77 - 3.20)	1.63 (0.79 18.20)	0.76 (0.52 - 2.93)	0.76 (0.52 - 1.21)	0.23	0.032*

*Values are given in numbers (%), medians (interquartile ranges), or mean (standard deviations), * indicates significant differences between the MAD successful and non-successful group.*

Table A.21 – NEP parameters for the mandible in protruded position for both definitions of MAD success

	All included patients (n=23)	Successful MAD therapy (n=14)		Non-successful MAD therapy (n=9)		P-value	
		Def 1	Def 2	Def 1	Def 2	Def 1	Def 2
N measurements	5.00 (5.00 - 5.00)	5.00 (5.00 - 5.00)	5.00 (5.00 - 5.00)	5.00 (5.00 - 5.00)	5.00 (5.00 - 5.00)	0.16	0.16
Flow drop							
Median	0.78 (0.41 - 0.97)	0.72 (0.38 - 0.93)	0.71 (0.26 – 0.90)	0.79 (0.39 - 0.98)	0.89 (0.70 - 0.98)	0.75	0.19
Max	0.91 (0.81 - 0.99)	0.89 (0.79 - 0.98)	0.86 (0.71 - 0.97)	0.95 (0.84 - 0.99)	0.99 (0.87 - 0.99)	0.49	0.08
Percentage below							
Median	2.49 (0.50 - 24.88)	3.48 (0.50 - 22.64)	3.48 (0.50 -29.35)	2.49 (01.00 - 36.07)	2.49 (1.00 - 28.61)	0.55	0.73
Max	17.91 (2.49 - 46.27)	15.92 (1.37 - 37.31)	16.17 (1.37 - 40.67)	39.30 (7.46 - 51.24)	17.91 (7.46 – 51.24)	0.33	0.47
$V_{0.2}/V_{0.2}$							
Median	-0.05 (0.02)	0.44 (0.02)	0.04 (0.02)	0.05 (0.02)	0.05 (0.02)	0.71	0.13
Max	0.13 (0.05)	0.13 (0.05)	0.13 (0.05)	0.13 (0.05)	0.14 (0.05)	0.88	0.60
$V_{0.2}/V_{1}$							
Median	0.30 (0.18 - 0.40)	0.31 (0.12 - 0.36)	0.31 (0.12 - 0.45)	0.26 (0.20 - 0.63)	0.26 (0.20 - 0.50)	0.71	0.80
Max	0.43 (0.26 - 1.75)	0.44 (0.27 - 1.99)	0.44 (0.27 - 2.77)	0.33 (0.26 - 1.69)	0.33 (0.26 - 0.81)	0.57	0.38
$V_{0.5}/V_{0.5}$							
Median	0.13 (0.06)	0.12 (0.06)	0.11 (0.05)	0.13 (0.06)	0.15 (0.07)	0.87	0.24
Max	0.36 (0.13)	0.35 (0.13)	0.37 (0.26 - 0.42)	0.36 (0.15)	0.40 (0.23 – 0.51)	0.86	0.49
$V_{0.5}/V_{1}$							
Median	0.71 (0.46 - 1.10)	0.78 (0.34 - 1.10)	0.78 (0.34 - 1.36)	0.69 (0.56 - 1.72)	0.69 (0.56 - 1.21)	0.49	0.61
Max	1.10 (0.73 - 4.06)	1.21 (0.78 - 6.38)	1.21 (0.78 - 8.48)	1.04 (0.67 - 4.14)	1.04 (0.67 - 2.12)	0.41	0.28

Values are given in numbers (%), medians (interquartile ranges), or mean (standard deviations).

Section D.5 – Questionnaire

Table A.22 – Questionnaire outcomes and duration of the measurements of the successful MAD therapy group versus the non-successful MAD therapy group based on the second definition of MAD success

	All included patients (n=25)	Successful MAD therapy (n=14)	Non-successful MAD therapy (n=9)	P-value
Q1: Time NEP	8 (7-9)	8.0 (7.0 – 10.0)	8.0 (6.5 – 8.0)	0.13
Q2: Comfortable NEP	7.7 (1.4)	8.0 (1.5)	7.3 (1.1)	0.26
Q3: Time FOT	7.9 (1.5)	8.1 (1.7)	7.4 (1.1)	0.26
Q4: Comfortable FOT	8 (7-8)	8.0 (6.8 – 9.3)	8.0 (7.0 – 8.0)	0.28
Q5: Time Spirometry	7.5 (1.8)	7.8 (6.0 – 10.0)	8.0 (7.0 – 8.0)	0.56
Q6: Comfortable Spirometry	8 (6-9)	8.0 (5.3 – 9.3)	8.0 (6.0 – 8.0)	0.54
Q7: Comfortable adjustable mouthpiece	7.2 (1.5)	7.6 (1.6)	6.7 (1.4)	0.17
NEP duration (min)	10 (10-12)	10.0 (10.0 – 12.3)	10.0 (9.0 – 10.0)	0.11
FOT duration (min)	25 (20-25)	25.0 (20.0 – 25.0)	25.0 (22.0 – 25.0)	0.92
Spirometry duration (min)	15 (10-15)	15.0 (12.3 – 15.0)	15.0 (10.0 – 16.0)	0.84

Values are given in numbers (%), medians (interquartile ranges), or mean (standard deviations), the duration of the measurements is based on the total duration, including multiple repetitions and different mandible positions. A high score on the questionnaire corresponds to very satisfied or comfortable.

Subchapter E – 3D-image of the ring