# What makes the responder to upper airway stimulation in obstructive sleep apnea patients with positive airway pressure failure?

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## Introduction

Treating obstructive sleep apnea (OSA) in patients with positive airway pressure (PAP) failure left many patients untreated or unhappy. Especially in moderate to severe cases with elevated body-mass index (BMI), therapy attempts with mandibular devices, tongue base or soft palate procedures turn out to be successful only in lower proportion of patients. With upper airway stimulation (UAS), sleep medicine can offer a new treatment modality for those cases—as long as patient selection was done properly. Here, for the hypoglossal nerve neurostimulation with breathing cycle detection, the absence of complete concentric collapse (CCC) was associated with good therapy outcome already during early feasibility studies (1). This collapse pattern was seen in about every fourth patient looking at 210 patients with OSA and PAP failure (2). So, several potential parameters may or may not influence therapy effect of UAS. What makes the paper of Schwab *et al*. (3) outstanding? It is the approach of upper airway imaging with something less cumbersome than drug-induced sleep endoscopy (DISE) and to get deeper insight of the therapy mechanismus.

The question is whether we can identify anatomical features as suggested by Schwab *et al*. (3) for the future candidate and discriminate those who should better not be recommended implant surgery? The following editorial would like to give an overview on so far discussed parameters influencing UAS therapy success and highlight the new data given by computed tomography (CT) scan evaluation in OSA patients.

## Sleep endoscopy and CCC at the soft palate

In 2013 and in 21 patients, Vanderveken *et al*. (1) published a milestone paper in UAS as they identified the absence of CCC as a strong predictor of inferior results. From then on, CCC was doubtless the strongest exclusion criteria for later studies. Ruling out CCC, prospective multi-center studies could show therapy success in 66% (4), 68% (5), or in 78% of 301 patients of a multi-centre registry (6). As most of the sleep surgeons regard this criterion to be well chosen, there is no data about UAS in CCC patients. There are first retrospective results that CCC pattern can be changed by soft palate surgery (7) but there is no data whether these previous CCC candidates turn out to perform with comparable responder rates regarding to initially non CCC patients. Therefore, with a prevalence of 20% to 25% in otherwise eligible OSA patients with PAP intolerance (2,8,9), DISE plays a centre role for patients selection. Furthermore, in already implanted patients, a DISE with activated UAS makes the whole upper airway effect visible and helped to explain the underlying mechanism of soft palate coupling (10,11). There are new reports (12) looking at implanted patients with a full-night polysomnography and a manometry with a comparison to DISE. They

conclude that DISE as a short moment evaluation underestimates lower obstruction of the upper airway as a potential reason for UAS failure and recommend additional diagnostics.

## Demographic aspects on age, OSA severity and overweight

Already in an office situation, the sleep physician or head and neck surgeon can select potential candidates by assessing demographic aspects and OSA severity. The Apnea-Hypopnea index (AHI) showed no difference between responders and non-responders in the German Postmarket study (5). Here, the baseline, month 6 and 12 assessment used home sleep tests (HST) with a 2 night's measurement for taking night-to-night variability into account; baseline range was an AHI from 15 to 65 events per hour. This is important to know when comparing this with the previous phase III study, the STAR trial (4). The STAR trial used a single polysomnography for baseline screening and month 12 assessment allowing a range of AHI 20 to 50/hour to be included. Despite these differences, responder rates to not differ obviously with 66% and 68% respectively. Furthermore, the multi-centre registry ADHERE has no AHI limitations as long as it was above 15/hour but presented even higher responder rates of 78% in 301 patients (6). Therefore, OSA severity measuring AHI seems to have no strong power to discriminate responders in advance.

These above mentioned studies (4-6) differ as well in the selection criteria regarding overweight: STAR study included up to BMI 32 $kg/m^2$, German Postmarket study up to 35 $kg/m^2$ and ADHERE register has no BMI limit. Having in mind the previously mentioned responder rates of these trials and the odds ratio between responders and non-responders of 0.921 (5), overweight with regard to BMI may not predict treatment success. Nonetheless, these BMI values demonstrated acceptable specificity [BMI 32 $kg/m^2$ 0.71; 95% confidence interval (CI), 0.57–0.82; e.g., 35 $kg/m^2$ 0.81; 95% CI, 0.69–0.90] (8). This makes the BMI minor to DISE evaluation as it seems that higher BMI is associated with unfavourable DISE patterns but once, these unfavourable pattern especially the CCC is excluded, BMI has low impact. Even more, when looking at the month 2 polysomnographic therapy adjustment data of 153 patients in a retrospective two centre study (13), there was no difference for AHI and $O_2$ saturation nadir between patients with a BMI below or above 32 $kg/m^2$, although the AHI was higher in the more overweight group (34.70 vs. 40.95/hour).

Age was no exclusion criteria as UAS is on-label only in grownups so far. There seems to be no influence by this as the odds ratio between responders and non-responders is 0.992 in the German Postmarket study (5). Even more, a retrospective case-control study of 31 OSA patients implanted with UAS elder than 65 years showed no significant difference compared to 31 UAS patients younger than 65 years for AHI, Oxygen desaturation index Epworth sleepiness scale (6.0 to 6.0/hour; 7.9 to 5.5/hour; 5.0 to 7.0 points). Both groups had no differences in baseline AHI (14).

## Previous sleep surgery interventions on the upper airway

Previous sleep surgery interventions are on debate to be predictors of UAS outcome. Especially, soft palate interventions are of interest as patients with status post tonsillectomy and/or uvulopalatopharyngoplasty (UP3) have a lower rate of CCC pattern in DISE than those without in 210 otherwise eligible OSA patients with PAP failure (18% vs. 30%) (2). Once selected via DISE for UAS, previous sleep surgical interventions at the upper airway showed no difference in postoperative AHI in a retrospective chart review of 47 patients (15). In contrast to this, status UP3 had a threefold higher risk of being non-responders in the German Postmarket study (5). Another retrospective single centre review categorized 25 patients into three groups: those with previous tonsillectomy and/or UP3 before UAS implantation, second, cases with soft palate interventions after UAS implantation, and third, with only UAS treatment (16). Here, cases with previous upper airway sleep surgery had higher therapy response (90%) than those without or, after UAS implantation. Here, different baseline AHI, BMI, and DISE collapse patterns need to be taken into account.

## Implantation technique, learning curve, and tongue motion pattern

The precise implantation technique is elementary and was modified after early reports (17,18). Especially, neuromonitoring guidance is of tremendous value for keeping out tongue retracting hypoglossal nerve branches (19). Nonetheless, despite technical support, anatomical variants need to be respected which occur quite often (20). The stimulated tongue motion is strongly

influenced by the stimulated hypoglossal nerve fibres. Therefore, cuff-placement excluding retracting nerve fibres is crucial. There are reports that especially a non-bilateral or a non-right protrusion of the stimulated tongue is associated with minor outcome (21). As the UAS system provides several electrode configurations with different electric fields, those patients who change their tongue motion patterns when changing the electrode configuration showed minor results (22). The authors advised, therefore, to reposition cuff-placement when during implantation a different tongue motions occurs while changing electrode configuration. So, surgeon's experience and learning curve does not only impact surgery time (23,24) but as well the proper cuff-placement. The most high-volume centres worldwide with significant experiences recruited for the ADHERE registry (6) what explains the outstanding therapy responder rates despite no upper BMI and AHI limit.

## Conclusions

Schwab and co-workers (3) come to the important conclusion that baseline CT scans have limited predictive power to discriminate responders from non-responders. Consistent with the lines above, there are no differences in age, BMI, and baseline AHI. The most significant difference between both groups appears to be the soft palate area—the same crucial region of the upper airway as identified in DISE technique (1). Nonetheless, this study is important for a better understanding of the UAS therapy effects on the airway opening during stimulation. Corresponding to the need of precise cuff-placements (and tongue motion patterns), they state that a cuff-placement which is more distal and away from retracting nerve fibres is associated therapy outcome. Although little, the radiation dosage has to be respected what makes a repeated version of this study unrealistic. If there would be no ethical discussion about radiation dosage, a study of OSA patients with PAP failure before DISE would be of high interest as here, already implanted patients have been selected for CCC during DISE.

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## Footnote

## References

1. Vanderveken OM, Maurer JT, Hohenhorst W, et al. Evaluation of drug-induced sleep endoscopy as a patient selection tool for implanted upper airway stimulation for obstructive sleep apnea. J Clin Sleep Med 2013;9:433-8.
2. Hasselbacher K, Bruchhage KL, Abrams N, et al. Sleep endoscopy and complete concentric collapse in OSA patients with PAP intolerance. HNO. (In press).
3. Schwab RJ, Wang SH, Verbraecken J, et al. Anatomic predictors of response and mechanism of action of upper airway stimulation therapy in patients with obstructive sleep apnea. Sleep 2018;41.
4. Strollo PJ, Soose RJ, Maurer JT, et al. Upper-Airway Stimulation for Obstructive Sleep Apnea. N Engl J Med 2014;370:139-49.
5. Steffen A, Sommer JU, Hofauer B, et al. Outcome after one year of upper airway stimulation for obstructive sleep apnea in a multicenter German post-market study. Laryngoscope 2018;128:509-15.
6. Boon M, Huntley C, Steffen A, et al. Upper Airway Stimulation for Obstructive Sleep Apnea: Results from the ADHERE Registry. Otolaryngol Head Neck Surg 2018. [Epub ahead of print].
7. Hasselbacher K, Seitz A, Abrams N, et al. Complete concentric collapse at the soft palate in sleep endoscopy: what change is possible after UPPP in patients with CPAP failure? Sleep Breath 2018. [Epub ahead of print].
8. Steffen A, Frenzel H, Wollenberg B, et al. Patient selection for upper airway stimulation: is concentric collapse in sleep endoscopy predictable? Sleep Breath 2015;19:1373-6.
9. Ong AA, Murphey AW, Nguyen SA, et al. Efficacy of Upper Airway Stimulation on Collapse Patterns Observed during Drug-Induced Sedation Endoscopy. Otolaryngol Head Neck Surg 2016;154:970-7.
10. Safiruddin F, Vanderveken OM, de Vries N, et al. Effect of upper-airway stimulation for obstructive sleep apnoea on airway dimensions. Eur Respir J 2015;45:129-38.
11. Heiser C, Edenharter G, Bas M, et al. Palatoglossus coupling in selective upper airway stimulation. Laryngoscope 2017;127:E378-83.
12. Wirth M, Schramm J, Bautz M, et al. Reduced upper obstructions in N3 and increased lower obstructions in REM sleep stage detected with manometry. Eur Arch Otorhinolaryngol 2018;275:239-45.

13. Huntley C, Steffen A, Doghramji K, et al. Upper airway stimulation in patients with OSA and an elevated BMI; A multi-institutional review. Laryngoscope 2018. (In press).

14. Zhu Z, Hofauer B, Wirth M, et al. Selective upper airway stimulation in older patients. Respir Med 2018;140:77-81.

15. Mahmoud AF, Thaler ER. Upper airway stimulation therapy and prior airway surgery for obstructive sleep apnea. Laryngoscope 2018;128:1486-9.

16. Steffen A, Abrams N, Suurna MV, et al. Upper-Airway-Stimulation before, after or without uvulopalatopharyngoplasty - a two-year perspective. Laryngoscope 2018. (In press).

17. Maurer JT, Van de Heyning P, Lin HS, et al. Operative Technique of Upper Airway Stimulation - An Implantable Treatment of Obstructive Sleep Apnea. Oper Tech Otolayngol Head Neck Surg 2012;23:227-33.

18. Heiser C, Thaler E, Soose RJ, et al. Technical tips during implantation of selective upper airway stimulation. Laryngoscope 2018;128:756-62.

19. Heiser C, Hofauer B, Lozier L, et al. Nerve monitoring-guided selective hypoglossal nerve stimulation in obstructive sleep apnea patients. Laryngoscope 2016;126:2852-8.

20. Heiser C, Knopf A, Hofauer B. Surgical anatomy of the hypoglossal nerve: A new classification system for selective upper airway stimulation. Head Neck 2017;39:2371-80.

21. Heiser C, Maurer JT, Steffen A. Functional outcome of tongue motions with selective hypoglossal nerve stimulation in patients with obstructive sleep apnea. Sleep Breath 2016;20:553-60.

22. Steffen A, Kilic A, König IR, et al. Tongue motion variability with changes of upper airway stimulation electrode configuration and effects on treatment outcomes. Laryngoscope 2018;128:1970-76.

23. Murphey AW, Baker AB, Soose RJ, et al. Upper airway stimulation for obstructive sleep apnea: The surgical learning curve. Laryngoscope 2016;126:501-6.

24. Thaler ER, Schwab RJ. Single-institution experience and learning curve with upper airway stimulation. Laryngoscope 2016;126:S17-9.