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SLEEP APNEA (B ROTENBERG, SECTION EDITOR)

Drug-Induced Sleep Endoscopy as a Tool for Surgical Planning

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Abstract

Purpose of Review To review whether drug-induced sleep endoscopy (DISE) aids in obstructive sleep apnea surgical planning, if it changes the initial proposal, and if so, does it contribute to increased surgical success or unnecessary morbidity?

Recent Findings A DISE and surgical outcomes multicenter cohort study ($n = 275$) reported no association for surgical outcomes with velopharyngeal and epiglottic collapse. Oropharyngeal and tongue base collapse on the other hand were associated with lower odds of surgical response.

Summary DISE changes surgical planning mainly in regard to the approach of the tongue base and epiglottis, as these structures usually do not collapse in the awake state. The decision of velopharyngeal surgery usually does not change, as the vast majority demonstrate velopharyngeal collapse in DISE. Whether DISE increases or not, surgical success is controversial, with conflicting published data. However, poorer surgical outcomes have been associated with velopharyngeal concentric, oropharyngeal lateral wall, and tongue base collapse.

Keywords Drug-induced sleep endoscopy · DISE · Upper airway exploration · Obstructive sleep apnea · Predictors of surgical success · Surgical planning

Introduction

Obstructive sleep apnea (OSA) is a disease associated with increased morbidity and mortality, which is cost-efficient to treat [1]. The first-line therapy is positive upper airway pressure (PAP); nevertheless, this treatment often fails due to lack of long-term compliance [2]. On the other hand, surgery, which does not rely on compliance, is a second- or third-line treatment because the results in unselected patients are suboptimal [3]. Selection appears to be the key point in achieving better surgical results [3].

Despite performing upper airway (UA) exploration in the consultation, patient selection is challenging due to fact that while sleeping, respiratory and muscle control differs from wakefulness. This difference has been demonstrated, with distinctive sites of obstruction in the awake and sleep state [4–7]. Therefore, unless there are evident anatomical traits (such as hypertrophied tonsils), the surgical results are suboptimal [8]. Unfortunately, the patients in whom these anatomical traits are evident represent less than 20% of the general OSA population that does not tolerate PAP [9].

The exploration of the UA during natural sleep, albeit the most accurate diagnostic tool, fails in daily clinical practice. Drug-induced sleep endoscopy (DISE) fulfills this need, offering the possibility of observing the UA in a state that resembles natural sleep. During this procedure, UA collapse and obstruction can be observed; moreover, different maneuvers can be performed, making this tool very appealing. Consequently, DISE has spread worldwide [10].

The million-dollar question is whether DISE modifies the surgical planning and if this change in plan is followed by an increase in surgical success.

The objective of this article is to review the current evidence of the literature on DISE as a tool for surgical planning in the adult population.

Articles are divided in three different subjects: (1) articles that compared awake and sleep UA exploration and mentioned the subsequent change in surgical plan, (2) articles

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comparing surgical results after clinical evaluation and DISE, and (3) articles approaching predictors of success or failure according to DISE findings.

Articles Comparing Wake and DISE

Certal et al. concluded in their systematic review, having searched for all articles published until May 2015, that the surgical plan changed after DISE in approximately 50% of the cases [11•]. After that review, only one article focused on the subject of change in surgical plan after DISE and the results were similar, as it changed it in 60.4% of the cases [12]. This change in surgical plan is motivated by the observation of tongue base and epiglottic collapse, as these structures do not usually collapse while the patient is awake despite maneuvers performed [13–16].

The decision of performing surgery in the velopharynx does not change in most of the patients. This is not surprising, as the vast majority of patients show collapse in the retropalatal region in DISE [17, 18••].

Comparing Surgical Results After Conventional Clinical Exploration and DISE

The best possible comparison in order to know which exploration is better is a prospective randomized controlled trial, as it is the experiment that can control the bias more efficiently. So far, there is no such trial; consequently, only case studies or cohorts can be discussed, these are identified in Table 1.

The conclusion of the systematic review was that there was not a clear increase in surgical success after DISE [11•]; nevertheless, this conclusion could be questioned as one of the articles reviewed has serious limitations that make their conclusions not reliable [24]. In the article by Yilmaz et al., 39 patients were randomly divided in two groups to treat palatal collapse according to the findings of DISE or the Müller Maneuver (MM) (after tongue base collapse was excluded with DISE) [24]. They performed expansion palatoplasty (EP) if the obstruction was lateral, anterior palatoplasty (AP) if the obstruction was anteroposterior, and both surgeries when the obstruction was combined. In the DISE group, there were more combined techniques, but the surgical results were equal. Their conclusion was that DISE only increased surgical time. The problem with this article is the methodology bias in surgical management, because the EP not only increases the lateral space treating lateral collapse, but also increases the anteroposterior space of the velopharynx, as the palatopharyngeus muscles are sutured anteriorly to the hamulus which moves the palate forward.

Pang et al. compared the results of a combination of EP and AP in two groups of patients in a two-center study [23]. In one center, the selection was performed after DISE and in the other, after awake exploration. Patients that underwent DISE had worse success rate than no-DISE (73.9% vs 88%) but this difference was explained by the change in body mass index (BMI) that was significantly reduced (6.7 units) in the no-DISE patients. Meanwhile, DISE patients had a small increase of 0.5 in their BMI.

Two studies reviewed their results comparing two cohorts, before and after performing DISE for surgical plan, with opposite results [21, 22••]. While for Huntley et al. DISE decreased multilevel surgery and increased success rate (86% after DISE vs 51.4% without DISE) [22••], for Golbin et al., the AHI reduction was similar in both cohorts despite performing transoral robotic surgery (TORS) in the DISE group when tongue base or epiglottic collapse was present, in addition to uvulopalatopharyngoplasty (UPPP) and tonsillectomy in the no-DISE cohort [21]. The positive results in the

Table 1 Comparing surgical results after conventional clinical exploration and DISE

Author/year	Number	Type of study	Results
Atkas 2014 [19]	20	Case series	Higher surgical success in the group with obstruction of the upper airway according to DISE Lower surgical success in the group with lower airway collapse according to DISE
Blumen 2015 [20•]	24	Case series	DISE identified collapses that can be the responsible of the surgical failure DISE also detected collapses that do not need to be treated for achieving surgical success
Golbin 2016 [21]	104	DISE cohort vs no-DISE cohort	DISE-selected patients did not obtain higher AHI reduction
Huntley 2017 [22••]	87	DISE cohort vs no-DISE cohort	DISE selection increases surgical success and decreases multilevel surgery
Pang 2016 [23]	73	DISE cohort vs no-DISE cohort	DISE- selected patients did not experience more success for the same practiced surgical technique
Yilmaz 2015 [24]	39	DISE cohort vs no-DISE cohort	No higher surgical success was observed with DISE patient selection based in the detection of anterior collapse in addition to the lateral wall

DISE drug-induced sleep endoscopy, *vs* versus

Huntley study may have been caused by the results after hypoglossal nerve stimulation (HNS) performed just in the DISE cohort, so they performed a second analysis excluding HNS patients and their results still remained with 82.4% success rate. The fact that the surgeries performed in both cohorts of Huntley's study were multilevel, even after excluding HNS patients, make this comparison more reliable than the one performed by Golbin et al. in our opinion, as in the latter there might be a selection bias when they compared their cohorts (it is possible that the DISE cohort had more complex patients than the no-DISE, as one might not offer unilevel surgery if multilevel obstruction is suspected after clinical examination). Moreover, the lack of increased reduction in the AHI after multilevel surgery agrees with other studies that performed surgery following the awake exploration but performed DISE just before the surgery. Surgery was not changed despite DISE findings [19, 20•]. Aktas et al. selected 20 patients with only collapse in the upper part of the UA performing MM and did UPPP plus tonsillectomy. The success rate of the patients with collapse in the lower part of the UA observed in DISE was low, 83% with lower collapse, that could not be observed during MM, were failures. The only patient that was successful with a lower collapse also had an upper collapse, while most of the patients that showed collapse in the upper part were success. The presence of collapse in two sites versus one site made no difference in success rate [19]. Blumen et al. also found that there were patients in which surgery was successful despite not treating the tongue base or epiglottic collapse observed during DISE. Moreover, despite performing surgery in all the areas demonstrating collapse visualized in the DISE, there have been failures. Therefore, surgeons should not be very optimistic of the results even when multilevel surgery is performed, as the collapse observed is the consequence of a whole set of pathophysiological and anatomic mechanisms [20•].

Predictors of Success or Failure

The necessity to improve surgical results is not to enhance statistical outcome, but to avoid proposing unnecessary painful surgery that is not going to ameliorate the burden of disease. Accordingly, the search for different obstructions that may help to predict good or poor surgical results is of the upmost importance.

As far as we know, the first article in the literature that focuses on this was published in 2003 by Iwanaga et al. [25]. They performed pre and postoperative DISE in 60 patients in addition to standard PSG. The surgical technique was UPPP accompanied by nasal surgery when necessary. Their best results were obtained in patients with whom anteroposterior (AP) palatal collapse or tonsillar collapse was observed, with a reduction in the AHI of 74.4% and 76%, respectively. On the other hand, patients with circumferential collapse (CC) at the velum had only a 53.3% reduction in the AHI. If the patients showed tongue base collapse in addition to the CC, the results were even worse, with only a 34% reduction in the AHI. Moreover, complete disappearance of the collapse after UPPP was not observed in any patient with a multilevel collapse, only in 5.3% of the patients with CC, 30% of patients with tonsillar collapse, and successfully, in all patients with AP palatal collapse.

The unsuccessful results of UPPP in patients with complete CC has also been reported in later studies [26, 27•, 28]. Koutsorelakis et al. found that patients with complete CC had an odds ratio of surgical failure of 5.27 [26]. Complete CC was associated with 0% of success rate after intermittent HNS and became an exclusion criteria for implantation [29]. Nevertheless, the exclusion of complete CC does not guarantee success in HNS, as complete AP collapse and complete epiglottis collapse were also associated to surgical failure [30]. Regarding patients with complete CC, these were poorer responders to lateral pharyngoplasty (LP) or EP [31], were good responders to limited palatal muscle resection (LPMR) instead, although patients with complete lateral collapse did not respond to LPMR [32].

Table 2 offers a summary of the findings observed during DISE suggestive of predictors of success or failure. It can be observed that the findings are heterogeneous in the different studies. For example, the presence of complete supraglottic collapse was found to be a predictor of failure in the Soares et al. study [37] but was no longer a predictor of failure when the same group performed TORS surgery with partial epiglottectomy in a later publication [35]. However, the presence of lateral velopharyngeal wall collapse was a predictor of poor response in this later study [35] but not for the first one because all their patients had an AP collapse at velum [37]. Therefore, in order to interpret the significant differences between responders and non-responders to surgery, it is of upmost importance to know the type of collapse observed and the type of surgery performed to solve it.

A new multicenter study has been accepted for publication with a sample size of 275, in which DISE videos were reviewed blindly by 4 investigators (in order to obtain uniformity in the classification system) [33••]. The VOTE classification was adopted [38] and patients with enlarged tonsils (grade 3 or 4) were excluded. The main results of the study were that oropharyngeal lateral wall-related obstruction was associated with poorer surgical outcomes (adjusted odds ratio 0.51; 95% CI 0.27, 0.93). That complete tongue-related obstruction was associated with a lower odds of surgical response in moderate to severe OSA (adjusted odds ratio 0.52; 95% CI 0.28, 0.98). Surgical outcomes were not clearly associated with the degree and configuration of velum- or degree of epiglottis-related obstruction (note that due to statistical size, the effects of the configuration of the epiglottis

Table 2 Predictors of success or failure

Author/year	Number	Surgery performed	Predictors of success	Predictors of failure
Blumen 2015 [20•]	24	UPPP + T ± LT	NM	Complete concentric collapse at vellum Complete lingual collapse
Green 2018 [33••]	275	Any palatal or pharyngeal technique, any tongue base surgery, HS or PE	NM	Oropharyngeal lateral wall obstruction Complete tongue obstruction
Hasselbacher 2018 [27•]	15	UPPP + T	NM, by design all patients had complete concentric collapse, only one patient continued with that collapse after surgery	NM
Hsu 2017 [31]	38	EP or LP ± TAP	NM	Complete concentric collapse at vellum[a]
Hwang 2017 [34]	31	LP + T + TORS or CELL	No factors found	No factors found
Iwanaga 2003 [25]	60	UPPP + T	NM	Concentric collapse at velum
Kim 2018 [32]	21	LPMR + T	Complete velum collapse AP or circular velum collapse No difference with oropharyngeal or tongue base collapse	Partial velum collapse Lateral velum collapse
Koutsourelakis 2012 [26]	49	UPPP + T or ZP ± TBRF ± HS	Velum AP collapse Partial tongue base or epiglottis collapse	Complete or partial concentric collapse at velum Complete AP collapse at tongue base or epiglottis
Lin 2015 [35]	39	TORS (with/without PE) ± UPPP + T or ZP	Absence of lateral velopharyngeal wall collapse	Presence of lateral velopharyngeal Wall collapse
Meraj 2017 [36]	101	TORS ± UPPP + T or ZP or EP ± epiglottoplasty	No factors found	No factors found
Ong 2017 [30]	126	HNS	NM	Complete AP or lateral velum collapse Complete epiglottic collapse
Soares 2012 [37]	34	UPPP + T or ZP ± HS ± LT ± GA ± tongue base resection ± tongue base suspension	NM	Severe (> 75%) lateral pharyngeal wall collapse Severe supraglottic collapse
Vanderveken 2013 [29]	21	NHS	NM	Complete concentric collapse at velum
Wang 2018 [28]	85	UPPP + T	Tonsil hypertrophy, mild velum AP collapse	Complete concentric collapse at velum and complete tongue base collapse

AP anteroposterior, *CELL* coblation endoscopic lingual lightening, *EP* expansion pharyngoplasty, *HNS* hypoglossal nerve stimulation, *HS* hyoid suspension, *LP* lateral pharyngoplasty, *LPMR* limited palatal muscle resection, *LT* lingual tonsillectomy, *NM* not mentioned, *PE* partial epiglottectomy, *T* tonsillectomy, *TAP* transpalatal advancement pharyngoplasty, *TBRF* tongue base radiofrequency, *TORS* trans oral robotic surgery, *UPPP* uvulopalatopharyngoplasty, *ZP* Z-palatoplasty. ^: multicenter study but DISE reviewed blindly by 4 ENT, only difficult cases with small tonsils were considered for the analysis

[a] Although patients with complete concentric collapse reduced less their AHI, they had important clinical improvement, patients with complete or partial collapse at the tongue base or epiglottis had the same AHI reductions as the ones without collapse in those areas

obstruction were not analyzed). Surgical response was inversely associated with tonsil size and body mass index. In this multicenter study, different surgical techniques performed in different centers, excluding HNS patients, were analyzed. Ninety-three percent of the patients had palatal surgery performed, of which, only 35% had isolated palate surgery. Sixty percent had tongue surgery, and partial epiglottectomy (15%) or hyoid suspension (11%), were also performed in some patients, mostly as a part of multilevel surgery (~ 90%), but also as an isolated surgical technique. Despite including the highest sample size regarding DISE and surgical outcomes, the authors did not find other significant correlations due to lack of statistical power. For example, complete versus partial obstruction of the palate seemed to achieve better results, although not statistically significant. The odds of surgical response after isolated palate surgery was estimated to be lower when the primary obstruction site involved the tongue, although this was not statistically significant [33••].

Figure 1 shows images of different collapses observed in DISE that have been found as predictors of surgical failure in different publications.

Discussion

DISE changes the surgical plan in more than 50% of the patients, in most cases this change regarded tongue base and epiglottic collapse, which was not evident in the UA awake exploration. It is not clear whether DISE patients have better surgical results than patients whose surgery was solely selected with UA awake exploration, the lack of prospective randomized trials approaching this issue and the heterogeneity of the studies approaching the surgical techniques and DISE characteristics make this presently impossible to answer. Nevertheless, there are certain types of collapse that can be observed associated with surgical failure. Complete CC in DISE is a contraindication for intermittent HNS and has poor surgical outcomes after UPPP. Oropharyngeal lateral wall-related obstruction and complete tongue-related obstruction have also been associated to poorer surgical outcomes.

The fact that there is not enough evidence that reviews whether DISE increases surgical success rates or provides reliable predicting factors of success or failure does not disqualify it for clinical practice. It is the authors' opinion that DISE plays an important role in surgical planning, and that the results should be incorporated with other clinical aspects (such as, age, BMI, skeletal morphology, etc.). According to Lin et al., AHI lower than 60 in addition to BMI < 30 kg/m^2 in the absence of lateral velopharyngeal wall collapse was associated to increased surgical response rate (86% of patients reduced their AHI more than 50% achieving a postoperative AHI < 15/h) [35]. The surgery performed was Z-palatoplasty or UPPP in addition to TORS of the tongue base and epiglottis.

Furthermore, DISE obstruction characteristics might help to choose one velopharyngeal technique over another, thus improving surgical results. For example, complete CC appears to have a poor surgical response rate when classical UPPP is the chosen technique [26, 27•, 28], even though complete CC is rare after UPPP [27•]. Nevertheless, patients were responders after LPMR [32], and after the barbed suture "alianza" technique [39•]. The study performed with the barbed suture technique shows that it is possible to treat complete CC at the velum even in previously tonsillectomized patients [39•]. The absence of tonsils was associated with poor surgical outcomes for multilevel surgery with UPPP and TORS for Thaler et al. [40]. Therefore, the presence of tonsils might be a predictor of better surgical results, even though they might not be grade 3 or 4 palatine tonsil hypertrophy in the Friedman classification. On the other hand, patients with lateral velopharyngeal collapse did not respond to UPPP [35] or to LPMR [32], but might be excellent candidates for LP, EP,

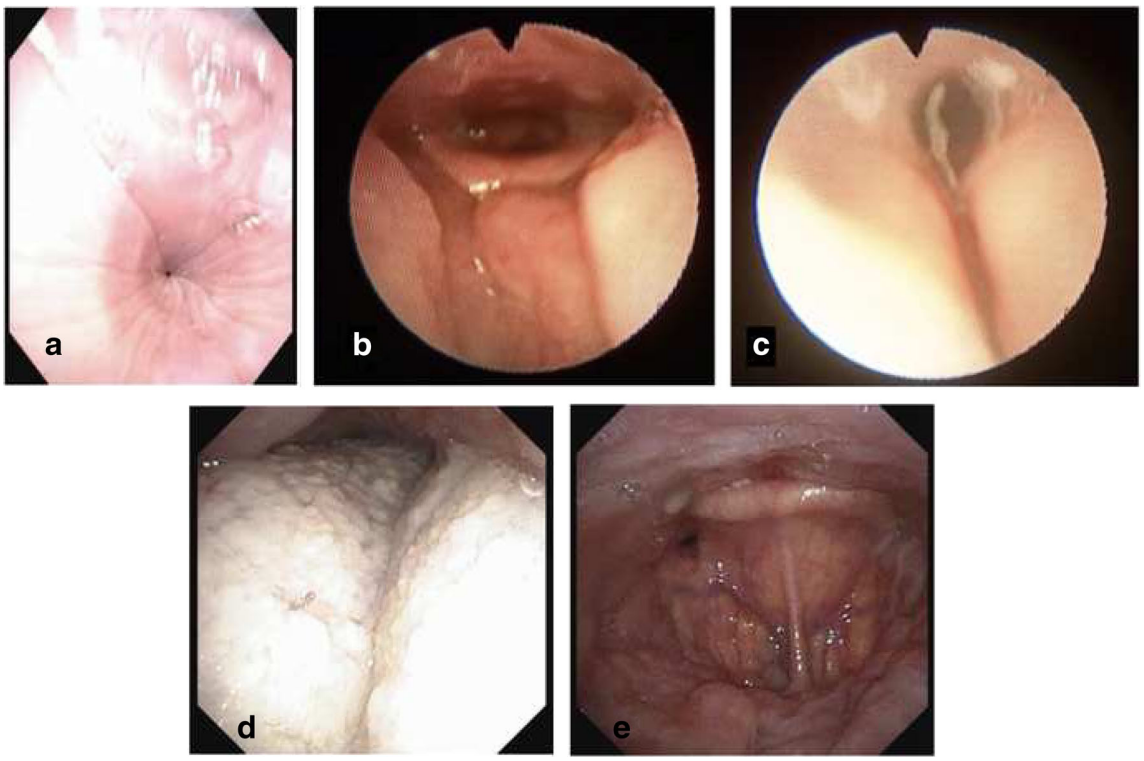

Fig. 1 DISE images showing collapses that have been associated to surgical failure. **a** Complete circumferential collapse at velum. **b**, **c** Two sequences of lateral oropharyngeal wall collapse. **d** Complete tongue base collapse. **e** Complete anteroposterior epiglottic collapse

or barbed reposition pharyngoplasty (BRP). This hypothesis must be proved in prospective trials.

It has not been clarified whether DISE helps to avoid unnecessary multilevel surgery or if it promotes multilevel surgery. A careful interpretation of DISE findings is essential. Not all tongue base or epiglottic collapse observed on DISE need to be treated in order to have surgical response [19, 20•]. Another study with drug-induced sleep computed tomography demonstrated that the resolution of epiglottic collapse was possible without primary epiglottic surgery [41]. An increased UA lumen was found in these patients and it was hypothesized that this may have caused a decrease in negative effort dependence that improved this collapse. This implies that the answer to whether it is necessary to treat all the collapses observed in DISE depends on the fluid dynamics of the UA. Nearly all collapses begin at the velopharynx and may progress downwards, after correcting the primary collapse, the remaining collapses down the line may be solved. New maneuvers while doing DISE such as the insertion of a nasopharyngeal tube may help to resolve the problem of performing unnecessary tongue base surgery [42]. Inserting a nasopharyngeal tube in cases of complete velopharyngeal collapse decreased or solved the obstruction of the lateral pharyngeal walls and epiglottis, however, did not modify the collapse downwards when the velopharyngeal collapse was partial [42]. The absence of improvement at the lower level of collapse, after the insertion of the nasopharyngeal tube, endorses the finding of Kim et al. in which patients with partial palatal collapse did not benefit from LPMR if they also had lateral wall or tongue base collapses [32]. In such cases, these lower level collapses should be interpreted as primary collapses that need to be addressed. This information supports the idea that DISE increases our understanding of the UA behavior, but interpretation is not easy and there is a need of better comprehension of these collapses and how they are changed after surgery. It is also true that after surgery, UA collapse can change and new collapses can be responsible for negative surgical outcomes [27•, 41, 43]. To deepen our knowledge on this, DISE studies pre and postoperative comparing successful and failure patients are necessary. Nevertheless, it is challenging to transport this into the clinical setting.

Even after treating all the areas of collapse and improving the UA lumen, there is still no guaranty of success [20•, 41]. Sleep surgeons cannot be completely optimistic. A holistic view of the patient and the pathophysiology of the UA collapse and sleep apnea is necessary to understand the problem. For example, tongue base collapse can be caused by a small space due to retrognathia, to excessive muscle relaxation, to lingual tonsil hypertrophy, or a combination of these factors. There are different physiological traits that play an important role on the UA collapse, that is: loop gain, arousal threshold, and muscle response [44]. Eckert reported that anatomical factors are responsible for OSA in 30% of patients while the rest have a combination of anatomical and physiological traits [45]. Despite arousal threshold can be lower after surgery, loop gain does not change. Moreover, a loop gain higher than 0.5 was predictive of 100% surgical failure [46•]. Unfortunately, the assessment of these non-anatomical traits is not possible in clinical practice, but hopefully, it will be possible in a near future and will help in the selection of OSA treatment.

Undoubtedly, the small sample size of some studies plays an important role in articles where no associations were found, translating less statistical power, for example, the article with the highest sample sizes had 101 in one single center and 275 patients in the multicenter study [33••, 36]. Nevertheless, other articles with small sample sizes showed robust conclusions; the exclusion criteria of complete CC for HNS was made after the observation of 100% failure rate in the five patients that showed this collapse whereas the success rate was 81% in the 19 patients that did not show the complete CC [29]. Another interesting observation from the study by Kim et al. with 21 patients is that the patients that showed a complete velopharyngeal collapse had better surgical response than those with a partial collapse (82.4% vs 0%) [32]. In fact, the patients that had a partial palatal collapse in addition to tongue or lateral pharyngeal wall collapse did not show any improvement after LPMR. The patients with partial velopharyngeal collapse demonstrated worse surgical response rates, although not statistically significant for Green et al. [33••].

On the other hand, it is possible that some of the associations found in some of the studies were not real associations if too many hypotheses were tested. This argument is less valid when different studies achieve the same results, the chances that different studies have the same error are low. Therefore, the existence of lateral wall collapse is probably associated with poor surgical response to Stanford's classical phase 1 surgery and maxillomandibular advancement should be offered to these patients [47, 48]. In Fig. 1, representative images of collapses associated with surgical failure are shown.

The definitions of success or failure used in the different studies might be in part responsible for the lack of predictive factors. Most of the authors use the classical Sher definition of a 50% reduction in the AHI plus a final AHI lower than 20/h [27•, 29, 30, 34], while others use lower than 15/h [33••, 35, 37] or even 10 events per hour [20•, 26]. The problem with the addendum of the *final AHI lower than* is that patients with a high AHI might have reductions higher than 50% but remain over the various final AHI limits, and are thus, classified as failures, despite the fact that a clear improvement of the disease is achieved. Therefore, this misclassification could be responsible for the lack of statistical significance of the comparison. Moreover, some clinical traits that improve after

surgery, for example, daytime sleepiness, may not always correlate with the AHI improvement and are hence misrepresented. In our clinical practice, we have observed patients with an important improvement in daytime sleepiness after surgery whose AHI had not changed very much. It is possible that in certain patients, the change in the number of obstructive apneas to hypopneas is responsible for this. Nevertheless, these patients usually show an increase in oxygen saturation; therefore, the subsequent decrease in the hypoxia load could be responsible for this improvement. Another explanation for the unchanged AHI after surgery despite clinical improvement is that some patients downshift to positional OSA after surgery [49, 50]. If during the sleep study, they sleep more time in supine position that they usually do at home, the AHI will not reflect the current state of the patient. PSG studies promote sleeping in supine position, as the sensors attached to the body make it difficult to change position.

There are certain limitations in this review, the lack of a common classification for DISE findings made difficult the extrapolations of the findings of one center to another. Moreover, DISE findings are technique dependent. It has been shown that there are differences if sedation is performed with propofol using bolus or a target-controlled infusion technique [51]. The updated European position paper on DISE tries to standardize the technique in order to overcome these problems [52••]. Nevertheless, propofol bolus technique was not used in any of the recent articles. Finally, even though DISE has shown a good intraobserver and interobserver agreement [53–55], there are certain areas like the tongue base that are difficult to observe and have worse concordance results. Even the presence or absence of complete CC can be challenging among experts [30].

Conclusions

Although sleep endoscopy changes the surgical plan in more than 50% of the patients, it is still not clear whether patients selected after DISE have better surgical results than those selected without it. The lack of predictive factors of success or failure does not disqualify DISE in clinical practice, as the information obtained appears to be useful in choosing one surgical technique over another, depending on the type of collapse observed. DISE requires careful interpretation, as not all the collapses observed need to be treated in order to have successful results. On the other hand, addressing all the collapses observed also does not guarantee success, reflecting the challenge in treating OSA patients.

Compliance with Ethical Standards

Conflicts of Interests The authors declare that they have no conflict of interests.

Human and Animal Rights and Informed Consent All reported studies with human subjects performed by the authors have been previously published and complied with all applicable ethical standards.

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- • Of importance
- •• Of major importance

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