Efficacy of upper airway stimulation on collapse patterns observed during drug-induced sedation endoscopy

Title: Efficacy of Upper Airway Stimulation on Collapse Patterns Observed During Drug-induced Sedation Endoscopy

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Abstract

Objective. Describe upper airway collapse patterns observed on drug-induced sedation endoscopy (DISE) during screening for a clinical trial, and to evaluate the impact of upper airway stimulation (UAS) on apnea-hypopnea index (AHI) based on collapse patterns found on preoperative DISE.

Study Design. Retrospective review of an ongoing prospective multi-institutional cohort study

Setting. 22 participating institutions of the STAR trial

Subjects and Method. 222 subjects were screened with DISE to determine eligibility for an implantable UAS device. Supine laryngoscopy was performed during moderate sedation (propofol and/or midazolam). Airway collapse pattern and severity was graded at four levels, including velum, oropharynx, tongue-base, and epiglottis. Patients with complete concentric collapse (CCC) at the velum were excluded from implantation. Collapse patterns and polysomnographic data for implanted patients were analyzed.

Results. The DISE evaluation lasted 12.9 ± 6.3 minutes on average with no adverse events. CCC at the velum was observed in 52 (23%) of screened subjects and were subsequently excluded from implantation. Of the 170 of subjects without complete concentric collapse, 126 (77%) underwent implantation: 121 (96%) had multi-level collapse and 5 (4%) had single-level collapse. Subjects with both multi-level collapse and single level collapse had a statistically significant reduction in AHI after implantation.

Conclusion. DISE is an efficient and safe method for determining UAS eligibility. The majority of patients had multi-level airway collapse, illustrating the limitations of single-level upper airway surgery in treating OSA. In this cohort, UAS is an equally effective

OSA therapy for patients with single- and multi-level airway collapse.

Keywords: upper airway stimulation; obstructive sleep apnea; sedation; sleep-disordered breathing; sleep surgery; drug-induced sleep endoscopy; drug-induced sedation endoscopy

Introduction

Obstructive sleep apnea (OSA) is a disorder defined by repeated complete (apnea) or partial (hypopnea) closures of the upper airway associated with intermittent hypoxemia and disturbed sleep.[1] This results in excessive daytime somnolence as well as an increased risk of cardiovascular events, motor vehicle accidents, and death.[2-5] Initial treatment for moderate to severe OSA is continuous positive airway pressure (CPAP), which may decrease cardiovascular mortality and prolong survival.[6,7] However, effective use of CPAP is limited due to suboptimal compliance, with almost 50% of patients reporting low satisfaction.[8-10] Surgical procedures that target specific areas of upper airway obstruction are an option, though patients may be hesitant to pursue this due to high morbidity and a lower success rate than CPAP.[11] Consequently, there has been an increased interest in developing alternative therapies for moderate-to-severe OSA and methods to identify sites of obstruction that must be addressed for effective OSA therapy.

Several techniques have been used to characterize patterns of obstruction, including the physical examination, awake fiberoptic nasal endoscopy, and cephalometric studies.[12-14] However, these techniques are performed while awake, and may not reveal the patterns of collapse found with reduced upper airway muscular tone during sleep. Drug-induced sedation endoscopy (DISE) was developed for fiberoptic examination of the upper airway in pharmacologically sedated patients in a state that simulates sleep.[15] The major advantage of DISE over other techniques is that it allows direct visualization of dynamic upper airway collapse. DISE has been shown to be a safe and reliable diagnostic test, and the structure-based assessment allows identification of upper airway sites that require treatment. [16,17]

Most surgical alternatives for OSA have focused on surgical removal of tissue responsible for airway obstruction. Although this strategy reduces obstructing tissue, it does not address the overall collapsibility of the upper airway, which may exist independently from obstructing tissue. Upper airway stimulation (UAS) is a novel implantable device for patients who are intolerant to CPAP, and does not require permanent alteration of the upper airway by tissue removal. In the clinical trial that validated the safety and efficacy of UAS, DISE was used to select patients who were likely to benefit from the therapy.[18,19] Therefore, UAS therapy became the first FDA-approved therapy to include DISE as a critical prerequisite to surgery. The purpose of this study is to report on the levels, patterns, and severity of upper airway collapse as observed during DISE evaluation of the subjects enrolled in the STAR trial, and to assess the success of UAS with regard to baseline DISE findings.

Methods

Study Design

The STAR trial is a prospective multi-center clinical trial to establish the safety and efficacy of an implantable UAS device (Inspire II, model 3024, Inspire Medical Systems Inc., Maple Grove, MN, USA) for CPAP-intolerant adults with moderate-to-severe OSA. Details of subject eligibility and study design have been previously published.[18] This manuscript reports on the use of DISE to determine UAS eligibility, and post-implant subject outcomes based on observed baseline patterns of collapse during DISE. IRB approval was not required to complete this report.

Drug-induced sedation endoscopy (DISE)

DISE was performed in the operating room by a participating otolaryngologist, trained using a standardized protocol of DISE sedation.[17,20] Sedation was performed using propofol and/or midazolam for induction of artificial sleep, which was titrated by either target-controlled infusion (TCI), or to a level of moderate sedation where the patient was unarousable to verbal stimulation. Procedural data, including procedure time, sedation time, and adverse events, were collected per protocol.

Collapse patterns were assessed during inspiration, and graded at the level of velum, oropharynx, tongue base and epiglottis using the VOTE classification.[17] Pattern of collapse was characterized as antero-posterior (AP), latero-lateral (LL), or concentric. Degree of collapse was characterized as complete, partial or no collapse. Subjects with complete concentric collapse (CCC) at the velum, and those who were otherwise not considered good candidates for the implant were excluded.

Upper Airway Stimulation (UAS) Device Implant, Titration and Follow-up

Patients who met the inclusion and exclusion criteria underwent implantation of the UAS device, which is comprised of an implantable pulse generator (IPG), respiratory sensing lead, and hypoglossal nerve stimulation lead. The subject was given a handheld remote to activate therapy prior to sleep and deactivate upon awakening, and allow for patient-controlled regulation of the stimulation amplitude within a programmed therapeutic range as determined during a sleep lab titration.

Each subject underwent a preoperative PSG to measure baseline AHI, and titration PSGs as needed after implantation, and additional long-term follow-up PSGs (at

12, 18 and 36 months), which were scored by a core lab using the AASM guidelines to ensure uniformity across all institutions.[21]

Statistical Analysis

All analyses were performed with SAS/STAT. A p-value of <0.05 was considered to indicate a statistically significant difference for all statistical tests.

Baseline DISE results were analyzed to determine the most common sites and patterns of airway collapse. Logistic regression was used to predict the association of velum CCC with patient demographics, including age, body-mass index (BMI), neck size, and AHI while the Fisher's Exact Test was used for gender.

Baseline DISE results were used to categorize patients into four groups of airway collapse, from single-level to four-level airway collapse, based on the VOTE score (e.g., single-level meaning any collapse at only one level: velum, oropharynx, tongue-base, or epiglottis, two-level meaning collapse at any two levels, etc.). The baseline and postoperative AHIs were compared in each of the four airway collapse groups using the paired t-test. Airway collapse was defined as partial or complete collapse, regardless of direction. McNemar's test was used to ascertain whether there is an association of AP collapse at the tongue base with AP collapse at the soft palate and ANOVA was used to determine if increasing collapse severity was related to increased AHI.

Results

A total of 222 subjects at 22 participating sites (15 United States, 3 Germany, 2 France, 1 Netherlands, and 1 Belgium) underwent DISE as part of the STAR trial. Patient demographics are shown in **Table 1**.

DISE Procedure

Propofol alone (68%), midazolam/propofol combination (20%) or midazolam alone (11%) were the sedatives used during the examination. Propofol alone and midazolam alone were used solely in the United States and Europe, respectively, while the midazolam/propofol combination was used in both the United States and Europe. Given the subjects' previous OSA history, CPAP intolerance, and need to recreate the upper airway collapse and apneas, oxygen desaturations were expected. The average minimum oxygen saturation was to 83.5 ± 0.7% (range 42-98%). The mean duration of the DISE examination was 12.9 ± 6.4 minutes (range 2-40 minutes), and there were no adverse events associated with sedation or examination.

Collapse Patterns

The velum and tongue base were the most common collapse locations. The frequency of collapse type by airway level is presented in **Table 2**. AP collapse was the predominant airway collapse direction at all sites, except at the oropharynx. There was a statistically significant association of AP collapse at the velum with AP collapse at the tongue base ($p=0.005$). CCC at the velum was not associated with age, gender, or AHI, though there was a statistically significant association with BMI ($p=0.04$) and neck size ($p=0.01$), as seen in **Table 4**. The relationship of palatal CCC with BMI, AHI, and neck size for all screened patients is shown in **Figure 2**.

Figure 3 shows that the majority of patients had multi-level airway collapse, with four-level collapse as the most common combination, followed by three-level collapse at the velum, tongue base, and epiglottis. **Table 3** demonstrates the percentage of subjects for each combination of collapse and baseline AHI for each collapse level severity. There was no correlation between airway collapse severity and baseline AHI (p=0.73).

Effect of UAS on Collapse Severity

A total of 126 subjects were implanted with the UAS. The prevalence of collapse severity in the implanted patients was similar to the total subjects screened with DISE. Patients predominantly had multi-level collapse, with four-level collapse being the most common at 50% (**Figure 3**), and single-level collapse as least common. UAS therapy was able to significantly improve the AHI in patients with single and multi-level collapse, including palatal and oropharynx collapse, initially seen at 12-months and sustained until 36-months ($p<0.05$) as seen in **Figure 4**. There was no difference in UAS effect size in patients with single level and multi-level collapse.

Discussion

The current study illustrates DISE as a valid procedure to evaluate patient candidacy for UAS. It is a rapid, safe and reliable examination to observe upper airway collapsibility in patients with OSA.[22,23] Although the primary cause of OSA is often thought to be due to obstructing tissue in the upper airway during sleep, increased airway collapsibility due to reduced neuromuscular activity is also associated with the pathophysiology of OSA.[24,25] The presence of both factors may limit the effectiveness of surgeries focused on the removal of obstructing tissue, which only addresses the

mechanical obstruction but not the blunted neuromuscular response. UAS addresses airway collapsibility, however the resulting expansion of airway diameter lessens the contribution of increased tissue mass.

The finding that DISE can be performed safely in the CPAP-intolerant population is consistent with other literature showing few if any adverse events during DISE.[17,26] DISE is typically performed in the operating room by an otolaryngologist and anesthesiology staff, and patients are continuously monitored with electrocardiogram and pulse oximetry during induced apneas and hypopneas. In the present study, there were no adverse events requiring intervention related to the anesthesia or the procedure itself. Given the short procedure duration and safety profile, DISE has been recommended as a patient selection tool for UAS, due to its ability to select patients with an increased probability of therapeutic success.[19] The FDA agreed on the importance of DISE as the minimum screening tool to determine eligibility for UAS implantation; however, otolaryngologists must undergo the appropriate training for DISE prior to performing UAS implantation. Therefore, UAS is the first therapy for OSA to require DISE as a prerequisite to surgical implantation.

The major advantage of DISE is identification of the sites, severity, and patterns of airway collapse under simulated sleep conditions. Collapse was primarily in the complete AP direction, with the velum and tongue base being the most commonly involved areas, in line with previous studies.[19,27] Early feasibility studies demonstrated that CCC at the velum predict therapy failure for OSA patients treated with UAS, as patients with CCC at the velum had no change in the AHI after upper airway stimulation, while those without CCC had a significant decrease in the AHI.[19,28] This finding

influenced the selection criteria for the pivotal large cohort study, which confirmed that patients without CCC at the velum are more likely to have therapeutic AHI reduction with UAS.

In the current study, 52 subjects (23%) had CCC at the velum, which could not be predicted by age, gender, or AHI; however, there was a small but statistically significant association with BMI and neck size. The latter findings are consistent with previous work.[27,29] Correlation of CCC at the velum with increasing BMI has been demonstrated in the past perhaps due to increasing amounts of parapharyngeal adipose tissue.[29-31] Because velum CCC cannot be accurately predicted by other demographic factors, DISE remains an important screening tool for identifying patients with this type of collapse. Conversely, approximately 80% of subjects with BMI ≤ 32 kg/m^2 undergoing DISE did not have CCC at the velum, and the vast majority of these patients can be expected to meet the UAS DISE selection criteria.

The high prevalence of multi-level collapse seen in this cohort illustrates the difficulty of resolving OSA with single-level surgery, and necessitates tailoring of multiple surgical procedures to address each level of obstruction. Long-term follow-up of at least three years after surgically treated OSA patients has shown variable decreases in AHI of 44-74%.[32-34] In comparison, upper airway stimulation in this large cohort study with predominant multi-level airway collapse demonstrated significant mean reductions in AHI of nearly 70%, which was maintained 36 months post-implantation.

Interestingly, this study demonstrates the long-term efficacy of UAS to decrease AHI in both single-level and multi-level collapse. The data suggest that hypoglossal

nerve stimulation may simultaneously address multiple sites of airway collapsibility, despite the primary mechanism of action of tongue base protrusion. Improvement in upper airway collapse using UAS is supported by previous case studies where imaging was used to confirm multi-level airway opening during acute stimulation.[35,36] Although UAS primarily activates the protrusor muscles of the tongue, such as the genioglossus, it is important to note that the palatal airway is directly coupled to the tongue base via the palatoglossus muscle.[37] In addition, forward motion of the tongue dorsum reduces contact with the soft palate and allows the velum to drop away from the posterior pharyngeal wall in a mechanism similar to the use of an oral appliance.[38,39] The ability of UAS to reduce the AHI in patients with multi-level airway collapse may be due to this coupling effect. The current results suggest that a single procedure, UAS implantation, has the potential to resolve both single-level and multi-level upper airway obstruction in a group of well-selected patients with OSA.

There are some limitations in the present study. Although DISE has been validated as a reliable tool, each test is scored in a subjective manner, and grading may differ from operator to operator. In this case, all operators were trained in performing DISE per clinical trial protocol, and operators were permitted to request secondary review to ensure accurate grading of each subject. Also, there were a limited number of subjects with single-level collapse although UAS implantation still significantly improved AHI in this group as well.

Conclusion

The current study shows that DISE is a quick and safe method in determining UAS eligibility and a majority of screened patients with BMI $\leq$ 32 kg/m^2 will have multi-level airway collapse without CCC at the velum, making them eligible for UAS. UAS is an effective therapy option for CPAP-intolerant OSA patients, with consistent improvement in AHI through 36 months post-implantation in patients with single-level or multi-level airway collapse.

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Table 1 – Baseline characteristics of patients

Variables	All Patients (n=222)
Age (years)	54.3 ± 0.7
Male (n, %)	188 (85%)
BMI (kg/m2)	28.6 ± 0.2
Neck Size (cm)	41.5 ± 3.3
Baseline AHI (events/hour)	32.0 ± 0.8

388 Table 2 – Frequency of collapse type by site of obstruction

All Screened Patient DISE Characteristics (total=222)	Complete			Partial			None	% with any collapse
	AP	**Lateral**	**Concentric**	**AP**	**Lateral**	**Concentric**		
Velum	52%	0%	23%	17%	0%	1%	6%	94%
Oropharynx	10%	4%	14%	19%	17%	5%	31%	69%
Tongue-Base	51%	1%	6%	28%	3%	3%	7%	93%
Epiglottis	33%	1%	3%	30%	5%	2%	27%	73%

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Table 3 – Distribution of screened patients by collapse severity. Data shown as mean ± standard error

	Velum	Oropharyn	Tongue-	Epiglottis	Distribution in screened patients (n=222)	Screened patient AHI	Distribution in Implanted Patients (n=126)	Implanted patient baseline AHI (n=126)	Implanted patient 12-month AHI (n=124)	Implanted patient 18-month AHI (n=121)	Implanted patient 36-month AHI (n=94)
Single-level collapse	•				2.7%	33.6 ± 4.1	1.6%	29.7 ± 3.5	9.3 ± 2.0 *	12.0 ± 2.1 *	7.7 ± 5.0 *
		•			0.5%		0.8%				
			•		0.9%		1.6%				
				•	0.0%		0.0%				
Two-level collapse	•	•			3.6%	30.5 ± 1.8	0.0%	27.7 ± 2.1	12.7 ± 3.5 *	13.1 ± 3.9 *	8.7 ± 1.8 *
	•		•		7.7%		7.9%				
	•			•	0.0%		0.0%				
		•	•		1.4%		0.0%				
		•		•	0.0%		0.0%				
			•	•	1.4%		2.4%				
Three-level collapse	•	•	•		10.8%	31.2 ± 1.5	10.3%	33.5 ± 1.9	19.0 ± 2.7 *	18.5 ± 2.5 *	16.9 ± 3.2 *
	•		•	•	18.5%		23.0%				
		•	•	•	2.3%		2.4%				
	•	•		•	0.5%		0.0%				
Four-level collapse	•	•	•	•	50.0%	32.8 ± 1.5	50.0%	32.1 ± 1.5	13.7 ± 2.0 *	11.5 ± 1.7 *	9.0 ± 1.7 *

* denotes $p<0.0001$ difference from baseline

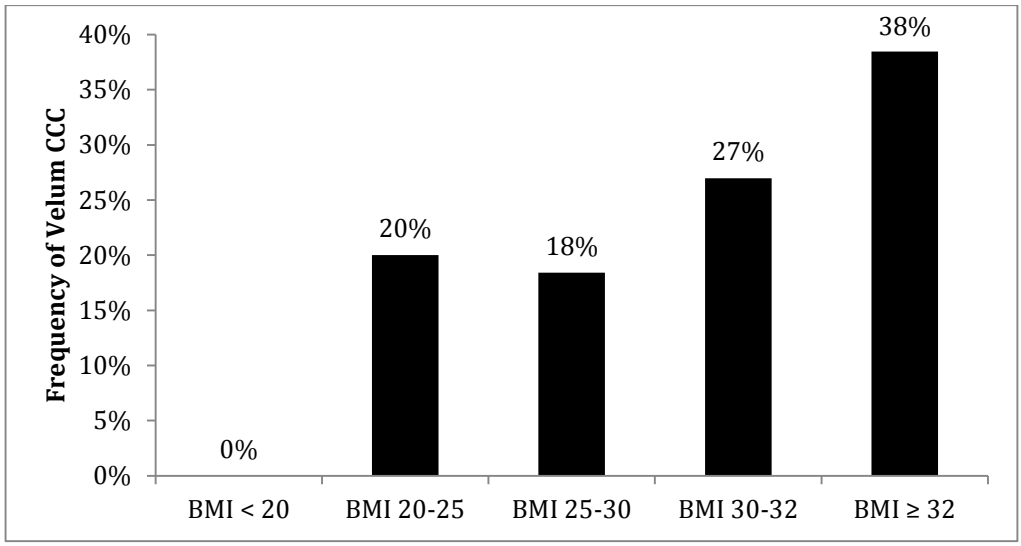
Table 4. Demographic Predictors of Palatal CCC

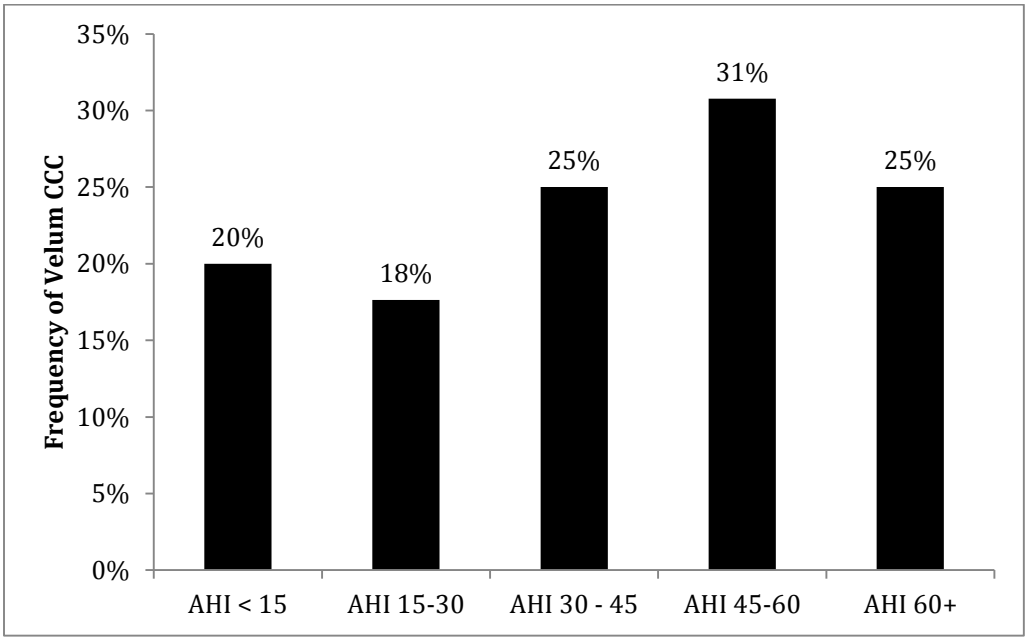
Variable	CCC Present		CCC Absent		p-value
	n	Mean ± SD	n	Mean ± SD	
Age (years)	50	54.4 ± 9.7	169	54.3 ± 9.8	0.91
Male	46		142		0.17
BMI (kg/m2)	48	29.3 ± 2.5	169	28.4 ± 2.6	0.04
Neck Size (cm)	47	42.5 ± 3.3	167	41.2 ± 3.2	0.01
Baseline AHI (events/hour)	48	33.2 ± 10.8	170	31.6 ± 12.3	0.41

Abbreviations: CCC, complete concentric collapse at velum; BMI, body mass index;

AHI, apnea-hypopnea index

Figures 2a, 2b and 2c – Frequency of velum complete concentric collapse, based on BMI, AHI, and neck size





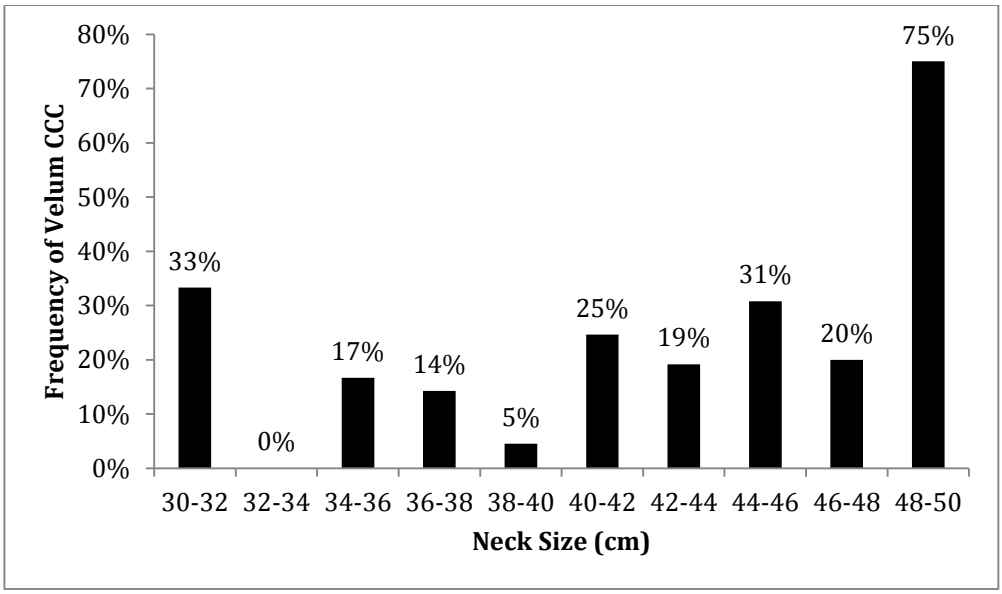

80%
70%
60%
50%
40%
30%
20%
10%
0%
Frequency of Velum CCC
33%
0%
17%
14%
5%
25%
19%
31%
20%
75%
30-32
32-34
34-36
36-38
38-40
40-42
42-44
44-46
46-48
48-50
Neck Size (cm)

Figure 3 – Collapse severity percentage in screened and implanted patients

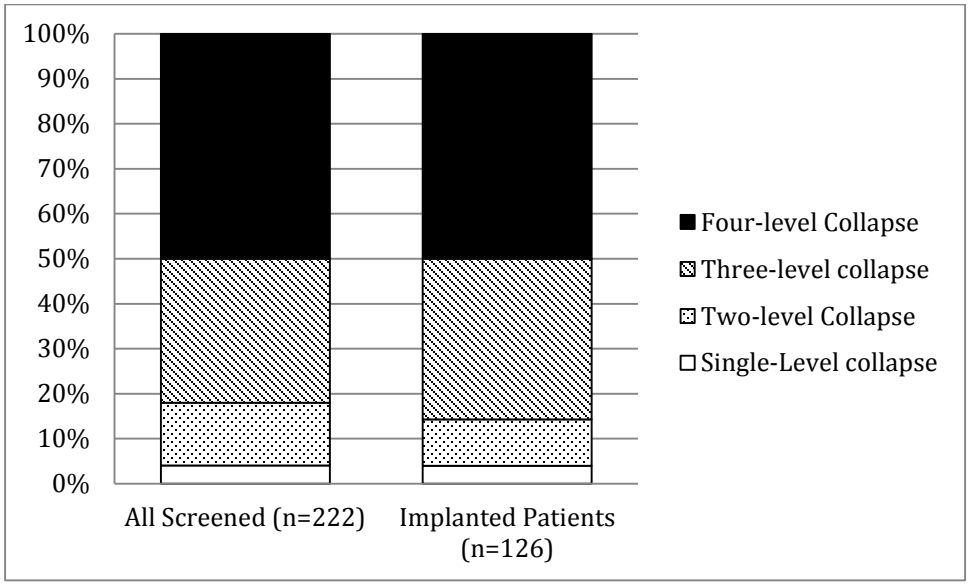


Figure 4 – Implanted patients have improved AHI, regardless of collapse severity