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Outcomes of Upper Airway Stimulation for Obstructive Sleep Apnea in a Multicenter German Postmarket Study

Clemens Heiser, MD[1], Joachim T. Maurer, MD[2], Benedikt Hofauer, MD[1], J. Ulrich Sommer, MD[2], Annemarie Seitz, MD[3], and Armin Steffen, MD[3]

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Abstract

Objective. Selective stimulation of the hypoglossal nerve is a new surgical therapy for obstructive sleep apnea, with proven efficacy in well-designed clinical trials. The aim of the study is to obtain additional safety and efficacy data on the use of selective upper airway stimulation during daily clinical routine.

Study Design. Prospective single-arm study.

Setting. Three tertiary hospitals in Germany (Munich, Mannheim, Lübeck).

Subjects and Methods. A multicenter prospective single-arm study under a common implant and follow-up protocol took place in 3 German centers (Mannheim, Munich, Lübeck). Every patient who received an implant of selective upper airway stimulation was included in this trial (apnea-hypopnea index $\geq$15/h and $\leq$65/h and body mass index $<$35 kg/m^2). Before and 6 months after surgery, a 2-night home sleep test was performed. Data regarding the safety and efficacy were collected.

Results. From July 2014 through October 2015, 60 patients were included. Every subject reported improvement in sleep and daytime symptoms. The average usage time of the system was 42.9 $\pm$ 11.9 h/wk. The median apnea-hypopnea index was significantly reduced at 6 months from 28.6/h to 8.3/h. No patient required surgical revision of the implanted system.

Conclusion. Selective upper airway stimulation is a safe and effective therapy for patients with obstructive sleep apnea and represents a powerful option for its surgical treatment.

Keywords

obstructive sleep apnea, surgical treatment, hypoglossal nerve, selective upper airway stimulation, German postmarket study

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Obstructive sleep apnea (OSA) has an increased prevalence over the prior decades, present in 6% of women and 13% of men in the United States.[1] Continuous positive airway pressure (CPAP) is the gold standard therapy; however, it is limited by adherence and acceptance issues. Alternative treatment options have been developed, including upper airway stimulation (UAS) per the unilateral respiration-synchronized stimulation of the hypoglossal nerve.[2,3] This approach to electrical stimulation based on implanted neuromodulation technology was demonstrated to be a safe and effective treatment for OSA in a recent large clinical trial.[3] For selected patients with moderate to severe OSA who were CPAP intolerant, the UAS system reduced OSA severity both objectively, as measured by apnea-hypopnea index (AHI) and oxygen desaturation index (ODI), and subjectively, through improved quality-of-life measures—namely, the Epworth Sleepiness Scale (ESS) and the Functional Outcomes of Sleep Questionnaire (FOSQ)—all evaluated at 12 months postimplantation.[3] Randomized withdrawal of therapy for 1 week at 13 months resulted in return of AHI, ODI, ESS, and FOSQ to baseline levels, and reactivation reestablished therapeutic efficacy as measured at 18 months.[4] More recently, long-term follow-up of the study cohort reported sustained treatment effects and therapy adherence after 24 and 36 months of implantation.[5,6] In addition, 2 single-center studies in a clinical practice setting demonstrated that UAS was associated with high adherence, low morbidity, and significantly decreased AHI.[7,8]

Previous studies have identified specific selection criteria for patients who are likely to respond to UAS.[9-13] Individuals with body mass index $<$32 or $<$35 kg/m^2 had a lower AHI at 6

[1]Department of Otorhinolaryngology–Head and Neck Surgery, Klinikum rechts der Isar, Technische Universität München, Munich, Germany
[2]Department of Otorhinolaryngology–Head and Neck Surgery, University-Hospital Mannheim, Mannheim, Germany
[3]Department of Otorhinolaryngology, University of Lübeck, Lübeck, Germany

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Corresponding Author:
Clemens Heiser, MD, Department of Otorhinolaryngology–Head and Neck Surgery, Klinikum rechts der Isar, Technische Universität München, Ismaninger Str 22, 81675 Munich, Germany.
Email: hno@heiser-online.com

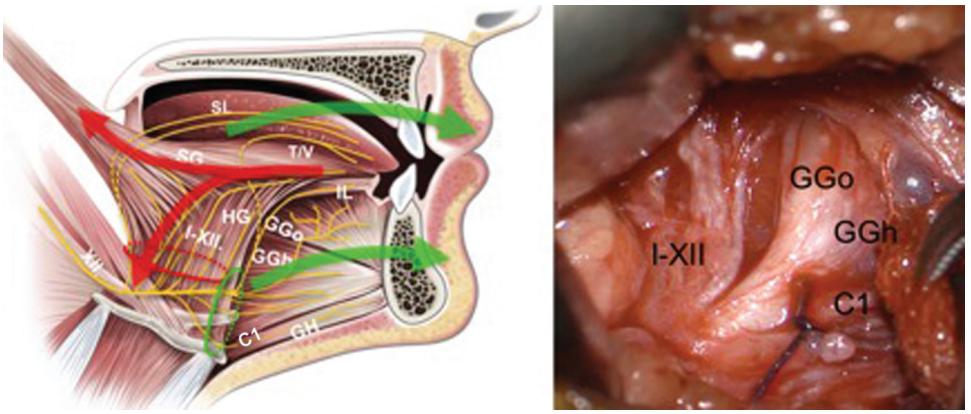

Figure 1. Schematic and intraoperative figure of the terminating hypoglossal nerve branches. Green ellipse indicates branches targeted for cuff placement. C1, first cranial nerve; GGo/GGh, oblique/horizontal genioglossus muscle; GH, geniohyoid muscle; HG, hyoglossus muscle; I-XII, lateral branches of hypoglossal nerve; SG, styloglossus muscle; SL/IL, superior/inferior longitudinal muscles; T/V, transversal/vertical intrinsic muscles; XII, hypoglossal nerve.

months with treatment.[3,9,12-14] A specific pattern of collapse—namely, complete concentric collapse at the retropalatal airway—during a screening drug-induced sedated endoscopy prior to implantation was associated with reduced level of response.[10] The complete concentric collapse pattern can be found in >20% of otherwise suitable candidates and is associated with higher body mass index and AHI.[15] These success/failure predictors merit additional supporting evidence from the clinical practice setting for their utility in ongoing patient selection.

This multicenter prospective study focuses on objective and patient-reported outcomes and therapy adherence of UAS for treatment of OSA in a clinical practice setting at 3 academic centers. The study intends to determine if treatment outcome reported in a previous controlled clinical trial setting can be achieved in a routine clinical setting.

Methods

This multicenter prospective clinical trial included OSA patients who received an implanted UAS system (Inspire Medical Systems, Minneapolis, Minnesota). The study was approved by the ethics committee at all 3 institutions and was registered as NCT02293746 on clinicaltrials.gov.

Patient Selection

Key study selection criteria were based on those established from the STAR trial.[3] Patients with a history of moderate to severe OSA and nonadherence to CPAP underwent screening for qualification of implantation as part of routine clinical practice. Patients with body mass index >35 kg/m^2 were excluded. Additional screening included a 2-night home sleep test and drug-induced sedated endoscopy. Patients were excluded if they presented with AHI <15 or >65, central sleep apnea >25% of total AHI, or complete concentric collapse at the velopharynx during drug-induced sedated endoscopy.

Implantation

The surgical implantation procedure was performed in accordance with previously established operative techniques.[16,17] The standardized operative procedure included (1) placing a cuff electrode on the distal branches of the hypoglossal nerve to stimulate the tongue protrusors, (2) inserting an implanted pulse generator in the right upper chest, and (3) placing a respiratory sensing lead between external and internal intercostal muscles of the ribs. The targeted stimulation site on the hypoglossal nerve aimed to recruit genioglossus and transversal/vertical muscles while excluding styloglossus and hyoglossus muscle activation. Furthermore, a branch of the first cranial nerve—which is responsible for the geniohyoid muscle activation and which runs parallel to the hypoglossal nerve—was also included when feasible. Both intraoperative nerve monitoring and visualization of tongue motion were used to confirm proper electrode placement,[17,18] as shown in **Figure 1**.

All patients were discharged on their regular diets and were advised to avoid strenuous physical activities involving the right arm—ipsilateral side of implant—for 2 weeks postoperatively.

Data Collection and Statistical Analysis

The device was activated 1 month after implantation, followed by a month of therapy acclimatization, with patients gradually increasing the stimulation amplitude to optimize both comfort and subjective effectiveness. Between months 2 and 6, in-laboratory titration studies were conducted to optimize therapy during polysomnography (ie, full polysomnography titration). While the majority of patients required only 1 titration night, some warranted a second titration to further optimize and individualize therapy. Fifteen patients had a second titration night after 3 months of implantation. This was conducted if the first titration night was not acceptable, and the decision was made at each implant center. During the second overnight polysomnography, advanced testing of specific electrode configurations, stimulation timing, and impulse settings was performed, all of which were not routinely tested during the first polysomnography. Two-night home sleep test studies were recorded with level III polygraphy systems to determine objective outcomes at 6

Figure 2. Treatment and follow-up pathway of selective upper airway stimulation for obstructive sleep apnea. DISE, drug-induced sedated endoscopy; PSG, polysomnography.

Table 1. Patients Characteristics at Enrollment (N = 60).[a]

Characteristic	Mean ± SD	Range
Age, y	56.8 ± 9.1	37-75
BMI, kg/m^2	28.8 ± 3.6	21.4-36.6
AHI, events/h	31.6 ± 14.4	13.4-64.5
ODI, events/h	28.5 ± 16.6	3.5-71.5
FOSQ score	13.2 ± 3.6	3.3-19.6
ESS	12.4 ± 5.7	2-24

Abbreviations: AHI, apnea-hypopnea index; BMI, body mass index; ESS, Epworth Sleepiness Scale; FOSQ, Functional Outcomes of Sleep Questionnaire; ODI, oxygen desaturation index.
[a]Men, n = 58; women, n = 2.

months without device adjustment. The objective outcomes of AHI and ODI were scored with standard 2007 scoring criteria,[19] with hypopnea scored according to 30% airflow reduction and 4% oxygen desaturation. Patient-reported outcomes included ESS and the FOSQ at baseline (preimplant) and months 2 and 6 (postimplant). The treatment and follow-up pathway, as applied, is shown in **Figure 2**.

SPSS 23.0 software (IBM, Chicago, Illinois) was used. Descriptive statistics were calculated for demographic variables. Paired *t* test was used to compare baseline and postimplantation values. Data are given as median and mean ± SD. *P* values ≤.05 were considered statistically significant.

Results

Characteristics of the Participants

Patient characteristics are summarized in **Table 1**. The majority of participants presented with moderate to severe OSA during the screening sleep studies and moderate symptoms of daytime sleepiness and diminished OSA-relevant quality of life.

All patients had failed CPAP as a first-line treatment. Among them, 14 patients had also attempted oral appliance therapy but could not maintain adherence, primarily due to insufficient efficacy. A total of 15 patients had prior upper airway OSA operations, which included uvulopalatopharyngoplasty (UPPP), uvulopalatal flap, genioglossus advancement, tongue base reduction, advancement/stabilization of the tongue base, and epiglottoplasty.

Surgical Implantation

The average implantation procedures were 160.0 ± 35.9 minutes in duration, ranging from 113 to 329 minutes. Right tongue base or bilateral protrusion was confirmed with perioperative stimulation testing among all patients. Only 1 patient did not show a clear protrusion during the implant procedure but subsequently demonstrated right tongue base protrusion at postoperative visits.

Polygraphic Outcomes

The objective outcome from the polygraphic study consisted of 2-night at-home sleep studies at baseline for screening prior to implant and again at 6 months postoperatively for therapy efficacy validation (see **Table 2** and **Figure 3**). The average values of the 2 home sleep studies were used for comparison analysis. Out of 60 participants, 56 completed the 6-month polygraphy studies. Of the 4 patients who did not complete the 6-month visit, 4 underwent a UPPP surgery after the 2-month titration studies and missed the 6-month visit.

Among the 56 patients who completed the 6-month visit, an average AHI reduction of 61% ± 24% compared with baseline was achieved. At the 6-month visit, 25% of patients presented with an AHI ≤5 events per hour; 59% patients, AHI ≤10/h; and 70% patients, AHI ≤15/h. Per the Sher criteria (AHI <20 with at least 50% reduction), 68% patients were classified as responders.[20] With the 4 patients who underwent a UPPP and missed the 6-month visit, a success rate of 63% was found. There was a statistically significant reduction in ODI, apnea index, hypopnea index, and minimal SpO_2 nadir from baseline to 6 months. Total and percentage sleep time with SpO_2 <90% decreased, though neither achieved statistical significance.

Patient-Reported Outcomes

At the 2-month visit, there was significant reduction in daytime sleepiness as measured by the ESS and significant improvement in daytime functioning as measured by the FOSQ compared with baseline. Both ESS and FOSQ scores further improved at the 6-month visit from the baseline as well as the 2-month visit (see **Table 3**).

Adverse Events

Two procedure-related adverse events were recorded. In both cases, bleeding occurred during tunneling of the

Table 2. Polygraphic Outcomes at Baseline and 6 Months.[a]

	Baseline	6 mo	*P* Value
AHI, events/h			<.001
Mean ± SD	31.2 ± 13.2	12.0 ± 9.8	
Median (range)	28.6 (12.3-64.5)	8.3 (0.8-34)	
ODI, events/h			<.001
Mean ± SD	27.6 ± 16.4	13.5 ± 10.7	
Median (range)	27.0 (3.5-60.9)	9.6 (0.5-35.5)	
Apnea index, events/h			<.001
Mean ± SD	18.1 ± 14.7	7.6 ± 7.8	
Median (range)	14.2 (2.2 -64.5)	4.9 (0-33.7)	
Hypopnea index, events/h			<.001
Mean ± SD	13.0 ± 7.2	4.4 ± 4.1	
Median (range)	12.4 (0-33.7)	3.2 (0.2-20.4)	
Central + mixed apnea index, events/h			.27
Mean ± SD	1.2 ± 2.3	0.8 ± 1.1	
Median (range)	0.4 (0-11)	0.3 (0-4.6)	
Min SpO_2, %			<.001
Mean ± SD	71.4 ± 11.4	80.4 ± 7.6	
Median (range)	73.8 (50.5-88)	81 (65-90.5)	
Mean SpO_2, %			.41
Mean ± SD	92.8 ± 1.9	93.2 ± 3.4	
Median (range)	93 (86.5-97)	93.5 (73-97)	
Total sleep time SpO_2 <90%, min			.07
Mean ± SD	45.3 ± 60.5	25.8 ± 34.8	
Median (range)	13.4 (0-272)	8.8 (0-141)	
Percentage sleep time SpO_2 <90%			.26
Mean ± SD	10.7 ± 13.9	7.1 ± 12.1	
Median (range)	3.2 (0-56.7)	2 (0-75.5)	

[a]Averaged 2-night results from all 56 subjects who completed the 6-month visit. $P < .05$ vs baseline.

stimulation lead from the neck incision to the device pocket. Five patients reported postoperative pain related to the incisions. There was 1 instance of acute tongue numbness and 1 incidence of dysarthria, and both resolved within 2 months without further incident.

Three device-related adverse events were reported, all 3 relating to painful stimulation sensation in the period after therapy activation. One of these was a complaint of mild pain at all 3 device locations, and this patient continues to be monitored. The other instances of postactivation pain resolved without intervention or issue, resolving as patients acclimated to therapy use. One patient complained of speech difficulties after the therapy was activated, but this was resolved through reprogramming the stimulation energy field parameters, thereby improving the patient's subjective experience while maintaining suitable objective tongue motion as assessed by the managing physician.

Therapy Use

Device interrogation at the 6-month visit indicated 42.9 ± 11.9 h/wk (range, 9-64 h/wk) of therapy use among all patients, based on recording by the implanted device. The average stimulation amplitude was 1.9 ± 0.6 V (range, 1.0-3.5) and 1.9 ± 0.6 V (range, 1.0-3.9) at the 2- and 6-month visits, respectively.

Discussion

In this multicenter prospective study, UAS reduced OSA severity and improved patient-reported outcomes. Seventy percent of the study cohort reached AHI <15 at 6 months' postimplant. This result was consistent with the STAR trial outcomes reported at 12, 18, and 36 months of follow-up.[3,5] Patient-reported outcomes measured by ESS and FOSQ demonstrated a similar degree of improvement as in the STAR trial. No serious adverse events were observed, and minor complaints and side effects were either managed in the outpatient clinic setting or resolved spontaneously via therapy acclimatization. Therapy acceptance and adherence were high, as shown by objective device usage data.

The study followed the current routine clinical practice for patient selection, operative techniques, and therapy titration. The key patient selection criteria included body mass index <35, AHI between 15 and 65, and absence of complete concentric collapse at the soft palate during drug-induced sedated endoscopy. The implant techniques were standardized in this study as well as in clinical practice to

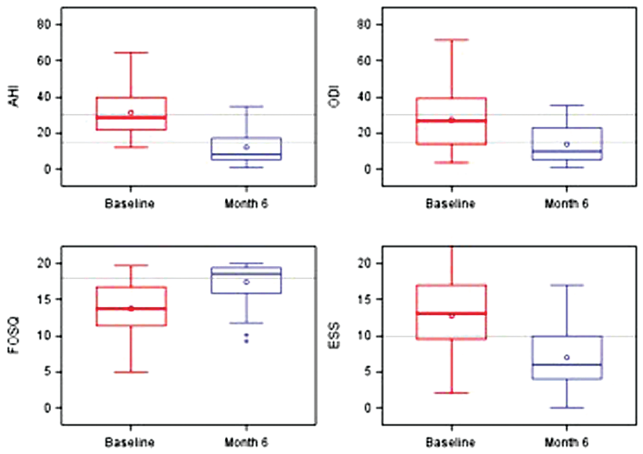

Figure 3. Primary outcomes of the clinical trial in terms of apnea-hypopnea index (AHI), oxygen desaturation index (ODI), Functional Outcomes of Sleep Questionnaire (FOSQ), and Epworth Sleepiness Scale (ESS) between baseline and 6-month visit. All results were statistically significant ($P < .05$ vs baseline).

include (1) the protrusor branches of the hypoglossal nerve, which innervate the genioglossus muscle, and (2) the stiffener branches of the transverse/vertical muscles, while excluding all retractor branches that innervate the styloglossus and hyoglossus muscles.[17] All patients enrolled in this study displayed either contralateral extension or bilateral protrusion of the tongue upon stimulation. Heiser et al showed a clear association of selective stimulation of protrusor muscles for better therapy outcomes, when excluding all branches of the retractor muscles.[18] The current study reflected a consistent implementation of the standardized operative techniques.[17] There is a considerable proportion of genioglossus muscle fibers that receive innervation from the hypoglossal nerve in the contralateral side, which may explain the bilateral protrusion observed, despite the overtly unilateral stimulation of the hypoglossal nerve (ie, crosstalk from right to left) seen in an extensive proportion of patients.[21]

Adverse events were rare. The surgical procedure was safe, and the few adverse events were solved without sequelae. Regarding the bleeding during tunneling, evidence with knowledge of patient anatomy would suggest that these minor bleeds are attributable to either an anterior branch of the external jugular vein or a prominent vein of the sternocleidomastoid muscle. Conservative management of such tunneling bleeds by external compression was the most appropriate approach to manage this complication. If necessary, a small fourth incision for direct visualization of the lacerated vein and accompanying closure with suture or equivalent may be performed. Neurapraxia of the hypoglossal and/or marginal mandibular nerves, potentially associated with this procedure, were infrequent and transient within this patient population, consistent with the STAR trial.

This multicenter study and an earlier single-center study reported objective therapy use of UAS of approximately 6 to 7 hours per night based on information retrieved from the implanted device after 6 months.[7,8] Although additional adherence data are needed for longer follow-up duration, the adherence of UAS at 6 months is considerably higher than the average 4.7 hours per night for CPAP use as reported in the APPLES study after 6 months[22] and 3.7 to 4.7 hours per night reported in the HomePAP study after 3 months.[23] This current study cohort included patients who previously could not adhere to CPAP. The improved adherence with UAS is suggestive of its clinical utility for longitudinal patient management for OSA symptoms and risks from OSA-related comorbidities, meriting further prospective study.

In addition, patients qualifying for this UAS therapy, a priori, skewed toward failure by virtue of being demonstrably refractory to successful treatment with CPAP, as a precondition to qualify for UAS. One plausible explanation may be that patients choosing to undergo significant surgery for such a device are probably better educated in terms of OSA and its sequelae with the necessity of treatment. It is widely accepted and reasonably well validated that patients who are recipients of concomitant educational, supportive, and behavioral interventions are improving their CPAP usage over time, and that is likely the case with UAS as well for this patient phenotype.[24] Finally, patients who are profound sufferers of untreated OSA would be more likely to select UAS versus patients with minimal symptoms and

Table 3. Patient-Reported Outcomes at Baseline and 2- and 6-Month Follow-up.

				P Value		
	Baseline	2 mo	6 mo	Baseline vs 2 mo	Baseline vs 6 mo	2 mo vs 6 mo
ESS				<.001	<.001	<.001
Mean ± SD	12.8 ± 5.4	9.0 ± 4.8	7.0 ± 4.5			
Median (range)	13.5 (2-24)	8.0 (0-21)	6.0 (0-17)			
FOSQ				<.001	<.001	.002
Mean ± SD	13.2 ± 3.5	15.2 ± 4.1	16.9 ± 2.9			
Median (range)	13.3 (5-19.8)	15.7 (5.1-20)	17.8 (9.2-20)			

Abbreviations: ESS, Epworth Sleepiness Scale; FOSQ, Functional Outcomes Sleep Questionnaire.

OSA, who would probably not opt for this treatment, given the moderately invasive surgical procedure and permanent in-dwelling electrotherapeutic device system. Our data support the already-published UAS study results showing that patients nonadherent to CPAP can be adherent to UAS if properly selected.

Of further interest as it pertains to hypothesis generation, a recent systematic review found that a 1-hour-per-night increase in CPAP use was associated with an additional reduction of systolic blood pressure of 1.5 mm Hg.[25] The improved UAS therapy use may have clinical implications for reducing cardiovascular risks associated with untreated OSA. This area, of course, needs to be studied through further clinical trials.

In comparing the surgical treatment of UAS and its safety profile with other OSA operations, the procedure seems to be safe and without long-lasting side effects for typical patients. Two cases (3%) were reported with bleeding during tunneling, both of which were resolved without any sequelae. Another instance occurred during previous phases of UAS study and was similarly resolved. Numbness of tongue and dysarthria for a few days after surgery were reported in 2 other cases. As compared with similar types of nerve dissection/surgery, the incidence numbers are acceptably low. In parotid surgery, the temporary facial palsy rate is around 40.2% on the first postoperative day and 1.6% at 12 months.[26] If the subjective dysarthria is a result of a palsy of the hypoglossal nerve, then the equivalent risk is <2% for the first postoperative days and 0% for the long term, representing a suitably low morbidity for essential hypoglossal nerve functioning in the postsurgical and chronic settings. The small numbers of reported numbness of the tongue cannot readily be explained by the UAS surgery, due to its widely accepted functions for efferent-only motor innervation; yet, perhaps the lingual nerve may occasionally be encountered (eg, ptotic sublingual gland and accompanying nerve) and traumatized through retraction or other elements of accessing, visualizing, and placing the stimulation cuff around the hypoglossal nerve.

Furthermore, this clinical trial shows that even the self-reported outcomes of the patients significantly improved (as measured by the ESS and FOSQ). Polysomnography measures alone do not capture important aspects of OSA. The quality of life depending on daytime sleepiness could be enhanced. This effect has clinical and economic relevance.

Overall, surgical treatment with a fully implanted electrotherapeutic device system for selective UAS appears to be a safe procedure in the clinical setting. Additionally, in the event that the therapy is ultimately unsuitable for a particular patient, there is no overt anatomy-altering element to this procedure, and it is essentially reversible for such patients who may choose to have an underperforming system completely explanted (ie, reversible vs a failed UPPP).

Conclusion

Selective UAS reduced OSA severity and improved patient-reported quality-of-life outcome measures. Therapy adherence was high after 6 months of follow-up. Surgical and stimulation-related morbidity were low. This multicenter study further strengthened the evidence that the treatment can be successfully translated from the previous controlled trial setting into routine clinical practice.

Author Contributions

Clemens Heiser, conception and design, data acquisition, data analysis and interpretation, drafting the article, final approval, accountability for all aspects of the work; **Joachim T. Maurer**, conception and design, data acquisition, data analysis and interpretation, drafting the article, final approval, accountability for all aspects of the work; **Benedikt Hofauer**, data analysis, drafting, final approval, accountability for all aspects of the work; **J. Ulrich Sommer**, data analysis, drafting, final approval, accountability for all aspects of the work; **Annemarie Seitz**, data analysis, drafting, final approval, accountability for all aspects of the work; **Armin Steffen**, conception and design, data acquisition, data analysis and interpretation, drafting the article, final approval, accountability for all aspects of the work.

Disclosures

Competing interests: Clemens Heiser—study investigator and consultant of Inspire Medical Systems (received personal fees, travel expenses, and research grants); Joachim T. Maurer—study investigator and consultant of Inspire Medical Systems (received personal fees, travel expenses, and research grants), consultant for Nyxoah, an invited speaker for Revent and ImThera; Benedikt Hofauer—study investigator of Inspire Medical Systems (received personal fees and travel expenses); J. Ulrich Sommer—study investigator of Inspire Medical Systems (received personal fees and travel expenses); Armin Steffen—study investigator and consultant of Inspire Medical Systems (received personal fees, travel expenses, and research grants).

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