

SCIENTIFIC INVESTIGATIONS

Phenotypic Labelling Using Drug-Induced Sleep Endoscopy Improves Patient Selection for Mandibular Advancement Device Outcome: A Prospective Study

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Study Objectives: Mandibular advancement device (MAD) outcome varies between patients. We hypothesized that upper airway collapse sites, patterns, and degrees assessed during baseline drug-induced sleep endoscopy (DISE) affect MAD outcome.

Methods: One hundred patients with obstructive sleep apnea (OSA) were included and underwent baseline type 1 polysomnography. MAD was fitted intraorally at fixed 75% maximal protrusion. A total of 72 patients completed 3-month follow-up polysomnography and baseline DISE. Response was defined as apnea-hypopnea index (AHI) reduction $\geq 50\%$, deterioration as AHI increases during MAD treatment compared to baseline.

Results: Adjusting for baseline AHI and body mass index, patients with tongue base collapse showed 3.69 higher odds (1.27–10.73; $P = .0128$) for response. Complete concentric collapse at the level of the palate (5.32 [1.21–23.28]; $P = .0234$) and complete laterolateral oropharyngeal collapse (6.62 [1.14–38.34]; $P = .0330$) related to deterioration. Results for tongue base collapse and complete concentric collapse at the level of the palate were confirmed in the moderate to severe OSA subgroup. Applying these results to this selected subgroup increased response rate with 54% and decreased deterioration rate with 53%. These results were confirmed using other response and deterioration definitions.

Conclusions: Three baseline DISE phenotypes identified during drug-induced sleep were significantly related to MAD treatment outcome: one beneficial, tongue base collapse, and two adverse, complete concentric collapse at the level of the palate and complete laterolateral oropharyngeal collapse. If confirmed in future prospective studies, these results could guide patient selection for MAD outcome.

Clinical Trial Registration: This prospective clinical trial (PROMAD) was registered on [Clinicaltrials.gov](https://clinicaltrials.gov) with identifier: NCT01532050.

Keywords: DISE, MAD, obstructive sleep apnea, OSA, personalized medicine

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BRIEF SUMMARY

Current Knowledge/Study Rationale: Mandibular advancement device (MAD) treatment is a noninvasive therapy for obstructive sleep apnea (OSA) showing high patient adherence. Because treatment outcome is patient specific, improvement of upfront therapeutic response prediction would be advantageous. This study assessed the effect of drug-induced sleep endoscopy (DISE) phenotyping as identified during induced sleep, on MAD treatment outcome.

Study Impact: Our findings suggest that DISE is a promising tool to identify beneficial and adverse DISE phenotypes for upfront patient selection for MAD treatment. The results correspond to the next step in the development and application of a DISE phenotype-specific management of OSA.

INTRODUCTION

Obstructive sleep apnea (OSA) is a highly prevalent disorder affecting up to 9% and 17% of middle-aged women and men, respectively.¹ OSA is characterized by repetitive upper airway narrowing (hypopnea) or complete collapse (apnea) during at least 10 seconds. OSA severity is quantified using the apnea-hypopnea index (AHI), representing the number of apneas and hypopneas per hour of sleep.²

The standard treatment for moderate ($15 \leq \text{AHI} < 30$ events/h) to severe ($\text{AHI} \geq 30$ events/h) OSA is continuous positive

airway pressure (CPAP), applying pressurized air to keep the upper airway patent.³ Although CPAP treatment efficacy is high, adherence to this therapy is often rather low,⁴ supporting the need for other treatments such as oral appliance therapy, sleep position trainers, and surgical solutions.^{5–7}

The most frequently prescribed oral appliances for OSA treatment are mandibular advancement devices (MAD), which protrude the lower jaw and reopen the upper airway.⁸ By protruding the lower jaw, the tongue moves forward. Because of palatoglossus coupling, as shown for upper airway stimulation therapy,^{9,10} moving the tongue forward with an MAD leads to

Table 1—Inclusion and exclusion criteria.

Inclusion Criteria	• Age 18 years or older
	• BMI \leq 35 kg/m ²
	• Presence of OSA as defined by the American Academy of Sleep Medicine task force (A + B + D or C + D) ⁴⁴
	A. Anamnesis (at least one of the following criteria)
	1. Unwanted sleepiness and/or fatigue in the daytime, unrefreshing sleep or insomnia
	2. Nocturnal arousals with breathing stops, gasping
	3. Snoring or breathing stops while sleeping, determined by the bed partner
	B. PSG: AHI \geq 5 events/h of sleep and AHI < 50 events/h of sleep
C. PSG: AHI \geq 15 events/h of sleep and AHI < 50 events/h of sleep	
D. The condition cannot be explained by another sleep disorder, internal or neurological disorder, medication or drug use	
Exclusion Criteria	• Presence of absolute dental contraindications
	- Functional restrictions of the temporomandibular joint
	- Insufficient dentition with pathological aspects
	- Insufficient retention for MAD use
	• Presence of other sleep disorders (eg, parasomnias)
	• Previous invasive upper airway surgery for sleep-disordered breathing
	• Craniofacial and/or upper airway anomalies due to genetic disorders
	• Use of benzodiazepine(s) and/or antidepressant(s)
	• History of psychiatric disease (including alcohol abuse)
	• History of fibromyalgia or chronic fatigue syndrome
• Unwilling to participate and/or not willing to give informed consent	

AHI = apnea-hypopnea index, BMI = body mass index, MAD = mandibular advancement device, OSA = obstructive sleep apnea, PSG = polysomnography.

opening the soft palate. Custom-made, titratable MADs are preferred, as they allow individual treatment optimization by titration and optimal retention.^{7,11,12} However, response to non-CPAP therapies such as MAD is patient dependent. MAD response rates range from 30% to 85%, resulting in 15% to 70% of the patients remaining undertreated.¹³ Upfront patient selection should thus be beneficial. Previous studies showed increased MAD response for patients who are young and female with supine-dependent OSA and who have lower AHI, mild airway collapsibility, and low loop gain, referring to a more stable ventilatory control system.^{13,14}

Upper airway collapsibility, in terms of the level(s), the degree, and the configuration of collapse, can be studied using drug-induced sleep endoscopy (DISE).¹⁵ Our research group has shown an adverse effect of complete concentric collapse at the level of the palate (CCCp), assessed during DISE, on upper airway stimulation (UAS) response.¹⁶ However, little research has been done on effects of site(s) and patterns of collapse during DISE on MAD treatment response. Therefore, the current study aims to assess the effects of site(s), degree(s), and pattern(s) of upper airway collapse assessed during DISE at baseline on the observed MAD treatment outcome.

METHODS

Study Population

This prospective clinical trial was registered on [Clinicaltrials.gov](https://clinicaltrials.gov) with identifier NCT01532050 and approved by the local ethical

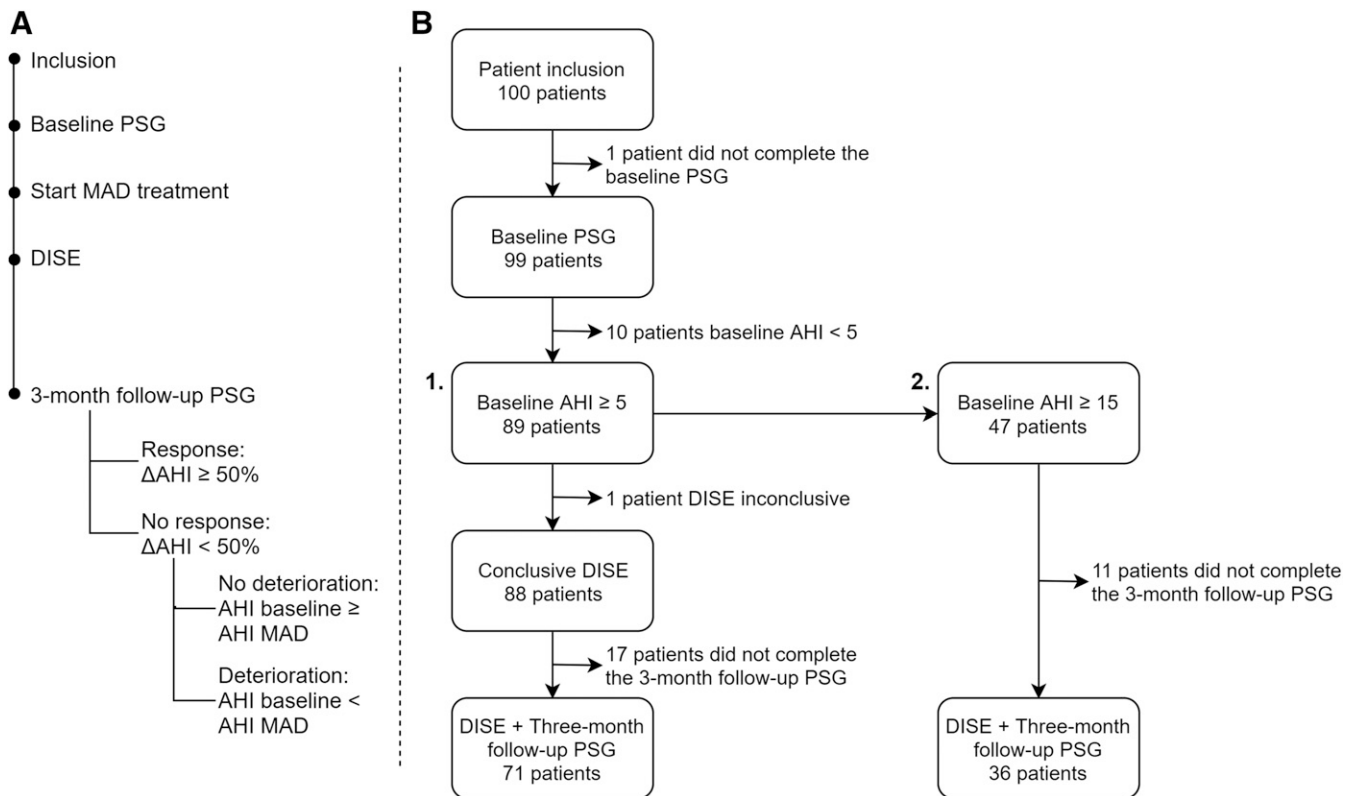
committee at University of Antwerp and Antwerp University Hospital. Written informed consent was obtained from all patients.

One hundred patients were prospectively recruited by the multidisciplinary team including a dental sleep professional, an ear, nose, and throat (ENT) surgeon and a board-certified sleep specialist responsible for patient care. **Table 1** shows inclusion and exclusion criteria.

The study protocol (**Figure 1A**) was previously published in detail by Verbruggen et al.¹⁷ At inclusion, all patients underwent new baseline type 1 polysomnography (PSG) to confirm inclusion criteria (AHI 5 to < 50 events/h). If eligible, custom-made MAD treatment (RespiDent Butterfly MAD, Orthodontic Clinics NV, Antwerp, Belgium), was started.¹⁸

The maximum protrusion was measured three times in each individual patient and averaged. To allow standardization, MAD was then placed at 75% of this individual patient's maximal protrusion without further titration, in which 100% is measured as the distance between maximal protrusion and maximal retrusion, more specifically the centric relation position. By doing so, the individual protrusion range of each patient was respected.

All patients underwent DISE. The multidisciplinary team members were blinded to the DISE results throughout the study. After 3 months, a follow-up type 1 PSG with MAD was scheduled. Response was defined as Δ AHI \geq 50%, deterioration as AHI with MAD > baseline AHI. To take into account the effect of different response definitions, the analysis for the patient subgroup with AHI \geq 15 events/h

Figure 1—Timeline study protocol (A) and patient flow (B).

The patient flow for all study patients (baseline AHI ≥ 5 events/h) is shown in arm 1, the patient flow for patients with moderate to severe obstructive sleep apnea (baseline AHI ≥ 15 events/h) is shown in arm 2. Reasons for dropout are given in the supplemental material. AHI = apnea-hypopnea index, DISE = drug-induced sleep endoscopy, MAD = mandibular advancement device, PSG = polysomnography.

was repeated for 6 other response definitions reported in literature^{19,20}: AHI < 5, AHI < 5 and Δ AHI ≥ 50%, AHI < 5 or Δ AHI ≥ 50%, AHI < 10, AHI < 10 and Δ AHI ≥ 50%, AHI < 10 or Δ AHI ≥ 50%. Furthermore, an additional deterioration definition with a cutoff of 10% deterioration was applied to the dataset.

Drug-Induced Sleep Endoscopy (DISE)

DISE was performed by an ENT surgeon experienced in DISE in a semidark and silent room. Patients lay on a hospital bed in the supine position. Electrocardiography, blood pressure, and oximetry were monitored. A flexible fiberoptic nasopharyngoscope (Olympus END-GP, 3.7 mm diameter, Olympus Europe GmbH, Hamburg, Germany) was inserted through one of the nostrils, without decongestion, to visualize the collapsible segment of the patient's upper airway. Subsequently, sedation was induced using 1.5 mg bolus midazolam injection and intravenous propofol administration using target-controlled infusion (2.0–3.0 μ g). Sedation level was continuously monitored using four bispectral index (BIS) monitoring sensor electrodes (BIS VISTA monitor and BIS Quatro; Aspect Medical Systems Inc., Norwood, USA) attached to the forehead. BIS values range from 0 to 100, with 0 representing no brain activity and 100 representing a fully awake patient. During our DISE procedure, values between 50 and 70 were targeted during at least 5 minutes.

During DISE, the sites of upper airway collapse were assessed using a standard scoring system (Figure 2). In each patient, collapse level(s), degree(s), and pattern(s) were registered: collapse at the level of the palate, oropharynx, tongue base, pharyngeal lateral walls and/or epiglottis, being complete or partial with anteroposterior, laterolateral, or concentric pattern. During an expert meeting, the video-recorded DISE procedures were analyzed and discussed by four experienced ENT surgeons. The results of this central, independent core scoring were used in all analyses.

Statistical Analysis

Statistical analysis was performed using statistical software packages JMP (JMP Pro 13.0.0. SAS Institute Inc., Cary, North Carolina, USA) and R (R Core Team, R Foundation for Statistical Computing, Vienna, Austria). Descriptive statistics were reported as mean ± standard deviation, median (quartile 1–quartile 2), or number and percentages. Normality was tested using the Shapiro-Wilk test. Normally distributed continuous variables were compared using paired or unpaired *t* tests, nonnormally distributed variables using the Wilcoxon signed-rank or Mann-Whitney *U* test.

Collapse patterns were compared between responders/nonresponders and deterioration/no deterioration with Fisher exact tests. Separate logistic regression models, explaining response or deterioration, were built for each collapse level with

Figure 2—Standard scoring system for DISE.

LEVEL	DEGREE	DIRECTION
Palate	Complete Partial None	Anteroposterior Laterolateral Concentric
Oropharynx		
Tongue base		
Pharyngeal lateral walls		
Epiglottis		

Rows represent the site of upper airway collapse, columns represent level, degree and direction. Originally published in Verbruggen et al.¹⁷ Reprinted with permission from the American Academy of Dental Sleep Medicine. Available from: <http://dx.doi.org/10.15331/jdsm.6250>. DISE = drug-induced sleep endoscopy.

and without correction for AHI and body mass index (BMI). All analyses were repeated for the patient subgroup with moderate to severe OSA (baseline AHI ≥ 15 events/h). Accuracy was assessed using positive and negative predictive values (PPV and NPV) and receiver operating characteristic analyses. Reported *P* values are two-sided, statistical significance was considered if *P* < .05.

RESULTS

Data Characteristics and Descriptive Statistics

One hundred patients with OSA (83% male; age 47.6 ± 10.0 years; BMI 26.9 ± 3.3 kg/m²; AHI 21.0 ± 11.2 events/h sleep) were included in the study protocol and underwent a new baseline PSG. One patient did not complete this PSG and 10 patients showed AHI < 5 events/h, confirming OSA in 89/100 patients. Overall, 72/100 patients underwent both DISE and PSG with MAD. DISE was inconclusive in 1 patient due to agitation, resulting in a final dataset of 71 patients with both conclusive DISE and PSG results (Figure 1B). No significant differences in baseline parameters were found between patients lost to follow-up (*n* = 17) and patients completing 3-month follow-up (*n* = 72; see supplemental material for dropout reasons and Table S1). No permanent adverse effects were noted related to the 75% protrusion, only showing mild, temporary side effects as is usual during the start-up of any MAD treatment. No one reported treatment for temporomandibular joint complaints after treatment start-up.

Thirty-six patients (50%) experienced mild ($5 \leq \text{AHI} < 15$ events/h), 27 (37.5%) moderate ($15 \leq \text{AHI} < 30$ events/h), and 9 (12.5%) severe ($\text{AHI} \geq 30$ events/h) OSA. Significant differences between baseline and follow-up with MAD were present for AHI, minimal O₂ saturation, oxygen desaturation index (ODI) and BMI (Table 2). Results on all parameters are shown in Table S2 (supplemental material).

In total, 33 patients (46%) were responder ($\Delta\text{AHI} \geq 50\%$), 39 patients (54%) were nonresponders, of which 17 (24% of total study population, 44% of nonresponders) deteriorated under MAD treatment in 75% of the maximal protrusion. Responders and nonresponders at 3-month follow-up did not significantly differ regarding baseline characteristics (Table S3, supplemental material).

In 71 patients, conclusive DISE results could be obtained. Palatal collapse was most commonly present (*n* = 68/71; 96%), followed by tongue base (*n* = 37/71; 52%), oropharyngeal (*n* = 22/71; 31%), pharyngeal lateral wall (*n* = 16/71; 22%) and epiglottic (*n* = 13/71; 18%) collapse. Most patients (*n* = 53/71; 75%) showed multilevel collapse (Figure S1, supplemental material).

Palatal collapse (Figure 3 and Figure S1 in the supplemental material) was present in both anteroposterior (57%) and concentric (38%) patterns. Oropharyngeal and hypopharyngeal collapse only occurred in laterolateral configuration, and tongue base collapse only in anteroposterior configuration. Epiglottic collapse was present in both anteroposterior (92%) and concentric direction (8%). No significant difference in proportion was present between responders and nonresponders for any collapse site (Table 3 and Figure S2 in the supplemental material).

Correlation analyses between baseline AHI, BMI, and ODI and the collapse patterns showed that patients with tongue base collapse had significantly lower BMI. Pharyngeal lateral wall collapse was related to significantly higher ODI. CCCp was associated with significantly higher AHI (Table 4).

Logistic Modeling

Next, each collapse site's relation to response or deterioration was tested using logistic modeling. Partial and complete collapse were pooled: "collapse" at a given level was compared to "no collapse." However, palatal collapse was highly prevalent (94.2%). Therefore, patients with complete palatal collapse (38/71, 54%) were compared to patients without (4/71, 6%) or with partial palatal collapse (29/71, 41%) (Figure 3). Apart from the five potential levels of upper airway collapse (palate, oropharynx, tongue base, pharyngeal lateral walls, and epiglottis), analyses were also performed for complete concentric collapse at the level of the palate (CCCp), related to UAS therapy response and CPAP pressure,^{16,21} and complete laterolateral oropharyngeal collapse (CLLCop), affecting CPAP pressure and OSA surgery outcome.^{21,22}

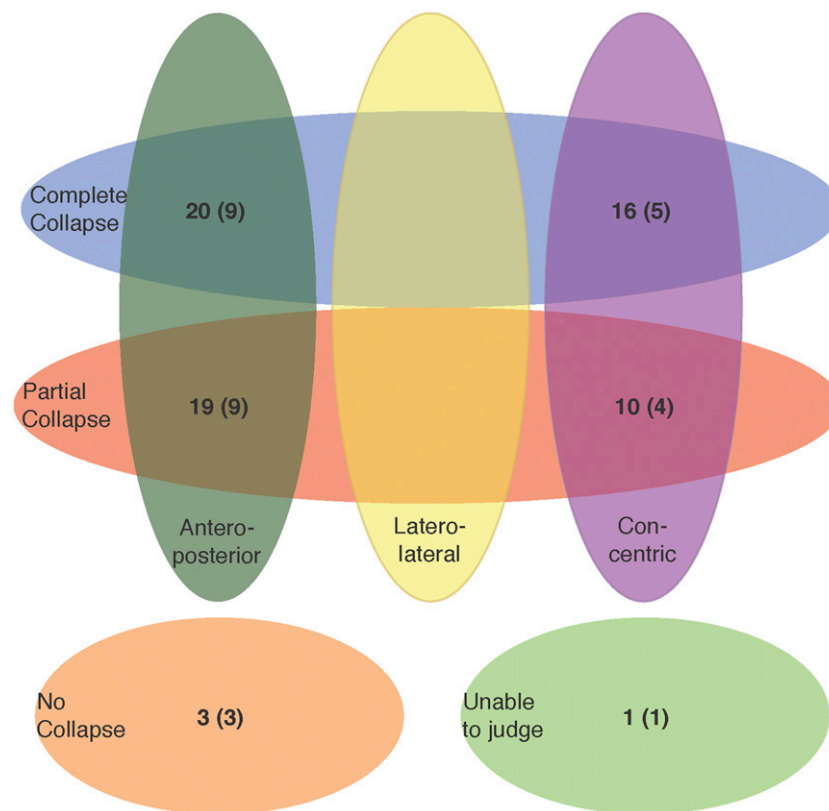
Simple logistic regression showed a significant relationship between response and tongue base collapse, increasing the odds for response with 2.74 (95% confidence interval [CI] 1.04–7.23; *P* = .0378). This significant relationship was preserved when corrected for AHI and BMI (*P* = .0128, odds ratio [OR] 3.69, 95% CI 1.27–10.73) (Table 5, Figure 4A). If corrected for baseline AHI and BMI, a PPV of 57.14% and NPV of 62.79% could be obtained with an area under the curve (AUC) of 0.68.

Regarding deterioration, an identical analysis strategy was followed. Significant relationships were found for CLLCp using simple logistic regression, and for CCCp and CLLCp using logistic regression corrected for baseline AHI and BMI

Table 2—Patient characteristics at baseline and 3-month follow-up.

Outcome Parameter	Baseline PSG (n = 72)	Follow-up PSG (3M) (n = 72)	P
Apnea-hypopnea index (events/h)	15.6 (10.5–23.4)	9.0 (5.0–15.1)	< .0001
Mean SaO ₂ (%)	95.3 (94.1–96.1)	95.3 (94.3–95.9)	.25
Minimal SaO ₂ (%)	86.9 (86.0–91.0)	89.0 (83.6–90.0)	.0020
Oxygen desaturation index (events/h)	4.2 (2.3–11.2)	2.0 (0.7–4.9)	< .0001
Body mass index (kg/m ²)	27.8 ± 3.3	28.1 ± 3.3	.0113

Values are presented as median (quartile 1–quartile 3) for nonnormally distributed data or mean ± standard deviation for normally distributed data. All parameters were compared using the Wilcoxon signed-rank test, except body mass index which was compared using a paired *t* test. Hypopneas scored according to the AASM 1999 rules (3% desaturation or arousals). ODI calculated as dips of 3% or more over the total time in bed. Significant values (*P* < .05) in bold. 3M = 3-month follow-up, PSG = polysomnography, SaO₂ = oxygen saturation.

Figure 3—Distribution for degree and direction of collapse in patients with palatal collapse.

Number of responders shown in brackets. Three patients could not be classified in this Venn diagram as they showed doubtful complete concentric collapse at the level of the palate (CCCp) (2 complete collapse, of which 1 responder and 1 partial collapse, of which 1 responder). Venn diagrams for the other collapse sites are shown in the supplemental material (Figure S2).

(Table 5). Concerning ORs, the strongest effect was present for CLLCop (6.62, 95% CI 1.14–38.34; *P* = .0330, PPV = 60%, NPV = 78.79%, AUC = 0.73), followed by CCCp (5.32, 95% CI 1.21–23.28; *P* = .0234, PPV = 60%, NPV = 76.12%, AUC = 0.74), resulting in a sixfold and fivefold increased likelihood for deterioration, respectively (Figure 4B and Figure 4C). A complete palatal collapse, regardless of collapse direction, resulted in a 3.65-fold increased probability for deterioration (95% CI 1.02–13.00; *P* = .0359, PPV = 66.67%, NPV = 80%, AUC = 0.73). If CCCp and CLLCop were combined in one

model and corrected for AHI and BMI, a PPV of 60%, NPV of 78.79%, and AUC of 0.73 was obtained. The significant effects of complete palatal collapse (*P* = .0215, OR 5.58, 95% CI 1.08–28.85), CCCp (*P* = .0202, OR 6.13, 95% CI 1.32–28.45) and CLLCop (*P* = .0483, OR 6.25, 95% CI 1.08–36.00) were maintained using the more stringent deterioration definition of an increase in AHI ≥ 10%, corrected for baseline AHI and BMI.

If these results would have been used as exclusion parameters in our initial dataset with fixed protrusion, the 46% response rate

Table 3—Number of patients per collapse site and results of Fisher exact tests (2-sided).

Site of Collapse		Complete Dataset					Baseline AHI ≥ 15				
		n			P		n			P	
		Total	Response	Deterioration	Response	Deterioration	Total	Response	Deterioration	Response	Deterioration
Complete palate	Collapse	38	15	12	.3465	.1630	20	9	5	.7380	.1962
	No collapse	33	17	5			16	9	1		
Oropharynx	Collapse	22	7	6	.1972	.7654	14	5	4	.3053	.1812
	No collapse	49	25	11			22	13	2		
Tongue base	Collapse	37	21	10	.0562	.5864	16	12	2	.0176	.6722
	No collapse	34	11	7			20	6	4		
Pharyngeal lateral walls	Collapse	16	8	5	.7811	.4999	11	5	3	> .999	.3428
	No collapse	53	24	11			25	13	3		
Epiglottis	Collapse	13	7	2	.5516	.7177	6	3	1	> .999	> .999
	No collapse	57	25	14			30	15	5		
CCCp	Collapse	16	5	6	.2604	.1868	11	6	4	> .999	.0570
	No collapse	55	27	11			25	12	2		
CLLCop	Collapse	7	1	4	.1192	.0516	5	1	2	.3377	.1858
	No collapse	64	31	13			31	17	4		

Significant values ($P < .05$) in bold. AHI = apnea-hypopnea index, CCCp = complete concentric collapse at the level of the palate, CLLCop = Complete laterolateral oropharyngeal collapse.

Table 4—Comparing mean baseline parameters in patients with and without collapse at the different collapse sites.

Site of Collapse	Complete Dataset (n = 71)								
	ODI (events/h)			BMI (kg/m ²)			AHI (events/h)		
	P	With	Without	P	With	Without	P	With	Without
Complete palate	.2228	9.4 ± 9.1	5.8 ± 4.9	.0978	20.6 ± 13.5	16.6 ± 8.5	.1740	27.9 ± 3.7	27.6 ± 2.6
Oropharynx	.6353	8.3 ± 6.4	7.5 ± 8.1	.3874	19.3 ± 8.1	18.6 ± 13.0	.6837	28.2 ± 2.9	27.6 ± 3.4
Tongue base	.0964	6.3 ± 6.5	9.3 ± 8.5	.0298	16.3 ± 8.7	21.6 ± 13.7	.0685	27.0 ± 2.8	28.6 ± 3.5
Pharyngeal lateral walls	.0246	11.9 ± 7.7	6.6 ± 7.2	.3395	20.9 ± 10.2	18.5 ± 12.1	.3438	28.3 ± 3.7	27.5 ± 3.1
Epiglottis	.8425	7.4 ± 6.7	7.7 ± 7.8	.3060	17.5 ± 9.1	19.2 ± 12.2	.5620	27.0 ± 2.8	27.9 ± 3.3
CCCp	.0759	11.4 ± 9.4	6.6 ± 6.6	.1936	25.9 ± 15.5	16.8 ± 9.5	.0386	28.9 ± 3.7	27.4 ± 3.1
CLLCop	.7487	8.4 ± 5.6	7.5 ± 7.7	.3362	19.8 ± 5.4	18.7 ± 12.1	.6587	28.9 ± 2.7	27.6 ± 3.3
Multilevel collapse	.3481	7.2 ± 6.5	9.7 ± 10.4	.4396	27.6 ± 3.0	28.4 ± 4.0	.1497	17.3 ± 8.8	24.0 ± 17.5

Values are presented as mean ± standard deviation. Comparisons were made using *t* tests. Significant values ($P < .05$) in bold. AHI = apnea-hypopnea index, BMI = body mass index, CCCp = complete concentric collapse at the level of the palate, CLLCop = complete laterolateral oropharyngeal collapse, ODI = oxygen desaturation index.

would have increased to 57% (21/37) if only patients with tongue base collapse were included and even further increased to 60% (18/30) if also patients with CCCp and/or CLLCop were excluded. If patients with CCCp would have been excluded, the deterioration rate would have decreased from 24% (45% of nonresponders) to 20% (11/55, 39% [11/28] of nonresponders), and to 21% (11/52, 42% [11/26] of nonresponders), if patients with CCCp and/or CLLCop were excluded. Among the patients with CCCp (n = 16), a nonresponder rate of 69% (11/16) and a deterioration rate of 38% (6/16) was noted. Patients with CLLCop (n = 7), showed a nonresponder rate of 86% (6/7) and a deterioration rate of 57% (4/7).

Results for Patients With Moderate to Severe OSA (Baseline AHI ≥ 15 events/h)

All analyses were repeated for the moderate to severe OSA subgroup. In total, 36 of the 47 patients with moderate to severe OSA completed 3-month follow-up (Figure 1B). Eighteen patients (50%) were responders whereas 6 (17%; 33% of nonresponders) deteriorated. Applying the Sher criteria²³ to the patients with a baseline AHI ≥ 20 events/h resulted in 12/26 patients (46%) who responded, whereas 14/26 patients (54%) did not respond.

The results obtained for patients with moderate to severe OSA were largely equivalent to those for all patients (Table 3 and Table 5). Fisher exact tests showed a significant difference

Table 5—Logistic regression relating sites of collapse to response (top) and deterioration (bottom) in the complete dataset and in patients with baseline AHI ≥ 15 events/h.

Site of Collapse	Response (Δ AHI $\geq 50\%$)							
	Complete Dataset (n = 71)				Baseline AHI ≥ 15 (n = 36)			
	Simple Logistic Regression		+ AHI + BMI		Simple Logistic Regression		+ AHI + BMI	
	P	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)
Complete palate	.3088	0.61 (0.24–1.58)	.2359	0.56 (0.21–1.47)	.5019	0.64 (0.17–2.39)	.4388	0.57 (0.13–2.40)
Oropharynx	.1289	0.45 (0.16–1.29)	.1060	0.42 (0.14–1.23)	.1692	0.38 (0.10–1.54)	.1676	0.37 (0.09–1.57)
Tongue base	.0378	2.74 (1.04–7.23)	.0128	3.69 (1.27–10.73)	.0063	7.00 (1.59–30.80)	.0041	8.45 (1.75–40.81)
Pharyngeal lateral walls	.7404	1.21 (0.39–3.70)	.8448	1.12 (0.36–3.50)	.7174	1.30 (0.31–5.39)	.6701	1.40 (0.29–6.67)
Epiglottis	.5150	1.49 (0.45–5.01)	.4457	1.61 (0.47–5.49)	> .999	1.00 (0.17–5.77)	.9928	1.01 (0.17–25.90)
CCC palate	.2013	0.47 (0.14–1.54)	.0938	0.34 (0.09–1.27)	.7174	0.77 (0.19–3.19)	.6512	0.70 (0.17–5.85)
Complete LL oropharynx	.0679	0.18 (0.02–1.56)	.0557	0.16 (0.02–1.45)	.1364	0.21 (0.02–2.06)	.1402	0.20 (0.02–2.10)
Site of Collapse	Deterioration (AHI _{baseline} < AHI _{with MAD})							
	Complete Dataset (n = 71)				Baseline AHI ≥ 15 (n = 36)			
	Simple Logistic Regression		+ AHI + BMI		Simple Logistic Regression		+ AHI + BMI	
	P	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)
Complete palate	.1009	2.58 (0.80–8.34)	.0359	3.65 (1.02–13.00)	.1164	5.00 (0.52–48.07)	.0894	6.30 (0.59–67.58)
Oropharynx	.6621	1.30 (0.41–4.11)	.5468	1.46 (0.43–4.95)	.1306	4.00 (0.62–25.68)	.2466	3.05 (0.44–21.04)
Tongue base	.5243	1.43 (0.47–4.31)	.6004	1.37 (0.42–4.54)	.5443	0.57 (0.09–3.61)	.5277	0.54 (0.08–3.71)
Pharyngeal lateral walls	.3945	1.74 (0.50–6.05)	.2534	2.21 (0.58–8.48)	.2727	2.75 (0.46–16.52)	.4603	2.22 (0.27–18.28)
Epiglottis	.4613	0.56 (0.11–2.83)	.4598	0.55 (0.10–2.89)	> .999	1.00 (0.10–10.51)	.9953	1.01 (0.09–11.45)
CCC palate	.1629	2.40 (0.72–8.04)	.0234	5.32 (1.21–23.28)	.0434	6.57 (0.99–43.78)	.0169	13.50 (1.32–138.04)
Complete LL oropharynx	.0455	5.23 (1.04–26.33)	.0330	6.62 (1.14–38.34)	.1716	4.50 (0.57–35.83)	.2669	3.60 (0.40–32.49)

Simple logistic regression = response ~ one site of collapse. + AHI + BMI uses the same model as used during simple logistic regression, taking into account AHI and BMI as confounding factors. Significant values ($P < .05$) in bold. AHI = apnea-hypopnea index, BMI = body mass index, CCC palate = complete concentric collapse at the level of the palate, complete LL oropharynx = complete laterolateral oropharyngeal collapse, OR = odds ratio.

in proportion between responders and nonresponders for patients with tongue base obstruction (Table 3). Simple logistic modeling (Table 5) showed a significant relation between tongue base collapse and response ($P = .0063$, OR 7.00, 95% CI 1.59–30.80) (Figure 4D). This relationship was sustained if corrected for AHI and BMI at baseline ($P = .0041$, OR 8.45, 95% CI 1.75–40.81, PPV = 81.25%, NPV = 75.00%, AUC = 0.82). The significant relationship between response and tongue base collapse was retained in four out of seven different response definitions. No further significant relationships were found for other collapse levels.

Regarding deterioration (Table 5), a significant relationship was found for CCCp using simple logistic modeling ($P = .0434$, OR 6.57, 95% CI 0.99–43.78) and if adjusted for baseline AHI and BMI ($P = .0169$, OR 13.50, 95% CI 1.32–138.04, PPV = 50.00%, NPV = 87.50%, AUC = 0.87) (Figure 4E). In this subgroup, no relationship was found between response or deterioration, and CLLCop (Table 5 and Figure 4F). This result was maintained using the more stringent definition of AHI increase $\geq 10\%$ ($P = .0472$, OR 10.98, 95% CI 0.83–145.18, if adjusted for baseline AHI and BMI).

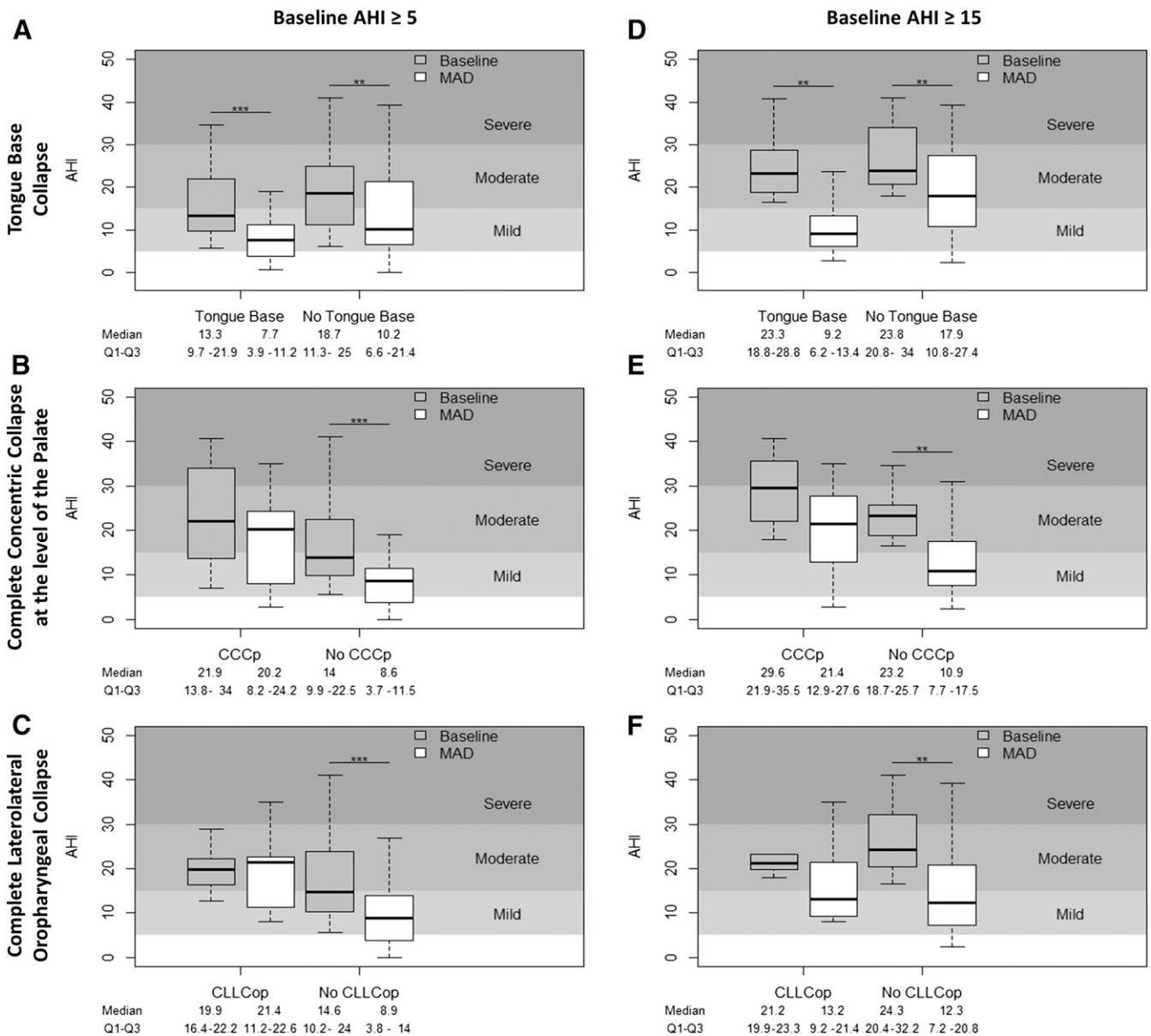
If these results would have been used as exclusion parameters in our initial dataset, the 50% response rate would have increased to 75% (12/16) if only patients with tongue base collapse were included, and further increased to 77% (10/13) if also

patients with CCCp were excluded. The deterioration rate would decrease from 17% (33% of nonresponders) to 8% (2/25, 17% (2/12) of nonresponders) if patients with CCCp would have been excluded. Among our patients with CCCp ($n = 11$), a nonresponder rate of 55% (6/11) and deterioration rate of 36% (4/11) was noted. Patients with CLLCop ($n = 5$), showed a nonresponder rate of 80% (4/5) and deterioration rate of 40% (2/5).

DISCUSSION

The key finding of this study is that presence of tongue base collapse during baseline DISE examination is strongly correlated to favorable MAD response in patients with OSA. A second finding is that patients with complete concentric collapse at the level of the palate (CCCp) and/or complete laterolateral oropharyngeal collapse (CLLCop) during DISE tend to deteriorate under MAD treatment. Considering DISE findings are often correlated with baseline parameters²⁴ and, as shown in Table 4, significant differences in baseline parameters were present in those with and without tongue base collapse, pharyngeal lateral wall collapse, and complete concentric collapse at the level of the palate (CCCp), the logistic models built in this study were adjusted for both baseline AHI and BMI. Because a significant

Figure 4—Change in AHI for each participant.



Change in AHI for each participant with (left) and without (right) tongue base collapse, complete concentric collapse at the level of the palate and complete laterolateral oropharyngeal collapse, taken into account all patients (left column) or only patients with baseline AHI ≥ 15 (right column). Outliers were omitted in this graphical representation. * $P < .05$, ** $P < .01$, *** $P < .0001$. AHI = apnea-hypopnea index, CCCp = complete concentric collapse at the level of the palate, CLLCop = complete laterolateral oropharyngeal collapse, MAD = mandibular advancement device.

correlation of 0.81 ($P < .0001$) was present between ODI and AHI, no additional correction was done for ODI. Despite this correction, the significant effects of tongue base collapse in favor, and, CCCp and CLLCop at disadvantage, were preserved for response and deterioration, respectively, clearly adding to the power of our findings. The results of this prospective study emphasize MAD treatment response in OSA patients is specifically related to the site, degree and pattern of upper airway collapse as assessed during DISE. Based on the results of this prospective trial, the authors introduce the concept of DISE phenotypic labeling, referring to the specific pharyngeal collapse during DISE that is a combination of a certain degree and

pattern at a particular level of the upper airway. According to the current results, tongue base collapse is a beneficial DISE phenotype and both CCCp and CLLCop are adverse DISE phenotypes toward MAD treatment outcome.

Compared to CPAP, MAD treatment shows, on average, lower treatment efficacy in unselected patients. However, because of higher MAD adherence relative to CPAP, similar overall clinical mean disease alleviation can be obtained.^{4,25,26} Previous research suggested increased MAD efficacy can be realized by improved patient selection.^{7,27-29} The current findings suggest DISE as a clinical procedure for upfront patient selection toward MAD treatment, including patients with

tongue base collapse for MAD treatment and counseling patients with CCCp and/or CLLCop of the probability toward MAD treatment failure.

In our study population, about half of the patients (52%; **Figure S1**) demonstrated tongue base collapse, whereas 23% showed CCCp and 10% CLLCop. If the current concept of beneficial and adverse DISE phenotypes would have been applied as inclusion and exclusion parameters for patients with moderate to severe OSA (AHI \geq 15 events/h) in our study population, the response rate (Δ AHI \geq 50%) would have increased from 50% to 77% if only patients with tongue base collapse without CCCp would have been included. An increase of 54% in response rate would have been obtained according to this conceptual approach of DISE phenotype-specific OSA management. If patients with CCCp were excluded, the deterioration rate under MAD treatment would decrease to 53%, from 17% to 8%. Furthermore, a PPV of 81.25%, NPV of 75% and AUC of 0.82 could be obtained for the logistic model explaining response including tongue base collapse and corrected for baseline AHI and BMI. A PPV of 50%, NPV of 87.5%, and AUC of 0.87 could be obtained for the model including CCCp, corrected for baseline AHI and BMI, explaining deterioration. These selection parameters would thus avoid patients being treated with MAD who tend to have lower likelihood for response and even high probability of deterioration.

Previous research using both awake endoscopy, DISE, and MRI, showed an increase in velopharyngeal cross-sectional area is associated with beneficial MAD treatment outcome.^{8,27,30–32} Regarding collapsibility, lower passive anatomical compromise predicts MAD treatment success,¹⁴ which might relate to the increased odds for deterioration we found in patients with CCCp and/or CLLCop.

DISE already showed its potential for upfront upper airway stimulation response prediction, in which CCCp was found to be a negative DISE predictor.¹⁶ In our study, a significant relationship was present between deterioration to MAD treatment and the presence of this CCCp DISE phenotype. Parallel to UAS findings, patients with CCCp as observed during DISE were no suitable candidates for MAD treatment. The finding that patients with OSA with anteroposterior tongue base collapse have significantly higher odds for being a responder under MAD treatment, might be explained by the longitudinal muscle direction at the level of the tongue base. UAS acts on these longitudinal muscles by increasing both the retrolingual and retropalatal region in an anteroposterior direction, suggesting mechanical palatoglossus coupling between these areas.^{9,10} As in our study tongue base collapse is found to be positively associated with MAD response, MAD and UAS treatment might act in a similar, longitudinal way, being optimal treatment options for patients with anteroposterior collapse patterns and suboptimal for nonanteroposterior collapse pattern resolution.

Increased BMI and AHI is associated with increased collapsibility of the upper airway.³³ Furthermore, CCCp is associated with increased BMI and AHI as well.²⁴ Therefore, based on the current result showing that CCCp is correlated with deterioration after MAD treatment, we hypothesize that deterioration to MAD treatment is correlated to high upper airway

collapsibility and as such is associated with this OSA phenotype. Regarding CLLCop, we hypothesize that this is an anatomical phenotype, correlated to tonsil hypertrophy, which plays a role in MAD treatment response. Future research, aiming at these specific outcome variables is needed to address both hypotheses.

In the absence of a gold standard titration protocol for MAD treatment,³⁴ the mandibular advancement was fixed at 75% of the maximal protrusion, whereas other studies^{19,27} performed a personalized titration to find optimal protrusion. Titration in our study population could therefore even have enhanced treatment response as in clinical practice in our hospital; most patients end up at their maximal comfortable protrusive position. However, the authors argue that the current approach was imperative to allow for a more objective and prospective comparison between baseline and MAD treatment outcomes.

Often, OSA study results are response definition dependent.^{19,20} Therefore, we assessed six additional response definitions. In four out of seven definitions, tongue base collapse significantly related to response. These results highlight our finding of tongue base collapse being a beneficial DISE phenotype for MAD treatment outcome. A more stringent deterioration definition (increase in AHI \geq 10%) also yielded similar results.

During this study, multiple hypotheses were tested. However, we choose not to apply any correction as this study was intended as a first exploration of relating DISE phenotyping with MAD treatment outcome. The authors stress that future prospective studies with the current results as primary outcome are needed to further quantify and confirm the current results.

A strength of our study is the prospective study design: patients started MAD therapy and underwent a DISE evaluation. However, the results of the DISE evaluation were blinded for both the patient and the clinical multidisciplinary team throughout the study. Therefore, DISE outcomes had no effect on the offered MAD treatment.

In addition, regarding the prevalence of the different collapse sites (**Figure S1** and **Figure S2** in the supplemental material), our study results are in line with previous reports in literature.^{16,24,27,35} Palatal collapse is the most prevalent site (94%), followed by tongue base (52%), oropharyngeal (31%), hypopharyngeal (23%) and epiglottic (18%) collapse. Multi-level collapse was present in 75% of the study patients. In previous studies, the prevalence of CCCp ranged from 10% to 32% whereas complete oropharyngeal collapse occurred in 1% to 7%.^{24,35–37} In our study, 23% of the patients showed CCCp, whereas 10% showed CLLCop.

A potential drawback of DISE is its so-called subjective nature depending on experience and the used scoring system.^{24,38–40} In our research setting, this point of criticism on DISE was tackled to a large extent by using a consensus scoring relying on four ENT surgeons with broad experience in DISE. For each level, degree, and direction, a consensus was made, limiting possible intra-rater and interrater variability. In clinical practice, the authors would like to stress the importance to have an ENT surgeon experienced in DISE performing the DISE evaluation in order to reduce intra-rater and interrater variability.

Another possible limitation of DISE is its accessibility in clinical practice. DISE should be performed in an operating theater involving multiple health care professionals. Recent studies^{41–43} suggest the possibility of upper airway collapse site prediction during natural sleep using polysomnographic signals. If the predictive value of this technique can be confirmed, this may reduce the need for DISE and make the results of this study potentially generally applicable to other techniques allowing assessment of the upper airway dynamics in patients with OSA.

In conclusion, DISE is a promising tool for upfront MAD patient selection. We defined three DISE phenotypes: one beneficial DISE phenotype associated with MAD response: tongue base collapse, and two adverse DISE phenotypes: complete concentric collapse at the level of the palate (CCCp) and complete laterolateral oropharyngeal collapse (CLLCop). Patients with a tongue base collapse DISE phenotype showed significantly higher odds for being responders whereas patients with a CCCp and/or CLLCop DISE phenotype tended to show deterioration to MAD treatment. To the best of the authors' knowledge, the association between the CLLCop DISE phenotype and MAD outcome is a new finding and not reported previously in the literature. Based on these results, the authors advocate the need for future prospective studies with the current results as primary outcome to further explore development and application of DISE phenotype-specific OSA management when prescribing non-CPAP therapies.

ABBREVIATIONS

AHI, apnea-hypopnea index
 BMI, body mass index
 CCCp, complete concentric collapse at the level of the palate
 CLLCop, complete laterolateral collapse at the level of the oropharynx
 CPAP, continuous positive airway pressure
 DISE, drug-induced sleep endoscopy
 MAD, mandibular advancement device
 ODI, oxygen desaturation index
 OSA, obstructive sleep apnea
 PSG, polysomnography

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