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ERS TASK FORCE REPORT

Non-CPAP therapies in obstructive sleep apnoea

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ABSTRACT: In view of the high prevalence and the relevant impairment of patients with obstructive sleep apnoea syndrome (OSAS) lots of methods are offered which promise definitive cures for or relevant improvement of OSAS.

This report summarises the efficacy of alternative treatment options in OSAS.

An interdisciplinary European Respiratory Society task force evaluated the scientific literature according to the standards of evidence-based medicine.

Evidence supports the use of mandibular advancement devices in mild to moderate OSAS. Maxillomandibular osteotomy seems to be as efficient as continuous positive airway pressure (CPAP) in patients who refuse conservative treatment. Distraction osteogenesis is usefully applied in congenital micrognathia or midface hypoplasia. There is a trend towards improvment after weight reduction. Positional therapy is clearly inferior to CPAP and long-term compliance is poor. Drugs, nasal dilators and apnoea triggered muscle stimulation cannot be recommended as effective treatments of OSAS at the moment. Nasal surgery, radiofrequency tonsil reduction, tongue base surgery, uvulopalatal flap, laser midline glossectomy, tongue suspension and genioglossus advancement cannot be recommended as single interventions. Uvulopalatopharyngoplasty, pillar implants and hyoid suspension should only be considered in selected patients and potential benefits should be weighed against the risk of long-term side-effects. Multilevel surgery is only a salvage procedure for OSA patients.

KEYWORDS: Mandibular advancement devices, maxillomandibular osteotomy, multilevel surgery, neuromuscular stimulation, uvulopalatopharyngoplasty, weight reduction

Since the first description of their application in the early 1980s by SULLIVAN *et al*. [1], continuous positive airway pressure (CPAP) and the more recent developments of automatic positive airway pressure and bilevel therapy have become the standard treatment of obstructive sleep apnoea syndrome (OSAS) [1]. Positive airway pressure has proven to improve symptoms, normalise the risk of traffic and workplace accidents, and reduce the elevated sympathetic activity and risk for cardiovascular morbidities, especially arterial hypertension. Most recently, it has been shown that CPAP normalises mortality in patients with severe OSAS [2, 3].

However, despite the efficacy of CPAP, many patients suffer from local side-effects at the nose or face, or discomfort due to the mask. Moreover, CPAP does not allow for a permanent resolution of respiratory disturbances during sleep, but only suppresses them while using the devices. Therefore, many patients look for more comfortable or curative treatment options. Both conservative and surgical alternative therapeutic approaches have been described. However, there is a need to discuss the scientific evidence for these therapies.

Thus, the European Respiratory Society funded a task force with the aim of screening the scientific

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literature on non-positive-pressure therapies, evaluating the studies according to the criteria of the evidence-based medicine, and giving recommendations for use in OSAS patients. The treatment of central sleep apnoea and periodic breathing was not in the focus of this work. The results of the task force will be presented in this report and in more detail in two following articles on conservative treatment options and two on surgical approaches.

METHODS

The members of the task force performed individualised literature searches for each topic area using electronic databases, hand searches of relevant papers, and screening of reference lists up to January 1, 2009. In addition, in May 2010 the authors screened the literature for more recent papers which might change the conclusions and recommendations relevantly. Reviews, guidelines and case reports were excluded. Studies were included only if data of at least three subjects were available and if sleep testing was performed using polygraphy (cardiorespiratory monitoring) or polysomnography. Studies were evaluated according to the Oxford Centre for Evidence-based Medicine's levels of evidence (tables 1 and 2) [4]. The level of recommendation (A, B, C or D) is given of the end of each section. All other tables are available in the online supplementary material (tables e1–e38).

Changes reported are significant at the $p<0.05$ level, unless indicated otherwise. If required, statistical analysis was performed to assess pre- *versus* postoperative differences in outcome parameters using either Mann–Whitney U- or paired t-test, as appropriate.

RECOMMENDATIONS OF THE TASK FORCE

1) There is a trend to worsening but not spontaneous cure of sleep disordered breathing (C).

2) Weight reduction is associated with a trend to improvement in breathing pattern, quality of sleep and daytime sleepiness, and is recommended to reduce this important risk factor (C).

3) Positional therapy can yield moderate reductions in apnoea–hypopnoea index (AHI) (younger patients, low AHI and less obese) but is clearly inferior to CPAP and, therefore, cannot be recommended except in carefully selected patients. Long-term compliance with positional therapy is poor (C).

TABLE 1 Evidence levels

1a	Systematic analysis (systematic review) of RCTs with homogenous results
1b	Particular RCT with limited dispersion
1c	Therapy, before its introduction all patients died
2a	Systematic review of cohort studies with homogenous results
2b	Particular cohort studies or RCT of lower quality
2c	''Outcomes'' research; ecological studies
3a	Systematic review of case–control studies with homogenous results
3b	Particular case–control study
4	Case studies and cohort studies or case–control studies of limited quality
5	Expert opinions

RCT: randomised controlled trial.

4) Apnoea triggered muscle stimulation cannot be recommended as an effective treatment of OSAS at the moment (negative recommendation C). Although tongue muscle training improves snoring, it is not efficacious in the treatment of sleep apnoea in general (negative recommendation B).

5) Mandibular advancement devices (MADs) reduce sleep apnoeas and subjective daytime sleepiness, improve quality of life compared with control treatments, and are recommended in the treatment of patients with mild to moderate obstructive sleep apnoea (OSA) (A). There is emerging evidence on the beneficial cardiovascular effects of MADs. However, tongue-retaining devices (TRDs) cannot be recommended (C).

6) Drug therapy is not recommended as treatment for OSA (most drugs C, for mirtazapine and protryptilline B).

7) Nasal dilators are not recommended for reducing snoring, or for improving sleep disordered breathing or sleep architecture in OSA (D).

8) Nasal surgery as a single intervention cannot be recommended for treatment of OSA (negative recommendation C).

9) Intranasal corticosteroids improve mild to moderate OSA in children with co-existing rhinitis and/or upper airway obstruction due to adenotonsillar hypertrophy (B). They may also show some benefit with respect to both symptoms and some sleep parameters. Intranasal corticosteroids can be recommended as concomitant therapy in these situations.

10) Tonsillectomy as a single therapy can be recommended for treatment of OSA in the presence of tonsillar hypertrophy in adults (C). Adenotonsillectomy can be recommended in the presence of adenotonsillar hypertrophy associated with paediatric OSA (C). Radiofrequency tonsil reduction is not recommended as a single procedure for the treatment of OSA (negative recommendation D).

11) Uvulopalatopharyngoplasty (UPPP) is a single-level surgical procedure effective only in selected patients with obstruction limited to the oropharyngeal area. When proposing UPPP, potential benefits should be weighed against the risk of frequent long-term side-effects, such as velopharyngeal insufficiency, dry throat and abnormal swallowing. UPPP cannot be recommended except in carefully selected patients (C).

12) Laser assisted uvulopalatoplasty has not demonstrated any significant effect, either on OSA severity or in symptoms or quality of life domains, and is not recommended (negative recommendation B).

13) Due to insufficient evidence, radiofrequency surgery of the soft palate may only be considered in patients with mild disease refusing or not requiring CPAP, as long as the

TABLE 2 Grades of recommendation

A	Consistent level 1 studies
B	Consistent level 2 or 3 studies or extrapolations of level 1 studies
C	Level 4 studies or extrapolations of level 2 or 3 studies
D	Level 5 or inconsistent studies of other levels

individual anatomy appears suitable. It cannot be recommended except in carefully selected patients (C).

14) Uvulopalatal flap as a single intervention can only be recommended in selected cases for treatment of OSA (C). Studies investigating the uvulopalatal flap with tonsillectomy for OSA show a significant improvement of the severity of OSA and quality of life, and this combined intervention can be recommended in selected patients (B).

15) Pillar® implants may be considered in patients with mild to moderate OSA, who are suitable with regard to their overall physical condition (not or only moderately obese, no or small tonsils and no sign of retrolingual obstruction), if conservative approaches are not accepted by the patient. Pillar implants cannot be recommended except in carefully selected patients (B).

16) Due to insufficient evidence, radiofrequency surgery of the tongue base as an isolated or combined procedure cannot be recommended and may only be considered in selected patients intolerant to conservative treatment as long as the overall condition appears suitable (non- or only moderately obese patients with retrolingual obstruction) (C).

17) Due to insufficient evidence, hyoid suspension cannot be recommended and may only be considered in carefully selected patients (C) and may be combined with other procedures in multilevel surgery (MLS) (B).

18) Procedures such as laser midline glossectomy and tongue suspension (Repose®) have a small role as a single treatment option for obese patients with moderate to severe OSA and cannot be recommended. There are at present no data about their role in patients with mild disease (negative recommendation C).

19) Genioglossus advancement cannot be recommended as a single procedure for the surgical treatment of OSA (C).

20) Maxillomandibular advancement (MMA) seems to be as efficient as CPAP in patients with OSA who refuse conservative treatment, particularly in a young OSA population without excessive body mass index (BMI) or other comorbidities, and is recommended in this circumstance (B).

21) Distraction osteogenesis (DOG) can be recommended in congenital micrognathia or midface hypoplasia (mandibular lengthening: B; midface advancement: C).

22) MLS cannot be recommended as a substitute for CPAP but as a salvage procedure for OSA patients in whom CPAP and other conservative therapies have failed. Surgical success of MLS for OSA is often unpredictable and less effective than CPAP (C).

CONSERVATIVE NON-CPAP TREATMENT OPTIONS

The natural course of OSA

Rationale

In the face of the high prevalence and the socioeconomic burden of OSAS the question arises if all patients have to be treated immediately after diagnosis or if spontaneous normalisation might be expected at least in a portion of patients.

Search strategy

Databases individually searched: PubMed and Medline. Keyword combinations: sleep apnoea AND progression OR natural course OR prognosis OR evolution OR long-term follow up. Of the selected papers, 24 studies reported data on the natural course of the disease.

Overview of the evidence

There is a lack of knowledge on the age of onset and the course of sleep apnoea. It is widely accepted that snoring typically begins between the ages of 30 and 40 yrs, and that the incidence of sleep apnoea increases between ages 40 and 65 yrs. These data, however, do not reveal the progression of the disorder with respect to its extent: neither concerning the AHI, nor clinical symptoms, nor comorbidity.

Only a small number of studies [3, 5–11] have investigated the natural course of sleep apnoea with respect to cardiovascular risk and mortality. The studies cited here monitored those patients who refused to undergo appropriate therapy. A small number of studies has been performed investigating the course of the disease in patients with low AHI. No long-term follow-up studies have been performed on sleepiness, the primary symptom of OSA.

The present state of knowledge on this matter considering only those follow-up studies with more than 20 participants can be summarised as follows: TISHLER *et al.* [12] studied healthy persons (*i.e.* AHI <5) and found a 5-yr incidence of 7.5% for OSA with an AHI >15, and of ~16% with AHI >10. The incidence of sleep apnoea was independent of age, sex, BMI, waist/hip ratio and serum cholesterol level. Interestingly, the influence of BMI diminished with increasing age. The Wisconsin Sleep Cohort Study and the Cleveland Family Study revealed a significant increase over the time in AHI, especially among male, obese, older and snoring patients [13, 14]. Studies in the elderly revealed a progression of OSA in correlation with age over the long term, but not with BMI [15]. The Sleep Heart Health Study found that the increase of the AHI upon an increase of the BMI over a 5-yr period was greater than a reduction of AHI under weight loss. The influence of body weight was significantly greater among males than among females [16]. In addition, PEPPARD *et al.* [17] reported a six-fold increase in odds ratio for the development of OSA, as accompanied by a 10% increase in body weight within 4 yrs.

There are conflicting results on the modulation of the severity of OSAS over time. While several investigators showed an increase of severity in mild to moderate sleep apnoea patients over time independently of the BMI, others failed to demonstrate deterioration of upper airway resistance syndromes or found improvements of respiratory disturbances [5, 18–24].

Conclusions and recommendations

There is a lack of population-based studies on the spontaneous course of OSA. However, both increasing incidence and progression of AHI have been demonstrated for patients with mild to moderate OSA between the ages of 40 and 60 yrs, even independently of possible change in BMI. In contrast, a similar evolution has not been proven among the elderly and among those patients with higher initial AHI. In all age groups, however, the primary risk factor for progression and elevated

incidence is the increase of body weight. An additional factor is evidently male sex.

At least in mild sleep-related breathing disorders future research should address the influence of concomitant diseases and their therapy on the course of sleep apnoea, the significance of snoring with respect to the development from snoring to sleep apnoea, development of cardiovascular risks in snorers and sleep apnoea (table e1).

The presented data show a trend to worsening of sleep disordered breathing over time. Most studies are retrospective and observational (case series). Based on these data, we state that a spontaneous improvement cannot be expected (C).

Weight reduction

Rationale

Obstructive sleep-related breathing disorders are caused by pharyngeal and/or laryngeal collapse. Pharyngeal fat deposits lead to a decrease in pharyngeal patency and underline the risk factor of obesity [25, 26]. Weight reduction will lead to a decrease in critical closing pressure (P_{crit}), and consequently decreases the severity of OSA [27].

Search criteria

Databases individually searched: PubMed and Medline. Keyword combinations: sleep apnoea syndromes AND weight reduction. Of the 47 selected papers, three studies reported data on the mechanisms of action of weight reduction (change in P_{crit}, change in pharyngeal cross-sectional area, change in respiratory mechanics).

Overview of the evidence

51 studies were identified, reporting on the effect of weight reduction in adults, 25 on diet instructions, 24 on surgical intervention (one study evaluated both) and three on pharmaceutical weight reduction. One study performed in extremely overweight adolescents was also included [28]. Six studies were published by the same study group. 17 studies on diet instruction intervention were case series, or evidence level 4. Surgical treatment (gastric banding, gastroplasty or gastric bypass) was evaluated in 24 studies, which were also all case series. Pharmaceutical weight reduction was reported in two case series in the same population and in one randomised controlled trial. Only studies with sibutramine were performed. 10 studies were based on polygraphy (seven diet studies, three surgery studies, one both). Seven of these polygraphic studies were performed in Finland. Weight changes have been calculated partly as change in kg, partly as change in BMI, partly as change in excess body weight (EBW) (and expressed as percentage EBW) or as change in percentage of ideal body weight (IBW). Therefore, an overall change in body weight related to change in AHI cannot be expressed (tables e2 and e3).

In the diet intervention studies, mean BMI reduction of 4.7 ± 2.5 kg·m^{-2} was accompanied by a decrease of the AHI by 21 ± 13 h^{-1} (44%) (table e2). 246 patients (39%) showed a partial improvement in AHI, while 145 patients (23%) were cured of OSA. In the surgery intervention studies, change in BMI was between 10–24.4 kg·m^{-2}. Three studies reported reduction of the percentage of IBW between 26.4 and 82% IBW (17–73%). The AHI decreased by 44 ± 22 h^{-1} (77%) (table e3) [29–31]. 94 patients (34.2%) showed a partial improvement in AHI, while 177 patients (64.4%) were cured of OSA. In the pharmaceutical intervention studies, change in BMI was between 1.8 and 2.6 kg·m^{-2}, accompanied by a decrease of the AHI between 2.8 and 16.3 h^{-1} (7–35.6%) (table e4) [32–34].

An increase in deep sleep could be observed from +4 to +17%, while other studies found no change in deep sleep, or even a small decrease [35]. In all but one study, rapid eye movement (REM) sleep increased by 1–10%. An improvement of sleepiness based on self-assessment scales was reported after diet and behavioural management, and after surgery, and after pharmaceutical weight reduction [31–41]. In one study an unchanged mean multiple sleep latency test (MSLT) was reported [41]. The evaluated study period was not always indicated; the longest study period was 7 yrs [40].

Conclusions and recommendations

Presented data show, under a weight reduction (BMI 0.2–24.4 kg·m^{-2}), a trend to improvement in breathing pattern, an increase in REM sleep (1–10%) and deep sleep (0 to +17%), and a decrease in daytime sleepiness. Most studies are retrospective and observational (case series), and while randomised controlled trials have been published in recent years, they report inconsistent results and, therefore, none provide high-level evidence. Weight reduction is recommended to reduce the important underlying risk factor of obesity. Most available studies have level 4 (C).

Positional therapy

Rationale

The number and duration of respiratory disturbances depend on body position and sleep stage [42–46]. The cross-section and the closing pressures of the pharynx differ according to body position and stage of sleep [47–49]. Ventilatory drive is dependent on body position. Thus, there is ample evidence suggesting a positive effect of a lateral position during sleep. Using the definition of positional OSA as a supine AHI of at least twice that in the lateral position, a prevalence of ~50% is reported [50].

Search criteria

Databases individually searched: PubMed and Medline. Keyword combinations: sleep apnoea AND positional therapy. A recent review on medical therapy of OSA was screened. 27 of the 39 articles found were excluded, mostly because they did not contain data on the efficacy of positional therapy in the treatment of OSA (table e5).

Overview of the evidence

Clinical experience and observational studies suggest that the patients exhibiting a large decrease in AHI in the lateral position compared with the supine position tend to have a lower AHI, to be younger and to be less obese [44, 51]. Accordingly, patients with a clear improvement of the AHI with positional therapy tended to be younger, to have a lower AHI and to be less obese [42, 52, 53]. It is not possible to extract from the data whether AHI, age or obesity is the best predictor of treatment success. It is more likely that these parameters are mutually interrelated.

Different devices such as tennis balls, vests, positional alarms, verbal instruction and pillows are used to avoid the supine position [53–58]. There are no data comparing the different devices, with the exception that verbal instructions seem to be less effective than a positional alarm [42, 59].

A number of short-term studies demonstrate significant but moderate effects on AHI. However, most studies were uncontrolled and small [52–54, 56, 57, 60]. More importantly, even in a subset of patients with clear positional sleep apnoea, effectiveness was limited. Two uncontrolled studies suggested some improvement of sleep stages or daytime symptoms with positional therapy [57, 58].

One study had a clinically meaningful follow-up period of 2 yrs [56]. Only 29% used the positional vest in this study after 2 yrs [56]. In a randomised crossover comparison with CPAP, positional therapy (elevation of head and shoulder) was clearly inferior in terms of the AHI [61].

Conclusions and recommendations

Patients with a clear improvement of the AHI with positional therapy tend to be younger, to have a lower AHI, and to be less obese. Positional therapy can yield moderate reductions in AHI but is clearly inferior to CPAP. Long-term compliance with positional therapy is poor. If positional therapy is used, sleep studies are recommended to document individual success. Long-term compliance has to be secured by follow-up studies.

Recommendation: positional therapy is not recommended for the treatment of OSA, except in carefully selected patients. If positional therapy is used, sleep studies have to be performed to document individual success. Long-term compliance has to be secured by follow-up studies (C).

Intraoral protrusion devices

Mandibular advancement devices

Rationale

MADs reposition the lower jaw forwards and downwards during sleep. The treatment aims to widen the upper airways in order to improve the upper airway patency, and reduce snoring and obstructive sleep apnoeas.

Search strategy

Databases individually searched: PubMed and Medline. Keyword combinations: sleep apnoea syndromes AND orthodontic appliances; functional or removable, activator appliances or mandibular advancement, sleep apnoea AND oral appliances, mandibular advancement devices, mandibular repositioning appliances, mandibular advancement splints or mandibular repositioning splints were individually used. Out of 79 articles in total, 29 were excluded because the topic was covered in the randomised controlled trials or the aims were not directly related to the efficacy of the device. 27 randomised controlled trials about treatment effects from MADs and five randomised controlled trials in particular topics were found (table e6). In addition, 18 other clinical trials that highlighted particular aspects of MAD treatment were identified.

Overview of the evidence

The 27 randomised controlled trials evaluated the effects of MADs compared with placebo treatment [62–70], CPAP [66, 69, 71–77] or between appliance designs [78–87]. Two studies reported long-term results after 2 and 4 yrs of treatment, respectively [86, 88]. The sample sizes in these studies ranged from 19 to 114 patients. The patients were overweight or obese (mean BMI 26–33 $kg \cdot m^{-2}$).

MADs have been shown to widen primarily the lateral parts of the upper airway [89] and to reduce pharyngeal collapsibility [90]. MAD treatment reduced sleep apnoeas compared with placebo in all studies [62–66, 68–70]. Treatment success with MAD, defined as an AHI of <5, was found in 19–75% of the patients and an index of <10 was reported in 30–94% of the patients [63–68, 70–79, 81, 82, 84, 85, 87, 91, 92]. Sleep apnoeas increased slightly and some patients discontinued treatment in the longer term [86, 88]. Milder sleep apnoea, supine-dependent sleep apnoeas, female sex and less obesity have been related to treatment success with MADs [63, 65, 70, 76, 82, 92, 93]. CPAP reduced sleep apnoeas more efficiently or gave a higher success rate in all studies [66, 69, 71–77].

Subjective daytime sleepiness decreased from MAD treatment compared with placebo according to many short-term studies [62, 64, 66, 68, 70], although control treatment may also give positive effects [64, 69]. The effect on sleepiness was usually similar between CPAP and MADs [66, 72, 74–77], but CPAP may produce a better outcome than MAD [69, 71, 73]. Snoring is more effectively controlled with CPAP than with MADs [72], but there is a better effect from MADs than placebo [63, 64]. Persistent snoring during MAD treatment may be a sign of a poor apnoea control [71]. Promising effects on blood pressure, cardiac function, endothelial function, markers of oxidative stress and simulated driving performance have been reported from MADs [66, 69, 84, 94–99].

Titratable custom-made MADs have been used in the majority of the efficacy studies. Comparison between device designs indicated that there are only minor differences in treatment effects between custom-made devices [78, 80, 83, 84], while a prefabricated device was less effective [85]. The degree of mandibular advancement is crucial, since a non-advanced device is ineffective on sleep apnoeas [62, 65, 70] and may even increase the apnoea frequency [62]. A titration procedure is therefore recommended to achieve optimal results [87, 91, 100, 101].

Initial side-effects, such as jaw discomfort, tooth tenderness, excessive salivation and/or temporary occlusal changes, were reported in slightly more than half of the patients [63, 65, 69, 71–74, 78], and more frequently from MAD than from a control plate [64]. After 1 yr, 76% of the patients continued treatment [92] and 65% were still using their devices after 4 yrs [88]. Compliance monitors have been introduced [102]. Compliance with MADs has been reported to be higher than with CPAP [66, 77] and MADs are often preferred by the patients [71, 72, 74, 75, 77].

Conclusions and recommendations

MADs are recommended for the treatment of patients with mild to moderate OSA (A) and in patients who do not tolerate CPAP. MADs reduce sleep apnoeas and subjective daytime sleepiness and improve quality of life compared with control treatments. There is emerging evidence on beneficial cardiovascular effects from MADs. CPAP more effectively reduces

sleep apnoeas, while the positive effects on symptoms and health are more similar between these treatments. Patients generally prefer MADs over CPAP. The device should be custom-made, evaluated and advance the mandible at least 50% of maximum protrusion. A titration procedure is essential. Re-evaluation with a new sleep apnoea recording is necessary, since the improvement of OSA symptoms is an imprecise indicator of treatment success. This is particularly important in patients with a more severe disease and in patients with concomitant health problems. Follow-up should be performed regularly over the long term.

Tongue retaining devices

Rationale

TRDs are designed to produce a suction of the tongue into an anterior bulb, move the tongue forwards and widen the upper airway dimensions during sleep, in order to reduce obstructive sleep apnoeas and snoring.

Search strategy

Databases individually searched: PubMed and Medline. Keyword combinations: sleep apnoea AND tongue retaining device or tongue stabilizing device were individually used for searches in PubMed. In total, three randomised controlled trials [59, 103, 104] and three other trials with small sample sizes were found (table e7) [105–107].

Overview of the evidence

The three randomised controlled trials [59, 103, 104] evaluated the effects of TRDs on sleep apnoeas and symptoms and analysed predictors (table e7). One randomised controlled trial showed significant effects from TRD on sleep apnoeas compared with a control device in patients with mild to moderate sleep apnoea [103]. A comparison between a tongue stabilising device and MAD in another randomised controlled trial showed a similar apnoea reduction from the two devices, although the patients preferred MADs [104]. TRD was compared with posture alarm and positional treatment in 60 patients with positional dependency and moderate OSA. TRD reduced sleep apnoeas in the supine position and gave some benefit for patients who continued to sleep in that position [59]. One of the clinical trials showed an effect of TRD on oxygen desaturations [106], while the other two studies did not show any reduction in sleep apnoeas from this type of treatment in small samples of moderate to severe sleep apnoea patients [105, 107].

Conclusions and recommendations

TRDs are not recommended for patients with OSA. They can be used in selected patients with mild to moderate OSA (C), when other treatments have failed or are not possible. These patients may have a trial with this device, provided that the treatment effect is monitored and the patients are strictly followed up. A few studies show reductions in sleep apnoeas from TRDs, although symptomatic effects are mainly unknown and compliance might be a limitation.

Training of the upper airway muscles and hypoglossus nerve stimulation

Rationale

The obstruction of the upper airways is accompanied by diminished neuromuscular activity of the dilating muscles [108]. In healthy subjects, these muscles stabilise the pharyngeal airway. In order to counterbalance the collapsible forces, the upper airway muscles have to contract more intensively [109]. The genioglossus muscle is one of the most important dilators. It pushes forward the tongue and enlarges the cross-sectional area of the upper airways. Its activity is increased in OSAS during wakefulness, which has been proposed to be a compensatory mechanism [110, 111]. Based on these findings the question arose of whether direct or indirect stimulation of the upper airway muscles optimise the dilating forces and increases the width of the upper airways. Present developments focus mainly on hypoglossus nerve stimulation. Electrical stimulation is performed during sleep to counteract respiratory disturbances whenever they appear. Conversely, training procedures have been developed aiming at improving the altered upper airway muscles. These training procedures are performed during wakefulness.

Search criteria

Databases individually searched: PubMed. Keyword combinations: neurostimulation OR electrical stimulation OR upper airway muscles OR genioglossus stimulation OR hypoglossus nerve stimulation AND sleep apnoea syndrome. 28 studies were found, of which 13 were included in the further evaluation. The other studies did not focus on the electrical stimulation of the upper airway muscles, but on physiological or pathophysiological aspects, effects of MADs or drugs on the upper airway muscles or surgical or anaesthesiological aspects (table e8).

Overview of the evidence

Acute efficacy of electrical stimulation on upper airway patency

Stimulation of the upper airway muscles with surface and intraneural electrodes has proven to reduce the resistance of the upper airways both in healthy persons and patients with OSAS [27, 112–118]. The stimulation of the genioglossus muscle most effectively reduces resistance and the critical pressure P_{crit} [113, 115, 116].

Efficacy of apnoea triggered neurostimulation in clinical use

There are conflicting results on the clinical efficacy of apnoea triggered neurostimulation. Intraneural stimulation of the hypoglossus nerve and transcutaneous electrical stimulation of the genioglossus muscle showed significant improvements of respiratory disturbances and sleep parameters without adverse effects [112, 119]. In contrast, other groups failed to find an enlargement of the upper airways by transcutaneous or intramuscular stimulation during wakefulness or sleep. However, undesirable contractions of the platysma or tongue were observed and arousals were induced [114, 116, 120, 121]. OLIVEN and co-workers [115, 116] studied the critical pharyngeal pressure under intraneural hypoglossus and intramuscular and surface genioglossus stimulation and demonstrated that the patency of the upper airways depends more on the effective stimulation of the genioglossus muscles.

Tongue muscle training by electrical stimulation

Electrical stimulation has proven to be effective in the rehabilitation of skeletal muscles after injury. It activates motor units in healthy muscles, which cannot be reached voluntarily. Based on these findings the question arises if training of the

pharyngeal muscles, especially the genioglossus muscle, during the daytime might improve the respiratory disturbances during sleep. Preliminary results of case studies and one cohort showed improvements of the AHI, daytime sleepiness and snoring [122, 123]. The only placebo-controlled double-blind study on tongue muscle training found an improvement of snoring but no significant reduction of AHI [124].

Oropharyngeal exercise

In addition to electrical stimulation of the upper airway muscles, the question of whether exercises may improve symptoms of OSAS has been studied. PUHAN *et al.* [125] showed a reduction, but not normalisation, of the AHI after didgeridoo playing. More recently, GUIMARAES *et al.* [126] randomised 31 patients with moderate OSAS to 3 months of oropharyngeal exercises or sham therapy. They found significant, but limited, reduction of the AHI. Moreover, snoring, daytime sleepiness, neck circumference and self-assessment questionnaires demonstrated improvements. It is unclear which of the several exercises was most relevant for the treatment effect.

Conclusions and recommendations

Apnoea triggered muscle stimulation cannot be recommended as an effective treatment of OSAS at the moment (C). Although oropharyngeal exercise has shown limited effects on snoring and respiratory disturbances, its role is not clear at the moment and, therefore, it cannot be recommended (B).

Drug therapy

Neuromediator modulators

Rationale

Although there may be a predisposing airway abnormality, it is changes in respiratory drive, airway tone or surface forces that cause airway closure during sleep. Pharmaceutical agents might reduce sleep apnoea by increasing respiratory drive, changing sleep structure (in particular suppressing REM sleep), increasing upper airway muscle tone, changing respiratory and cardiovascular reflexes that may perpetuate apnoeas and reducing surface forces that encourage closure of the upper airway.

Search strategy

Databases individually searched: PubMed and Medline. Keyword combinations: Sleep apnoea/apnoea (drug* or pharmacological and (treatment*)) or progesterone or progestogen or medroxy* or ''tricyclic anti depressant*'' or protriptyline or amitriptyline or imipramine or ssri or fluoxetine or clonidine or modafinil or stimulant* or Buspirone or doxapram or dopram or naloxone or narcan or ''opiod antagonist*'' or nicotin* or ''ACE inhibitor*'' or ACE-inhibitor* or cilazapril or captopril or enalapril or fosinopril or imidapril or lisinopril or perindopril or quinapril or ramipril or trandolapril or ''anti hypertensive*'' or anti-hypertensive* or antihypertensive* or baclofen or mirtazapine or steroid* or *steroid or fluticasone.

Reports on snorers or subjects with predominantly central apnoeas were excluded. Even with these filters a large number of low quality studies were identified. For nearly all of the drugs that have been trialled in the past 20 yrs there is at least one randomised controlled trial and so uncontrolled studies and review articles were excluded.

Overview of the evidence

25 studies (24 papers) were identified, reporting the effects of 24 drugs and recruiting between them 413 subjects. Due to small size, a lack of detail in reporting the methods, in particular randomisation, and incomplete data, few of the studies scored higher than 2b for level of evidence. Three studies included protriptyline, their results were subjected to meta-analysis and scored as 1a (table e9) [127].

Protriptyline is a tricyclic antidepressant that inhibits re-uptake of serotonin and noradrenaline. It might reduce the proportion of REM sleep in people with REM predominant OSA and increase the airway tone mediated by serotonin acting on the genioglossus *via* the hypoglossal nerve. However, there was no impact on respiratory indices but there was an improvement in daytime symptoms in two out of three trials, presumably due to a nonspecific alerting effect of the drug. Adverse side-effects, such as dry mouth and urinary symptoms, were commonly reported. Protriptyline does not have any place in the routine treatment of OSA [128–130].

Specific serotonin re-uptake inhibitors such as paroxetine have been investigated as possible treatments for OSA. In a small single night study, paroxetine 40 mg had no impact on AHI compared to placebo with severe OSA [131]. By contrast, in a study with 6-week treatment arms paroxetine 20 mg was shown to reduce AHI to 23.3 compared with 30.3 for placebo. There was a positive impact on respiratory events in non-REM sleep but no effect in REM sleep, and no improvement in daytime symptoms [132].

Mirtazapine is another drug with antidepressant activity that acts as an agonist at some serotonin receptors and can also increase serotonin secretion. This might increase sertonergic tone to the hypoglossal nerve, which could be particularly helpful during REM sleep. Reductions in the AHI were reported in one study [133] but could not be reproduced in two multicentre trials, while many participants reported side-effects of sleepiness and weight gain [134]. The drug cannot be recommended for use in OSA.

Cholinergic agonists have been investigated as possible treatments for OSA. In a single night study 10 subjects had an AHI of 41 on physostigmine compared with 54 on placebo [135]. The greatest impact was on apnoeas during REM sleep and there was an inverse relationship with BMI, such that slimmer subjects had a greater fall in AHI. The drug was given intravenously, making it impractical for home use. There have been no studies with oral cholinergic agents.

Acetazolamide inhibits carbonic anhydrase, producing a metabolic acidosis that increases ventilatory drive. It was shown to reduce the AHI in a study of 10 subjects but there was no positive impact on daytime symptoms after 1 week of treatment [130]. The subjects who had responded best to the drug were offered a more prolonged trial of treatment but only one could tolerate it in the long term. It has no role in the routine management of OSA.

In a single night study with 10 subjects, phosphocholinamin was given as a topical nasal lubricant administered twice overnight which resulted in an AHI of 14 compared with 24 with placebo [136]. In view of the duration of the study it is not

known whether this might improve daytime symptoms but the drug was not recommended for long-term use due to anxiety about aspiration causing lipoid pneumonia. There are no published studies of any other candidate substances.

Among the other drugs that have been trialled, naltrexone, theophylline and aminophylline have been shown to reduce the number of respiratory events overnight but this was at the expense of sleep continuity and total sleep time, which makes them unsuitable agents for the treatment of OSA. Omeprazole has been said to reduce the frequency of attacks of apnoea in subjects who had both OSA and gastro-oesophageal reflux disease, but no sleep studies were performed on treatment and the attacks may well have been episodes of laryngospasm due to acid reflux, not episodes of OSA. Medroxyprogesterone, doxapram, clonidine, mibefradil, cilazapril, buspirone, ondansetron and sabeluzole have all been investigated and none has been shown to reduce the frequency of respiratory events in people with OSA or to improve daytime symptoms.

Conclusions and recommendations

At the present time there is no evidence that any drug is likely to benefit an unselected patient with OSA. Small studies have reported positive effects of certain agents on short-term outcomes. Longer studies with measures of symptomatic responses of cholinergic agents and upper airway lubricants are supported by the results of single night studies already published. It is likely that better characterisation of the predominant mechanisms of OSA in individual patients will lead to better results and this also needs further study. Drug therapy is not recommended as treatment for OSA (most drugs C; for mirtazapine and protryptilline B).

Nasal steroids

Rationale

A particularly frequent cause of nasal obstruction is allergic rhinitis, either seasonal or perennial. There are a number of reports suggesting worsening of subjective sleep quality and quality of life measures in both adults and children with allergic and perennial rhinitis [137]. *Vice versa*, CANOVA *et al.* [138] demonstrated an increased prevalence of perennial allergic rhinitis in patients with OSA (11%) compared to case controls (2.3%). In addition to the obstructing effects of allergic rhinitis, inflammation of the nasal mucosa may contribute to the development of adenotonsillar hypertrophy, one of the most frequently observed abnormalities in children with OSA. Intranasal corticosteroids are commonly used to treat rhinitis. A recent Cochrane review on intranasal corticosteroids showed significant efficacy of intranasal corticosteroids in improving nasal obstruction symptoms and in reducing adenoid size [139]. Consequently, this may influence the anatomic component by decreasing upper airway resistance at the nasal, adenoidal, and/or tonsillar levels. Therefore, topical nasal steroids may influence sleep apnoea severity both in children and adults.

Search criteria

Databases individually searched: PubMed and Medline. Keyword combinations: sleep apnoea and intranasal corticosteroids, sleep apnoea and inhaled corticosteroids, sleep apnoea and intranasal steroids, sleep apnoea and corticosteroids, nasal steroids and sleep apnoea, sleep apnoea and fluticasone, sleep apnoea and triamcinolone, sleep apnoea and budesonide, OSAS and corticosteroids.

Overview of the evidence

We identified only one single-centre study with a small sample size that investigated the effects of intranasal corticosteroid application for 4 weeks on polysomnographically diagnosed sleep parameters in adult patients with moderate OSA and co-existing (perennial or seasonal) rhinitis [140]. There was a modest but significant decrease in AHI and an improvement in nasal airflow resistance; however, there were no significant improvements in oxygenation indices, sleep quality or snoring noise.

Five studies with a total of 136 children (age range 1–14 yrs) with mild to moderate OSA were identified. Two studies were conducted as open clinical trials without a control group, one study investigated the effects of budesonide and montelukast, using a case control design, and two studies were conducted as prospective, randomised, placebo-controlled trials. Most of the children included in these reports had evidence of co-existing rhinitis with or without adenotonsillar hypertrophy. All included reports observed significant treatment-associated improvements in the AHI (mean pre-treatment AHI range 3.7–11 *versus* treatment-associated mean AHI range 0.3–6). Three reports furthermore showed significant improvements in oxygenation indices and two studies demonstrated improved sleep quality. The data are, however, inconsistent with respect to sleep architecture and adenoidal size (table e10) [140–145].

Conclusions and recommendations

Intranasal steroids, as a single intervention, are not recommended for treatment of adult OSAS (C). Intranasal steroids are recommended for childhood OSAS in the presence of co-existing rhinitis and/or upper airway obstruction due to adenotonsillar hypertrophy (B).

Nasal dilators

Rationale

The nasal vestibule is a major site of resistance to airflow in healthy subjects. A high nasal resistance may increase snoring. Activation of the alae nasi and alar retraction reduce resistance to airflow and improve ventilation. Nasal dilators might improve sleep and breathing by widening the nostrils. They are fitted to exert a dilating force on the nasal valves by means of its elasticity.

Search strategy

Databases individually searched: PubMed and Medline. Literature search using the terms obstructive sleep apnoea AND nasal dilator (no limits) was performed. Original studies published in English before April 2010 were included. In addition, the reference list of the included trials was evaluated. In total, 14 studies (two randomised controlled trials and 12 other clinical trials) could be identified, published between 1988 and 2005.

Overview of evidence

Nasal dilation increases nasal cross section by 14–25% and is associated with a distinctive and sustained reduction in nasal resistance and the oral fraction of ventilation during sleep

[146]. External nasal dilators are well tolerated [147]. They were able to reduce the maximum snoring intensity in one study [148], but in another study snoring was not influenced at all [149]. Sleep architecture remains almost unchanged in patients with habitual snoring [147, 149] and is improved slightly in patients with OSA [146]. OSA severity was reduced in one study with 10 patients with OSA and nasal obstruction [146], but not in another study with 30 patients with OSA [150], and in a study with 18 patients with upper airway resistance syndrome there was no additional effect on sleep disordered breathing [151]. It is possible that there are parameters predicting the efficacy of the devices, such as hyperplasia or hypertrophy of the lower turbinates, septal deviation, allergic rhinitis, no or only minor pharyngeal obstruction, or age <55 yrs (table e11) [152].

Internal nasal dilation reduces nasal resistance by 31–65% [153, 154] and thereby improves the airflow [45]. Devices have a weak effect on snoring in patients without nasal pathology [155], even in populations with different external nose structures (Caucasians and Japanese) [156], but their use resulted in a substantial decrease in snoring noise in patients with habitual snoring and/or OSA [157]. The devices have only little or no effect on the number of apnoeas, hypopnoeas and oxygen saturation during sleep, or hypersomnolence during the day (table e12) [154, 157, 158].

In summary, the published data do not support the hypothesis that nasal dilators are effective in reducing snoring, or in improving sleep disordered breathing or sleep architecture in OSA. Nasal dilators are not recommended for reducing snoring, or for improving sleep disordered breathing or sleep architecture in OSA (D).

SURGICAL THERAPY

Pathophysiological impact of nasal obstruction in the development of OSA

Breathing through the human nose appears to have an effect on both ventilation and upper airway muscle tone. In an experimental study, MCNICHOLAS *et al.* [159] previously demonstrated increased ventilation during nasal ventilation compared with mouth breathing. WHITE *et al.* [160] investigated the effects of local nasal anaesthesia on ventilation during sleep in healthy males. The application of lidocaine resulted in a four-fold increase in the number of both central and obstructive apnoeas, suggesting a stimulating effect of nasal airflow on respiratory muscle activity and upper airway stability. The latter has been confirmed by BASNER *et al.* [161], who demonstrated that nasal ventilation was associated with higher upper airway dilator muscle activity than breathing through the mouth in healthy volunteers. More recently, KOUTSOURELAKIS *et al.* [162] investigated the relationship between breathing route and apnoeic events in patients with OSA and controls. Patients with OSA had more frequent oral breathing epochs during sleep than controls. Oral breathing epochs furthermore correlated with respiratory disturbances during sleep.

It may be argued that nasal obstruction may predispose to sleep disordered breathing. In fact, a number of studies demonstrated an increased number of arousals, more frequent sleep stage changes, and/or an increase in the number of obstructive apnoeas and hypopnoeas during sleep associated with nasal occlusion under experimental nasal obstruction [163–165]. Similarly, there is evidence of sleep-related breathing disorders associated with nasal obstruction as a result of bilateral nasal packing after nasal surgery [166–169]. One potential limitation in these reports may be the potential influence of general anaesthesia on the prevalence of postoperative upper airway obstruction. In a recent report, however, ARMENGOT *et al.* [170] demonstrated equivalent episodes of nocturnal hypoxaemia, both in patients who had nasal packing postoperative nasal surgery and in those who had nasal packs for epistaxis but did not receive surgery.

In summary, there is evidence of a protective effect of nasal breathing on upper airway stability. The current literature furthermore suggests that patients with OSA are more likely to breathe through the high resistance pathway of the mouth, thereby promoting more negative intraluminal pressure in the pharynx, and predisposing to pharyngeal occlusion and, thus, OSA events. Moreover, there is evidence on both inducing and worsening of sleep disordered breathing due to nasal occlusion.

Effects of nasal surgery on OSA

Rationale

Due to the impact of nasal obstruction, improved nasal patency is expected to alleviate sleep disordered breathing. Furthermore, there is an expected relationship between nasal airway obstruction and CPAP tolerance, providing a physiological basis for improved CPAP compliance after nasal surgery [171]. Accordingly, the aim of this review is to assess the efficacy of nasal surgery on sleep apnoea severity, sleep quality and symptoms in adults with diagnosed OSA.

Search criteria

The authors performed searches in Pubmed and Medline. In addition, the authors underwent a manual search of the reference section of each cited article. Keyword combinations: OSA and nasal obstruction, OSA and nasal surgery, sleep apnoea and nasal surgery, sleep apnoea and nasal obstruction, sleep apnoea and nose, nasal ventilation and OSA. Studies with snorers only or those with sleep breathing disorders other than OSA, and studies in which nasal surgery was associated with other surgical procedures in the treated subject (*i.e.* adenotonsillectomy or others) were excluded.

Overview of the evidence

14 reports with adult patients suffering from mild to severe sleep disordered breathing and nasal obstruction have been published either as case series or retrospective analyses, and one report [172] was conducted as a prospective, randomised, sham-controlled trial (table e13) [172–183]. The most frequently observed pathologic finding in the preoperative ear, nose and throat examination was nasal obstruction due to deviated nasal septum. Accordingly, septal surgery (submucosal resection with or without turbinectomy) was the most frequently applied surgical technique in these reports. All the studies (n=5) that have performed rhinomanometry reported significant postoperative improvements in total nasal resistance, indicating postoperative improvements in nasal airway patency in the patients.

Only two studies [180, 181] reported significant improvements with regard to respiratory disturbances. One study [177] reported a significant improvement in AHI and sleep architecture in those with normal preoperative cephalometric measurements, but no beneficial effect in a group of patients with abnormal cephalometric measurements. There have been improvements in either sleepiness scales or daytime energy levels in six reports, and a reduction in therapeutic CPAP pressure required to alleviate OSA in two studies.

Conclusions and recommendations

Nasal surgery as a single intervention is not recommended for treatment of OSAS (C). Nasal surgery is recommended for reducing high therapeutic CPAP pressure due to nasal obstruction (C).

Tonsillectomy and tonsillotomy

Rationale

The main upper airway anatomical alterations correlating with OSA include an enlarged tongue, soft thick palate, web posteriorised in relation to the oropharynx, long and thick uvula, and/or hypertrophic tonsils. Of note, those studies attempting to correlate the presence of anatomical alterations with disease severity found the highest correlations for tonsillar hypertrophy [184, 185]. While substantial bilateral tonsillar hypertrophy in adults is rather rare, adenotonsillar hypertrophy is the most common aetiology of OSA in children. The aim of this literature search was to assess the efficacy of surgical tonsillectomy on sleep apnoea severity, sleep quality, and symptoms in adults with OSA and tonsillar hypertrophy.

Search criteria

Databases individually searched: PubMed and Medline. Keyword combinations: tonsillectomy and obstructive sleep apnoea, tonsillotomy and obstructive sleep apnoea, tonsils and sleep, tonsillar hypertrophy and sleep apnoea, adenotonsillectomy and sleep apnoea. Studies with tonsillectomy by means of radiofrequency ablation, studies with tonsillectomy as part of UPPP or MLS, and reports on surgical outcomes of the upper airways without explicit information on sleep results in relation to tonsillectomy were excluded.

Overview of the evidence in adults

All reports have been published either as case series or retrospective analyses (table e14). Common to most of the reports is the lack of quality of life measures, the absence of a control group, and the lack of reporting surgical complication rates. More recent studies, however, reported consistent and significant improvements in the AHI after tonsillectomy. Despite significant improvements in respiratory parameters, there was evidence of residual sleep disordered breathing in most reports. More recent trials by MARTINHO *et al.* [186] and NAKATA *et al.* [187] investigated patients with OSA who where either intolerant to a CPAP trial or required high CPAP pressures to treat upper airway obstruction due to tonsillar hypertrophy. Based on these reports tonsillectomy play a role similar to nasal surgery in increasing the use of CPAP in patients with tonsillar hypertrophy, or when CPAP therapy is not possible as the first choice of therapy.

Overview of the evidence in children

38 ''particular case–control studies'' (n=10; evidence level 3b), case–control studies of limited quality (n=2; level 4), and case series without controls (n=26; level 4) investigating patients between 1 and 20 yrs of age who underwent (adeno)tonsillectomy were included in the analysis (table e15). Common to most reports is that the indication for surgery was based on evidence of upper airway obstruction, either by means of clinical signs or symptoms and/or poly(somno)graphically diagnosed sleep disordered breathing. Most studies investigated the effects of tonsillectomy as a combined procedure with adenoidectomy. The study population was very heterogeneous, including children who underwent tonsillectomy because of snoring, suspected OSA, poly(somno)graphically verified sleep apnoea (using an apnoea index (AI) >1 or AHI >5 h^{-1} as a diagnostic cut-off), recurrent tonsillitis, and/or symptoms of upper airway obstruction without further explanation. Follow-up studies were performed between a few days postoperatively and up to 12 months after surgery.

All studies showed significant postoperative improvements in respiratory parameters.

Furthermore, there is some evidence of improved sleep architecture and improved quality of life scores, OSA symptom scores, and/or child behavioural scores. The literature also provides evidence for beneficial treatment effects beyond the reported outcomes on sleep parameters and quality of life scores, such as rapid increase in growth rate [188], improvement in insulin like growth factor-I levels [189], and improvements in systemic inflammation, lipid profiles and endothelial function [190]. Notably, most of the studies that investigated children with moderate to severe OSA observed persistent sleep disordered breathing in a clinically relevant proportion of children. Complete resolution of OSA was reported to be as low as 25% [191]. This raises important issues regarding the efficacy of adenotonsillectomy as the only intervention for OSA in children. Accordingly, repeated sleep testing has been recommended, particularly in those with persisting symptoms of upper airway obstruction (such as snoring) and/or in those with severely abnormal preoperative polysomnography results [192].

Conclusions and recommendations

Tonsillectomy as a single intervention is recommended for treatment of adult OSA in the presence of tonsillar hypertrophy (C). Adenotonsillectomy is recommended for treatment of childhood OSA in the presence of adenotonsillar hypertrophy (C).

Radiofrequency surgery of the tonsils

Rationale

New techniques of tonsillectomy or tonsil volume reduction (tonsillotomy) are developed in order to reduce postoperative pain and bleeding rates. Temperature-controlled radiofrequency tonsil reduction is performed by introducing a probe into the tonsil and then heating to temperatures ranging from 40°C to 70°C. A plasma field consisting of highly ionised particles is formed at the probe's surface that breaks down the molecular bonds of local tissue, with a reduction in heat dissipation to surrounding structures. The key innovation of radiofrequency tonsil reduction is the concept of subtotal

intracapsular tonsil reduction that avoids injury to the pharyngeal constrictor muscles.

Search criteria

Databases individually searched: PubMed and Medline. Keywords: radiofrequency tonsillotomy and radiofrequency tonsil surgery for sleep apnoea. Articles dealing with paediatric samples, MLS, infectious tonsillar disease reviews, meta-analysis, case reports and guidelines were excluded.

Overview of the evidence

Four studies matching the inclusion criteria of this paper were found (table e16 and e17). No polysomnographic data were available in these studies.

NELSON [193] showed that performing radiofrequency ablation of the tonsils with the use of a two-needle probe does not damage the underlying pharyngeal muscle *in vitro*. A reduction of 70.8% in tonsil size was achieved in an *in vivo* study (n=9) without postoperative bleeding. Moderate to severe postoperative pain on day one was present in four out of nine patients but disappeared over a 1-week period. An important improvement in subjective outcome, speech comfort, swallowing and throat irritation was reported. The same group confirmed these findings in a 12-month follow-up study in 12 patients with obstructive tonsil hypertrophy [194]. FRIEDMAN *et al.* [195] reported a reduction of 53.6% in tonsil size after 12 weeks. The amount of tonsil reduction had a wide range and was unpredictable. Only mild postoperative pain was observed in all patients. No intra- or postoperative bleeding was noticed. However, radiofrequency tonsil reduction was not recommended as a standard technique for tonsil reduction. ERICSSON and HULTCRANTZ [196] compared efficacy and side-effects of tonsillotomy (n=31) and tonsillectomy (n=43) in patients with recurrent tonsillitis or obstructive hypertrophy. The tonsillotomy group had less intra-operative bleeding and no postoperative bleeding, while the tonsillectomy group had six postoperative bleedings. Postoperative pain was significantly less in the tonsillotomy group. In a follow-up study 1 yr after radiofrequency tonsillotomy, ERICSSON and HULTCRANTZ [196] showed that both tonsillotomy and tonsillectomy equally and effectively improved quality of life.

Conclusions and recommendations

Radiofrequency tonsil reduction appears to be a minimally invasive procedure with limited morbidity compared with tonsillectomy. The amount of tonsil reduction is significant but unpredictable. No conclusion on efficacy in OSA can be drawn since none of the studies included polysomnographic data. Radiofrequency tonsil reduction appears to have fewer side-effects such as intra- and postoperative bleeding and less postoperative pain. Tonsil re-growth might occur but has not been studied thoroughly. Radiofrequency tonsil reduction is not recommended as a single procedure for the treatment of OSA (D).

Uvulopalatopharyngoplasty and laser-assisted uvulopalatoplasty

Rationale

UPPP and laser-assisted uvulopalatoplasty (LAUP) aim to diminish anatomical upper airway obstruction at the oropharyngeal level by reducing soft palate redundancy [197]. UPPP enlarges the retropalatal airway by trimming and reorienting the posterior and anterior lateral pharyngeal pillars, and by excising the uvula and the posterior soft palate [197]. LAUP is an office-based surgical procedure that progressively shortens and tightens the uvula and palate through a series of carbon dioxide laser incisions and vaporisations [197]. In the large majority of apnoeic patients, upper airway collapses occur at multiple levels, *i.e.* both at the retropalatal level and behind the tongue base. Therefore, a surgical success with UPPP or LAUP can only be anticipated when pharyngeal collapse is limited to the retropalatal area, which is rarely the case in obese patients or those with severe sleep apnoea [198]. For these reasons, surgical procedures dedicated to the soft palate have been essentially studied in selected mild to moderate OSA populations with predominant oropharyngeal narrowing.

Search criteria

Databases individually searched: PubMed and Medline. Keyword combinations: sleep apnoea AND uvulopalatopharyngoplasty. Sleep apnoea AND LAUP or laser assisted uvulopalatoplasty. Limit: clinical trial; no other limitations. Only prospective studies were taken into account.

Uvulopalatopharyngoplasty

Overview of the evidence. Randomised clinical trials comparing UPPP to no treatment or sham surgery groups are lacking. Different definitions of clinical success are proposed, the most common that we will use in this review is a more than 50% reduction in AHI with a post-surgery AHI <20 per h of sleep. The number of patients assessed is generally limited, with only few publications evaluating UPPP alone without adjunctive surgical procedure. Even prospective studies demonstrate nearly systematic inclusion biases. At the end, the majority of the available papers are clinical case series ranked as level 4 evidence. Interpretation of the ''UPPP studies'' is even more complex owing to the existence of many surgical techniques dedicated to the soft palate [199].

Overall, UPPP has a reported success rate of ~50% in unselected populations of mild to moderate sleep apnoea [197, 198]. In prospective studies (table e18) the mean success rate (50% reduction in AHI, an AHI of ⩽20, or both) ranged from 30 to 78%. Such differences from one study to another are probably reflecting selection biases with potential good candidates being previously selected [200]. These studies also mainly included young or middle aged and lean subjects with mild to moderate sleep apnoea.

Failure of UPPP is usually attributed to secondary sites of obstruction located more caudally in the upper airway or to persistent retropalatal collapse due to an increased thickness of the soft palate after the procedure [199, 201]. The percentage of patients attaining UPPP success was 52% in the case of isolated oropharyngeal obstruction compared with 5% in situations of associated retrolingual narrowing [202]. However, selecting appropriate patients for UPPP surgery remains challenging, as physical examination, imaging techniques, upper airway pressure measurements and endoscopic examination are not systematically used, and no evidence exists demonstrating that any criteria are sufficiently useful in predicting good surgical outcomes [200]. FRIEDMAN *et al.* [203] developed an anatomic staging system based on tongue–palate position, tonsil size and

BMI to classify patients. In a case series, changes in AHI were significantly correlated with Friedman tongue position and tonsil size [200]. Patients with retrolingual collapse or narrowing, demonstrated by clinical criteria or by techniques evaluating upper airway size and/or function, should not be selected for UPPP surgery.

In the few studies having examined long-term evolution after surgery, efficacy of UPPP seems to diminish over time [88]. This seems to justify a long-term follow-up of these patients. UPPP is substantially less effective than the use of oral appliances [88, 204].

Other outcomes, such as subjective [205, 206] or objective sleepiness, sleep structure and fragmentation, quality of life [207] or cardiovascular changes, have been rarely reported. However, improvements of the Pittsburgh Sleep Quality Index, the Epworth Sleepiness Scale (ESS) [206], low grade inflammation [208], and endothelial function [209] have been described.

Serious life-threatening complications, including intubation difficulties, bleedings and acute upper airway obstruction, have been observed after UPPP with a 1.5% incidence and a mortaliy rate of 0.2% in a large prospective study including 3,130 patients [210]. Long-term side-effects (*e.g.* swallowing, globus sensation, voice changes or nasopharyngeal stenosis) persisted after UPPP in 58% of the patients [211]. Finally, having undergone UPPP has been proposed as a risk factor for CPAP non-compliance [212]. Leaks and mouth dryness are increased when using CPAP in patients with prior UPPP and may impair CPAP tolerance.

Conclusions and recommendations. UPPP is a single-level surgical procedure working only in selected patients with obstruction limited to the oropharyngeal area. UPPP cannot be recommended except in carefully selected patients (C). When proposing UPPP, potential benefits should be weighed against the risk of frequent long-term side-effects, among which velopharyngeal insufficiency, dry throat and abnormal swallowing, are the most common. Analysed studies were prospective but with selection biases, and therefore do not provide high-level evidence (C).

Laser-assisted uvuloplasty

Overview of the evidence. Two randomised controlled trials are available [213, 214]. FERGUSON *et al.* [213] compared LAUP to conservative treatment in 46 mild OSA patients with a mean follow-up of 7 months. There was a statistically significant but not clinically relevant 21% reduction in AHI after LAUP (from 19 to 15 h^{-1}) No improvement was found for subjective sleepiness and quality of life. Surgery reduced snoring intensity and frequency. LARROSA *et al.* [214] failed to find a difference between LAUP and a Sham surgery in sleepiness, quality of life or respiratory disturbances. After LAUP surgery, the airway is further compromised by oedema in the early postoperative period with a potential risk of OSA exacerbation (table e19).

Conclusion and recommendation. In mild OSA, LAUP has not demonstrated any significant effect neither on OSA severity nor in symptoms or quality of life domains and is therefore not recommended (B).

Radiofrequency surgery of the soft palate

Rationale

The term ''radiofrequency surgery'' in the context of palatal interventions is usually focused on interstitial electrosurgical treatment with stiffening of the tissue. Furthermore, cutting devices based on radiofrequency energy have also been developed to excise palatal tissue (radiofrequency assisted uvulopalatoplasty, RAUP) [215–217]. Finally, various combinations have been proposed, for example the combination of interstitial radiofrequency surgery and RAUP [218]. Tissue excision is usually performed as a single step procedure, whereas the interstitial application routinely requires repeated treatment session.

Search criteria

Databases individually searched: PubMed and Medline. Keyword combinations: ''radiofrequency'', ''palate'' and ''sleep apnoea''. Only studies using radiofrequency surgery as an isolated approach were analysed. Studies with patients with primary snoring were only selected with regard to morbidity and complications. In addition, a recent review was evaluated regarding potential additional publications [219]. Studies were excluded if they either did not provide sufficient objective outcome measures [220–222] or the baseline AHI was <5 [223] or 10 [220, 224, 225] and the primary intention was to treat snoring.

Overview of the evidence

The data concerning OSA is limited and can hardly be compared due to the differences in devices and surgical techniques.

Improvements in respiratory parameters have been described in groups of mild to moderate and more severely affected patients under interstitial radiofrequency at the soft palate [226, 227]. Moreover, RAUP has been shown to be superior to interstitial radiofrequency surgery, but was associated with higher postoperative morbidity [217]. However, there are inconsistent findings in daytime sleepiness or other sleep parameters. A more recent, placebo-controlled study has shown that a single step radiofrequency intervention at the soft palate is not effective for the treatment of OSA (table e20) [228].

No serious adverse events after interstitial radiofrequency have been reported, though overall complication rates ranged from 0% to 50% [229–233]. The most frequently reported complication was mucosal erosion/ulceration. A small number of studies reported moderate complications in terms of severe palatal damage (palatal fistula, uvula loss/sloughing) [229, 230, 234, 235]. Postoperative pain was minimal in nearly all published papers [236–239]. No significant impact on fundamental frequency and formant frequency of vowels was detected. Postoperative morbidity of radiofrequency tissue resection or combined approaches appears higher [217, 218]. Nevertheless, postoperative pain after RAUP is still significantly less pronounced and postoperative morbidity is still significantly lower compared to LAUP [216].

Conclusions and recommendations

No controlled trials are available in sleep apnoea. All case series demonstrate a significant reduction in AHI after radiofrequency surgery. Radiofrequency surgery cannot be recommended, except in carefully selected patients (C).

Uvulopalatal flap

Background

The uvulopalatal flap has been introduced as a modification of the classic UPPP [240]. By the removal of the oral mucosa and salivatory glands, and incisions bilaterally into the posterior pillar an uvulopalatal flap is created. This flap is rotated upwards and sutured into the defect. The main disadvantage compared to UPPP is that despite preservation of all muscles no visible uvula is left acting as lubricating structure for the palate.

Search criteria

Databases individually searched: PubMed and Medline. Keyword combinations: ''uvulopalato or uvulopalatal and apnoea'' and Boolean logic. 26 articles were further analysed. 13 articles were excluded (on the basis of language, reviews, expert opinions and not related with sleep disordered breathing).

Overview of the evidence

The evidence levels of the studies identified vary between 3b and 4. The data's evidence is restricted by the fact that the 12 studies are published by only three working groups. Therefore, it seems possible that several subjects might be included in multiple publications.

The procedure can be performed under local and general anaesthesia [241–243]. Complaints and complications are similar to a gentle UPPP [240]. Transient nasal regurgitation has been reported in 4% of the cases [241]. Permanent velopharyngeal incompetence or nasopharyngeal stenoses have not been reported so far. All working groups (six out of 12 studies) combined the uvulopalatal flap with other surgeries of the nose and/or the tongue base [240]. POWELL *et al.* [240] compared classic UPPP with the uvulopalatal flap in a group of 80 patients undergoing MLS (level of evidence 3b). The tongue base procedures were identical in both study groups. Both UPPP and the flap showed comparable results with regard to effectiveness for OSA, amount of tissue removed and complications. Six papers investigated the effect of an isolated uvulopalatal flap without any other surgeries at the same time [241, 244–248]. The AHI decreased significantly from 45 to 14 within 6–12 months after surgery. Surgical success (defined as 50% reduction in AHI and reduction of AHI below 20) was calculated as 81.5%. Significant improvement of quality of life as measured with the Mental Health 5 questionnaire [245]. Short Form 36 (SF-36), ESS and Snore Outcome Survey (SOS) were reported compared to baseline. All series were done by the same working group (table e21 and e22).

Conclusions and recommendations

Studies investigating the uvulopalatal flap with tonsillectomy for OSA show a significant improvement of the severity of OSA and quality of life. No controlled studies exist comparing the uvulopalatal flap to other treatment modalities for OSA. The levels of evidence of all studies were classified as 4 (C). So far, no cut-off points concerning BMI and AHI were identified limiting the use of the uvulopalatal flap. Therefore, it has to be kept in mind that surgical success rates decrease with increasing BMI and AHI in general. Various study groups found that the uvulopalatal flap may be combined with other surgeries of the nose and the tongue base in the sense of MLS with acceptable perioperative risk (3b). The uvulopalatal flap turned out to be as effective as UPPP (3b).

Due to a lack of evidence, uvulopalatal flaps are not recommended to treat simple snoring. Uvulopalatal flaps can be recommended for OSA in patients with palatal obstruction (C). Uvuloplatal flaps are a safe procedure that can be combined with other types of surgery within the upper airway to address OSA (B).

Pillar method

Rationale

The Pillar method consists of placing three cylindrical, non-resorbable polyethylenterephthalate implants (18 mm long) into and parallel to the midline of the soft palate with a distance of 3 mm to each other. The implants themselves, as well as the surrounding fibrosis, are intended to reduce three-dimensional flutter of the soft palate and therefore inspiratory airway resistance [249].

Search criteria

Databases individually searched: PubMed and Medline. Keyword combinations: ''palate'', ''implant'' and ''sleep apnoea''. Only prospective studies were included. For the analysis of clinical outcome, only studies using the Pillar® technique as an isolated approach were analysed. Studies concerning snorers were only selected with regard to morbidity and complications. There is no experience in children so far.

Overview of the evidence

There are six case series and two randomised, placebo-controlled, double-blind trials (table e23). Placebo treatment consisted of inserting an empty delivery tool (no implant preloaded). Most studies included only patients with an AHI between 10 and 30, BMI <32 kg·m^{-2}, no or small palatine tonsils, and no sign of retrolingual collapse. Only FRIEDMAN *et al.* [252] included more obese patients (BMI <40 kg·m^{-2}). The six case series showed a reduction of the AHI $>50\%$ and postoperative AHI <10 in 15–50% of the cases 3–15 months after the procedure [250–254]. Both randomised, placebo-controlled, double-blind studies show a superiority of implants over placebo. However, results are conflicting, as STEWARD *et al.* [255] found a non-significant increase of AHI, in contrast to FRIEDMAN *et al.* [250], who reported a pronounced reduction of AHI. The ESS showed significant improvement in all case series and in the level 1b study conducted by FRIEDMAN *et al.* [250]. No difference was found compared to the placebo group in the study of STEWARD *et al.* [255]. Functional parameters as assessed by questionnaires such as the SF-36 [250] and the Functional Outcomes of Sleep Questionnaire [255] demonstrated a significantly greater improvement in the treatment group compared to placebo.

Only minor discomfort, such as minor sore throat or foreign body sensation, was reported within the first 4 days post-procedure. Infections, mucosal irritations or ulcerations at the implant entrance site were reported in $<1\%$ of the patients. Pain could be managed with simple analgesics such as paracetamol. There was no significant speech or swallowing disturbance after the procedure [256–260]. A partial extrusion happened in 10.3 % of the patients or 4.1% of the implants in average.

Conclusions and recommendations

Pillar® implants as an isolated procedure are superior to placebo and the respiratory results remain stable over the first 15 postoperative months but the overall success rate is limited. Therefore Pillar implants cannot be recommended and may only be considered in patients with mild to moderate OSA, who are suitable with regard to their overall physical condition (not or only moderately obese, no or small tonsils, no sign of retrolingual obstruction), if conservative approaches are not accepted by the patient (B).

Tongue base and hypopharynx

Radiofrequency surgery of the tongue base

Rationale

Interstitial radiofrequency surgery of the tongue base was first investigated in a porcine model using a temperature-controlled radiofrequency device. The procedure turned out to be safe and was transferred to the use in patients suffering from OSA. Various different devices are available, although the majority of the published trials have used temperature-controlled radiofrequency surgery.

Search criteria

A literature search was performed in PubMed (US National Library of Medicine, Bethesda, MD, USA). Keyword combinations: ''radiofrequency'', ''tongue'' and ''sleep apnoea''. In addition, a recent review was evaluated regarding potential additional publications. For the analysis of clinical outcome, only studies using interstitial, transoral radiofrequency surgery as an isolated approach were analysed. Studies using combined approaches in terms of MLS were only selected with regard to morbidity and complications. Data regarding a transcervical radiofrequency approach were excluded. One study was excluded due to the high number of dropouts and the inhomogeneous mixed patient sample (snoring and OSA).

Overview of the evidence

In general, despite one comparative trial [261] only noncontrolled case series have been published. All studies have shown a statistically significant reduction in daytime sleepiness and all but two demonstrated a statistically significant reduction in AHI, although the overall effect seems limited (table e24) [262, 263]. Most trials presented follow-up periods of between 1 and 4 months. The longer term follow-up study (28 months) showed an increase in AHI indicating a relapse of OSA [264]. In contrast, STEWARD *et al.* [265] have documented the stability of the results at least over a median follow-up of 23 months. A series of noncontrolled trials has been published regarding combined radiofrequency surgery at the tongue base and the soft palate [266, 267]. However, WOODSON *et al.* [261] compared multilevel radiofrequency surgery at the tongue base and the soft palate with CPAP and placebo (sham CPAP). Although the AHI did not improve in the radiofrequency group, subjective and functional outcome measures improved significantly. Postoperative pain appears to be comparable to UPPP with tonsillectomy [263]. The postoperative complication rate varies between 0 and 41%, and is mostly below 5% [229, 232, 233, 263, 267–270]. A severe potential complication is the formation of an abscess of the tongue base [229, 232, 262, 271]. No changes of swallowing or speech were observed [232, 263, 267, 271]. The addition of radiofrequency surgery to other surgical approaches, such as UPPP, nasal surgery, tonsillar surgery, palatal implants or hyoid suspension, did not lead to an increase in morbidity [270, 272–277].

Conclusions and recommendations

The majority of the studies demonstrated a statistically significant, but limited, reduction in AHI and daytime sleepiness, although the data were based on noncontrolled case series with short follow-up periods (level of evidence 3b). Therefore, radiofrequency surgery of the tongue cannot generally be recommended as an isolated or combined procedure and may only be considered in selected patients with mild to moderate sleep apnoea intolerant to conservative treatment, as long as the overall condition appears suitable (non- or only moderately, obese patients with retrolingual obstruction) (C).

Hyoid suspension

Rationale

Hyoid suspension aims to avoid the back positioning of the tongue during sleep. Meanwhile, most surgeons favour the suspension of the hyoid to the thyroid cartilage with and without myotomies of the supra- and infrahyoid muscles.

Search criteria

Databases individually searched: PubMed and Medline. Keyword combinations: ''hyoid suspension and apnoea'' and Boolean logic. Variations of the catchwords were admitted. The remaining 21 articles were included in the analysis (table e25).

Overview of the evidence

The evidence levels of the studies identified vary between 3b and 4. The perioperative risk of surgery is generally increased in OSA. In addition, temporary dysphagia up to 4 weeks, self-limited aspiration within the postoperative period, haematomas, seromas and disturbance of wound healing, as well as temporary articulation distortions, have been reported. Most authors use the hyoid suspension as a component of MLS for severe OSA secondarily after CPAP failure (table e25). Only three short-term studies investigated the effect of an isolated hyoid suspension for OSA [278–280]. The AHI decreased significantly from 36 to 21 after the hyoid suspension (table e26). The ESS score fell significantly from 8 at baseline to 5 after surgery [278, 280]. Two studies [281, 282] compared MLS with and without hyoid suspension. The concept including hyoid suspension was significantly more effective than the control group.

Conclusions and recommendations

The published data have to be regarded as preliminary. Randomised studies comparing the hyoid suspension with CPAP do not exist. The hyoid suspension is an invasive surgical technique, although the complication rate is moderate. Therefore, hyoid suspension may be combined with other procedures in MLS. The method may be considered in CPAP failure. Surgical success rates decrease with increasing BMI and AHI (C).

Due to a lack of evidence, hyoid suspension is not recommended for simple snoring. Hyoid suspension as an isolated procedure can be recommended for OSA in patients with retrolingual/hypopharnygeal obstruction (C). Hyoid suspension is a safe procedure that can be combined with other types of surgery within the upper airway (B). Hyoid suspension as a

part of a MLS concept can be recommended for OSA in patients with combined retropalatal and retrolingual/hypopharnygeal obstruction (B).

Tongue base and hypopharynx: partial tongue base resection and other treatments

Search criteria

Keyword combination: tongue base surgery for sleep apnoea and hypopharyngeal surgery for sleep apnoea. Inclusion: studies where tongue base resection or tongue suspension were part of a multilevel approach are included. Medline search: tongue base surgery for sleep apnoea and hypopharyngeal surgery for sleep apnoea up to January 1, 2009. Reference lists of all identified articles were searched for additional studies.

Overview of the evidence

Laser midline glossectomy. It has been hypothesised that removal of a midline portion of the tongue base and excess tissue such as redundant lingual tonsils would enlarge the hypopharyngeal airway [283]. The intervention carries an inherent risk for significant postoperative pharyngolaryngeal oedema and requires a temporary tracheotomy. FUJITA *et al*. [283] and MICKELSON and ROSENTHAL [284] included patients with severe persistent OSAS after UPPP and selection was based upon clinical examination and fibre-optic laryngoscopy with Mueller manoeuvre. Side-effects were considered minor and no persistent voice changes or dysphagia were reported. ANDSBERG and JESSEN [285] found a 50% reduction in apnoea index in 56% of the subjects after 8-yr follow-up. Of note, 23% complained of postoperative complications 98 months postoperatively (table e27).

Other approaches for tongue base reduction (plasty – resection) are summarised below and in table e28.

Tongue base reduction with hyoepiglottoplasty. CHABOLLE *et al.* [286] and SORRENTI *et al.* [287] performed a subtotal tongue base reduction through a cervical approach preceeded by lingual neurovascular bundle identification and derouting, epiglottal verticalisation, mouth floor horizontalisation, and hyoid bone repositioning, termed tongue base reduction with hyoepiglottoplasty, mostly combined with UPPP. A 100% success rate was achieved at 6-month follow-up in severe OSA patients with severe macroglossia and hyolingual abnormalities in the absence of craniofacial deficiencies. Three out of 10 patients had swallowing abnormalities 6–19 months postoperatively, but all were able to resume a normal diet. The most relevant complication was a submental abscess which was attributed to the use of non-absorbable sutures.

Lingualplasty. WOODSON and FUJITA [288] modified the technique of laser midline glossectomy (LMG) to include lingualplasty in which tongue excision is extended more posterior and lateral. Candidates for lingualplasty were those with CPAP intolerance and upper airway collapse caused by large lingual tonsils or tongue base, rather than lateral wall collapse. Lingualplasty requires preoperative tracheotomy and, as described in the original paper, removal of additional lingual tonsils or redundant tissue of the epiglottis or arytenoids was included. In their series of 22 patients, eight had combined lingualplasty and UPPP, the remaining had lingualplasty alone. There was a significant perioperative complication rate (27%), but no long-term complications, and the authors concluded that lingualplasty was more effective than LMG alone.

Lingual tonsillectomy. During LMG, the central part of the tongue is resected. Theoretically, this technique might have limited efficacy in selected patients with swollen lingual tonsils. LI *et al.* [289] compared the efficacy of combined treatment by extended uvulopalatal flap (EUPF) with either midline glossectomy or lingual tonsillectomy (LT) in a series of 12 consecutive non-obese OSA patients. They found that EUPF+LMG was highly effective in treating OSA in selected patients with type 2 obstruction (83% success), whereas EUPF+LT was found to have no effect on OSA.

Palatopharyngoglossoplasty. DJUPESLAND *et al.* [290] developed a modified surgical technique based upon a combination of UPPP and removal of redundant tissue at the lateral aspects of the tongue base. AHI decreased from 54 h^{-1} (range 10–98 h^{-1}) to 31 h^{-1} (range 0–61 h^{-1}) in 20 OSA patients 8.7 months after palatopharyngoglossoplasty [291]. The AHI improved >50% in 50% of the patients (n=10).

Uvulopalatopharyngoglossoplasty. This technique combines UPPP with a bilateral resection of redundant soft tissue at the lateral aspects of the tongue base [292]. Screening oximetry and ambulatory polysomnography were repeated. The response rate in 19 OSA patients 6–12 months after surgery was 67% and no major complications were encountered.

Glossopexia. The glossopexia consists of a combination of a tongue resection plasty and an anterior suspension of the tongue using strips of fascia lata [293]. All of eight patients with persistent OSA after UPPP were tracheotomised and had subjective improvement, but reliable improvement documented by polysomnography after 12–24 months was obtained in only two patients. In addition, postoperative cephalometry did not reveal a change in the vertical or horizontal position of the hyoid bone or in the dimensions of the posterior airway space, but relevant side-effects, such as decreased sensitivity of the chin and tongue, immobility of the tongue, decreased sense of taste and slight difficulties of articulation, persistent oedema of the tongue, rejection of the fascia lata and serious infection of the tracheotomy spreading to the mediastium were reported. Therefore, this technique has no role in the surgical management of OSA.

The role of these modified techniques of glossopexia, palatopharyngoglossoplasty and uvulopalatopharyngoglossoplasty, and LT in the surgical treatment of OSA is unclear as no later reports on these techniques have been published so far.

Tongue base suspension. The Repose® system (InfluENT Inc®) is a minimally invasive surgical kit that uses a titanium screw and permanent suture to anchor/stabilise the tongue base to the inner mandibular cortex. Tightening of the suture provides support to the anterior hypopharyngeal airway and tongue base, thus preventing collapse at the retrolingual level. According to DEROWE *et al*. [294], the aim is not to permanently move the tongue forward, but rather to stabilise the tongue base level by adding rigidity of the scar tissue encased suture anchored anteriorly. The treatment is reversible as the

suture can be removed. Patient selection was based upon fibre-optic examination and Mueller manoeuvre. The incidence of postoperative complications ranged from 15 to 33%, and included infections with floor of mouth sialadenitis, dysphagia, odynophagia, development of floor of mouth cyst or haematoma. THOMAS *et al.* [295] performed a randomised controlled trial comparing tongue advancement (mandibular osteotomy) with tongue suspension (Repose®). All patients underwent a simultaneous UPPP. There was no significant difference between both procedures in terms of response, postoperative pain, speech impairment or swallowing difficulties (table e29).

As the aim of the tongue suspension is to stabilise and support the tongue base, rather than to advance it, it not surprising that MILLER *et al.* [296] and TERRIS *et al.* [297] failed to find relevant changes in the posterior airway space. A significant improvement in airway collapse at the palatal and tongue base level was demonstrated when Repose® was combined with UPPP [295, 297].

Patients with moderate to severe OSA have upper airway collapse at multiple levels of the upper airway involving the retropalatal and retroglossal region and varying contributions from the lateral pharyngeal walls. Therefore, some authors proposed a combined retropalatal/retroglossal approach by simultaneously performing a UPPP and a tongue suspension procedure (Repose®) [296, 298–300]. It is hard to delineate the relative contribution of each single procedure to the final outcome [299, 301]. SORRENTI *et al.* [298] suggested a limited role for tongue suspension in the surgical treatment of OSA as the results were inferior to those reported with genioglossus advancement and hyoid suspension in the treatment of retrolingual collapse. A second issue raised by these authors is the high cost of the Repose® kit and the probable poor stability of the suture over time [298].

Summary

Most studies on soft tissue tongue base surgery, excluding radiofrequency, were performed in subjects with severe OSA and concomitant obesity. In some reports, patients had already undergone upper airway surgery and were considered UPPP failures; others included patients who refused CPAP treatment. This selection bias is likely to affect the subjective appreciation of the results by the patients, which is mostly in contrast with the objective polysomnographic findings. The reviewed studies reported on significant improvements in snoring and daytime sleepiness. An improvement in the Functional Outcomes of Sleep Questionnaire score was reported in the study by WOODSON *et al.* [302] on tongue suspension.

Those studies that are limited to the use of one particular surgical technique have limitations in terms of number of patients included, design and time of follow-up. For those with a multilevel approach it is difficult to definitively define the efficacy of each procedure in terms of its contribution to a potential surgical cure.

Conclusions and recommendations

From the present data, it can be concluded that tongue base soft tissue procedures, such as partial resection of the tongue base and tongue suspension (Repose®), cannot be recommended as a single treatment option for obese patients with moderate to severe OSA. The additional value of these techniques lies in the limited morbidity, the lack of cosmetic changes and the possibility to combine them with other procedures in a multilevel approach. There are at present no data to support their role in patients with mild disease (C).

Genioglossus advancement

Rationale

Genioglossus contraction enlarges both the velo- and the oropharynx and lowers the critical pressure without affecting the stiffness [116]. Nevertheless the genioglossus is only one of many muscles that act in concert to prevent flow limitation in the pharynx. Genioglossus advancement aims to enlarge the hypopharyngeal air space, bringing forward the base of tongue.

Search criteria

Databases individually searched: PubMed and Medline. Keyword combinations: genioglossus advancement, genioplasty and sleep, genioplasty and obstructive sleep apnoea, hypopharyngeal surgery and sleep, hypopharyngeal surgery and obstructive sleep apnoea, tongue surgery and obstructive sleep apnoea.

Overview of the evidence

Genioglossus advancement consists in an advancement of the genial tubercle and genioglossus muscle. A sliding genioplasty can be performed with a complete manipulation of the chin position that is moved forward with a portion of the inferior mandibular border and attached muscles. The second technique consists of a geniotomy with a rectangular bicortical osteotomy centered over the genial tubercle. Recently, a minimally invasive procedure has been developed (the Repose® system) which tries to reproduce the same effect with a tongue base suture suspension.

No study has investigated the effect of isolated genioglossus advancement for OSA. In MLS, when genioglossus advancement is the only hypopharyngeal procedure associated with velar surgery, genioglossus advancement demonstrated an improvement of postoperative AHI (table e30) with a success rate of 60% [303, 304] in five series including 117 patients. The earliest studies realised between 1999 and 2004 in patients with severe OSAS demonstrated the best efficacy of genioglossus advancement on AHI.

Conclusions and recommendations

Genioglossus advancement seems to be efficiently used in MLS for treatment of hypopharyngeal airway impairment. Current research aims to optimise the identification of proper candidates for this surgery. Further studies are needed to identify an optimal strategy for targeted treatment of severe OSAS patients. Genioglossus advancement cannot be recommended as a single procedure for the surgical treatment of OSA (C).

Maxillomandibular advancement

Rationale

This surgery specifically addresses hypopharyngeal or tongue base obstruction in order to enlarge the retrolingual and retropalatal airway. An advancement of 10–15 mm of the maxilla and the mandible is necessary to be efficient when

there is no maxillomandibular abnormality. In case of maxillomandibular abnormality the advancement must be more pronounced. The classical procedure consists in bilateral sagittal split ramus osteotomies with rigid internal fixation and Le Fort I osteotomy with rigid internal fixation [305–316]. The Stanford group [305] performs pharyngoplasty with or without hyoid myotomy suspension (phase I). MMA is performed in a second step (phase II) in case of failure of phase I. The rationale for using phase I is to avoid more radical and high-risk surgery when unnecessary, particularly in moderate OSA. Conversely, other groups proceed directly to MMA. Sometimes, mandibular elongation using osseous distraction followed by a Le Fort I advancement osteotomy is an efficient solution for difficult situations in order to obtain an easy advancement of 12–14 mm in 3 weeks [317]. This procedure needs close communication with the orthodontist. Successful surgery depends on proper patient selection, proper procedure selection and experience of the surgeon [197, 318].

Search criteria

Databases individually searched: PubMed and Medline. Keyword combinations: maxillomandibular advancement and sleep, maxillomandibular advancement and obstructive sleep apnoea, orthognathic surgery and sleep.

Overview of the evidence

The level of evidence is based on 12 series published between 1989 and 2006 (table e31) [305–316]. The baseline AHI varied between >20 and >30, success was defined by a post-surgical AHI between <10 and <20. The mean follow-up was performed between 6 weeks and 52 months. The success rate varied between 67% and 100% [305–307]. The discrepancy can be explained by different polysomnographic techniques [305–307]. A quarter of the remaining respiratory abnormalities were central events [306]. All series, including 298 patients, demonstrated an improvement of postoperative sleep macrostructure (table e31) [306–308]. Changes in excessive daytime sleepiness and MSLT after MMA were rarely documented.

PRINSELL [307] demonstrated a lowering of systolic and diastolic blood pressure after MMA, associated with weight loss. RILEY *et al*. [305] reported that >50% of the patients treated by MMA no longer require antihypertensive medicines. However, there are no sufficient data on the efficacy of MMA on cardiovascular parameters.

In all series, patients usually undergo MMA surgery only after a complete clinical and cephalometric examination to evaluate the three major anatomic regions of potential upper airway obstruction: nose, palate (oropharynx) and base of tongue (hypopharynx) [305–316]. In some cases, pre-surgical evaluation is performed by a multidisciplinary team including a maxillofacial surgeon, a neurophysiologist and a pulmonologist [308, 314]. Selected patients are often male patients with an AHI >30, aged <60 yrs, with a BMI <30 $kg \cdot m^{-2}$, and without relevant cardiovascular and pulmonary comorbidities (table e31).

All patients have to undergo overnight polysomnography according to widely accepted methods [319]. Alternatives to in-laboratory full polysomnography, especially in-home monitoring without EEG analysis, are not used due to insufficient detection of hypopnoeas or central events.

BETTEGA *et al*. [308] identified hypertrophic tonsils in 40% and hypopharyngeal obstruction at the tongue base in 80% of the surgical candidates. This is generally explained by small oral cavities with a normal tongue size. All patients performed cephalometry before undergoing MMA in the 12 series (table e32). However, the results of the cephalometric analysis are not always reported [308]. OSA patients may present with pharyngeal narrowing at basal lingual level, sometimes in combination with retrognathia (SNB <77°) or dolichofacial appearance [320]. Patients with a BMI <30 $kg \cdot m^{-2}$ have shorter anterior floor of cranial base, a smaller mandible and retroposition of the mandible compared with severely obese patients [321]. These skeletal differences are associated with narrower velopharyngeal and linguopharyngeal spaces, predicting better surgical success. There is no sufficient evidence whether successful treatment by MADs is predictive for successful MMA surgery.

Several complications have been reported, including cardiac arrest without sequellae and dysrythmia [310], local infection, perforation of the palate, a maxillary pseudarthrosis, malocclusion, and dysgnathia due to mandibular deficiencies [305–309, 311–314]. All patients developed transient anaesthesia of the cheek and chin area. Residual neurosensitive deficit (hypoesthesia of the lower lip) was the most common complication, which did not affect quality of life in these patients. Patients who have a prior pharyngoplasty have temporary postoperative velar insufficiency (phonetic deficit and liquid regurgitation) improved by cautious speech therapy. Most of the patients accept changes in facial appearance, which can be predicted by preoperative computer imaging. The average postoperative off-work time is between 2 weeks [307] and 10 weeks [308, 309]. Full in-laboratory polysomnography should be performed between 2 and 6 months after surgery.

MMA has been shown to be effective over the long term [311, 322–324]. While WAITE *et al.* [310] confirmed long-term skeletal stability (12 months) based on cephalometric analysis, PEPIN [325] and others [92, 197, 311–329] demonstrated a deterioration of the results with a rate of success of 60% on a long-term basis. Ageing and weight gain appear to significantly impair long-term results.

Conclusions and recommendations

MMA seems to be as efficient as CPAP in patients with OSA who refuse conservative treatment [330], particularly in a young population without excessive BMI or other comorbidities. Therefore, MMA is recommended in this selected group of patients. However, essential benefit should be weighed against the risk of complications. The one-time cost of early MMA is probably far less expensive than multiple less successful surgeries or lifetime use of CPAP. Current research aims to optimise the identification of proper candidates for this surgery (B).

Distraction osteogenesis

Rationale

DOG is a surgical procedure applied in order to provide a lengthening of the bone associated with a stretching of the soft surrounding tissues [331]. Bone is osteotomised, and after a latency period, the device is activated progressively (~1 mm per day) to induce bone healing and new bone

formation. DOG can provide wide expansion and is thus very useful for the correction of severe maxillofacial anomalies in young children [332]. The procedure is used in different aetiologies of OSA especially in paediatric craniofacial malformations.

Search criteria

Databases individually searched: PubMed and Medline. Keywords combinations: distraction osteogenesis and sleep, distraction osteogenesis and obstructive sleep apnoea, surgery and sleep, surgery and obstructive sleep apnoea.

Overview of the evidence

Most of the articles are focused on mandibular DOG in paediatric micrognathia (table e33) (42 publications) [197, 317, 331–370]. They include several case reports and some retrospective and prospective series. The level of evidence remains low in such series (2b–4) with short series, lack of complete objective assessment, undefined criteria for patient selection and short-term follow-up. Only eight articles, from 1998 to 2009, were selected as they met the following criteria: mandibular lengthening in micrognathia, the confirmation of the diagnosis of sleep apnoea syndrome and objective evaluation of the benefit of the treatment. Other publications provide, however, interesting evidences of DOG benefit on children's respiratory status in order to avoid tracheostomy or to remove it.

DOG is used in craniofacial disorders associated with severe airway impairment as a result of micrognathia or midface hypoplasia. Retrusion of the inferior third of the face with micrognathia (Pierre Robin sequence, bilateral hemifacial microsomia (due to growth disturbance of the mandibula), Treacher Collins syndrome, Nager syndrome, temporomandibular joint (TMJ) ankylosis) might require mandibular advancement [336, 337, 347, 348, 355, 356, 364, 368]. Airway impairment is localised in the retroglossal area. Retrusion of the upper third of the facial skeleton (midface hypoplasia and retrusion) may need maxillo-zygomatic advancement (Le Fort III or monobloc advancement). In this case, airway impairment is localised on the velopharyngeal area. Syndromic faciocraniosynostosis (such as Crouzon, Apert or Pfeiffer syndrome) induces midfacial retrusion with velopharyngeal tissue obstruction [335]. The benefit on morphological improvement is associated with an enlargement of the posterior airway space. In significant numbers of these patients, tracheostomy is indicated when obstruction remains refractory to conservative management (particularly in neonates). But tracheostomy also provides significant morbidity and mortality (0–3%) in young patients. Thus, in selected children, DOG is proposed to prevent tracheostomy or to achieve decannulation.

Indication of DOG remains controversial [354], particularly in non-syndromic micrognathia and Pierre Robin sequence. Non-surgical handling in mild obstruction permits improvement in an important majority of cases [354], because of sufficient mandibular growth potential [351] and increase of tongue neuromuscular tone [364] within the first year of life. The review of the literature underlines the efficacy of DOG in OSA and breathing difficulties. However, there is no consensus on precise indications and timing of the procedure. Because of the potential complications of DOG in the neonate period, some authors avoid DOG in the first months [354, 356], and apply delayed distraction to decanulate tracheostomised children after 18–24 months [356]. In contrast, other authors use DOG in the first months of life in severe cases to avoid tracheostomy [341, 352, 363, 370]. GENECOV *et al.* [367] studied 81 patients with mandibular micrognathia (mostly Pierre Robin sequence) and airway obstruction syndrome over 11 yrs (mean age 1.2 yrs). Tracheostomy was prevented in 96%, and decannulation achieved in 92%. AHI decreased from 35–50 to 5–15 in 65 patients (two remained >35). The airway benefit of the DOG was evaluated by cephalometric analysis and three-dimensional computed tomography in several studies [341, 355, 368]. Cross-sectional space and skeletal lengthening increased significantly.

Faciocraniosynostosis (Crouzon, Apert or Pfeiffer syndrome) induce midfacial retrusion leading to variable sleep-related breathing disorders due to velopharyngeal obstruction in young patients and adults [339]. Midface advancement can relieve the obstruction and thus decrease sleep apnoea events and also lead to decannulation of tracheostomised patients. DOG can provide large magnitude advancement of the facial skeleton by progressive stretching of all the surrounding tissues compared to one-stage procedures. Two types of osteotomies can be performed: Le Fort III osteotomy (advancement of facial skeleton without cranial shape correction) or monobloc osteotomy (frontofacial advancement) within the first years of life. However, there are only few publications analysing the benefits on upper airway obstruction (table e34). There is less evidence on the efficacy of midface advancement on airway obstruction as compared to mandibular lengthening (C).

Numerous reports have demonstrated that DOG is also effective in adults [317], but it remains currently an optional treatment in selected patients (*e.g.* in TMJ ankylosis sequelae [347] and in facial cleft lip/palate sequellae). The procedure is limited by the risk of malocclusion due to incorrect distraction vectors parallelism, the length of the procedure, and discomfort of the device. Actually maxillomandibular advancement (MMA) can be provided in a single stage, without need of bone graft with a good stability and efficiency.

Conclusions and recommendations

Although there are only few publications to correctly evaluate its benefits, DOG is usefully applied and can be recommended in congenital micrognathia or midface hypoplasia. These indications may increase in the future, with less invasive procedures and adapted devices. Controversies, however, exist on early use to avoid tracheostomy in micrognathia. DOG may be indicated in selected adults or adolescents as MMA is surgically difficult to achieve. The efficiency of distraction advancement in OSAS treatment can be scored B in mandibular lengthening and C in midface advancement.

Multilevel surgery

Rationale

Most OSA patients have multilevel disease, including nasal obstruction, retropalatal and hypopharyngeal obstruction. The goal of MLS is to improve nasal airway blockage and both to enlarge the retropalatal airway and the retrolingual airway. At

least surgery aims to correct anatomical abnormalities in the upper airway contributing to its collapse in the hypopharyngeal space during sleep. Nasal reconstructive surgeries include septal and/or bony intranasal reconstruction, alar valve or alar rim reconstruction and turbinectomy. UPPP, often combined with adenotonsillectomy, aims to trim and reorient the posterior and anterior lateral pharyngeal pillars by excising the uvula and the posterior portion of the palate. Mandibular osteotomy with genioglossus advancement, hyoid myotomy suspension, laser midline glossectomy with lingualplasty, and radiofrequency tongue base reduction (RTBR) aim to enlarge the retrolingual space.

Search criteria

Databases individually searched: PubMed and Medline. Keyword combinations: multilevel surgery and obstructive sleep apnoea, multilevel surgery and sleep, surgery and sleep.

Overview of the evidence

33 series including 1,431 patients published between 1992 and 2009 (table e34) [243, 273–275, 277, 281, 284–286, 288, 289, 291, 295, 299, 308, 313, 316, 371–387].

SUNDARAM *et al.* [388] recently reviewed the literature on surgery for OSA. No randomised trials could be identified. The authors emphasised methodological difficulties: variety of outcome measures, lack of long-term follow-up data and lack of consensus on the definition of ''surgical success''. The result of MLS efficiency was not reproducible in different studies. However, LIN *et al.* [389] focused on outcomes of OSA patients treated with MLS in a meta-analysis of 49 studies including 1,978 patients with a mean follow-up time of 7.3 months. The recalculated success rate was 66.4% with an overall complication rate of 14.6%.

Studies evaluated here differed in terms of the preoperative AHI between >5 and >30, the definition of success (post-surgical AHI <10 to <20) and follow-up (6 weeks to 39 months) (table e35) [372, 373, 382, 384]. Success rate varied between 22.7% to 78% (mean 60.9%) [299, 308]. Only RILEY *et al*. [375] and CHABOLLE *et al*. [286] reported a significant improvement in slow wave and REM sleep after MLS (table e36). The microarousal index or ESS scores were rarely reported by the authors [281]. There is no evidence of improvement in cardiovascular parameters after MLS.

As CPAP is the standard treatment for adult OSA, all attempts at improving effectiveness and adherence have to be undertaken prior to MLS. However, MLS may be considered in younger OSA patients in whom CPAP is unsuccessful or has been rejected for a long period.

In most of the series, patients usually undergo MLS surgery only after nasofibroscopy and a complete clinical and cephalometric examination to evaluate the three major anatomic regions of potential upper airway obstruction: nose, palate (oropharynx) and base of tongue (hypopharynx) [243, 273–275, 277, 281, 284–286, 288, 289, 291, 295, 299, 308, 313, 316, 371–387]. The Friedman staging system is necessary to score the palate position and the tonsil size [275]. In some cases, presurgical evaluation is performed by a multidisciplinary team, including a maxillofacial surgeon, a neurophysiologist and a pulmonologist [308]. Severity of OSA disease was not a criterion for exclusion. Selected patients are often male, have an AHI >20, are aged <70 yrs and have a BMI <40 $kg \cdot m^{-2}$ (table e37). Patients with a history of respiratory or cardiac failure during the past year are excluded from performing MLS [299]. For BETTEGA *et al.* [308], all OSA patients undergoing MLS have to be nonsmokers or have stopped smoking at least 1 month prior to surgery. At least patients with obvious micrognathia, bony anatomic abnormalities, without obvious palatal obstruction and patients who had previously failed surgical treatment with UPPP are thought to respond insufficiently to MLS.

All patients have to undergo overnight polysomnography prior to MLS surgery [319], which allows for detection of REM-related OSAS. MLS seems to be more effective in REM OSA patients. KAO *et al.* [385] reported a 100% success rate in patients with AHI <30 treated by MLS. It dropped to 50% in patients with AHI >50. LIU *et al.* [386] observed a higher success rate for OSA patients with an apnoea index <25. EUN *et al.* [373] observed a significant improvement of post-operative AHI after MLS (UPPP and RTBR) in 28 REM OSA patients (8.1 ± 6 *versus* 14.5 ± 7; $p<0.001$), while there was no change in 62 non-REM OSA patients (21 ± 21 *versus* 23.1 ± 10; $p=0.374$).

The success rate of MLS on AHI is about 53.6% at 6 months according to the analysis of the results of the 1,431 patients who underwent MLS. VICENTE *et al.* [299] studied the long-term efficacy of UPPP and hyoid myotomy suspension for severe OSA and reported a 78% success rate at 3 yrs after MLS surgery. NERUNTARAT [243] observed the same results at 39 months for 49 OSA patients treated by UPPP and genioglossus advancement. ANDSBERG and JESSEN [285] observed the same results at 8 yrs.

BETTEGA *et al.* [308] identified hypertrophic tonsils in 40% and hypopharyngeal obstruction at the base of tongue in 80% of the surgical candidates. This is generally explained by small oral cavities with a normal tongue size. Cephalometry was performed in most of the patients before undergoing MLS in the 32 series (table e38). Patients with a BMI <30 $kg \cdot m^{-2}$ have shorter anterior floor of cranial base, a smaller mandible and retroposition of the mandible compared with severely obese patients [321]. These skeletal differences are associated with narrower velopharyngeal and linguopharyngeal spaces and predict better efficacy of MLS. Some authors performed the Muller manoeuvre during cephalometry to predict hypopharyngeal collapse [299, 389]. However, cephalometric radiographs did not differ between responders and nonresponders to MLS, hence, they are unable to predict surgical success.

A variety of side-effects can occur after MLS surgery, including velopharyngeal insufficiency, dysphagia, persistent dryness and nasopharyngeal stenosis (UPPP or uvuloflap), mandibular fracture, lesions of the roots of the teeth, infection, permanent anaesthesia of the lip and seroma (genioglossus advancement), odynophagia, postoperative oedema or excessive bleeding, often associated with incised epiglottis, requiring a protective tracheotomy (partial glossectomy), and tongue restriction (lingualplasty) [288]. Many patients have had subjective alterations in taste immediately postoperatively, which resolved spontaneously. Rare complications included angina pectoris

[381], dysphagia and cricopharyngeus, haematoma of the mouth floor [376] and long-lasting hypoglossal nerve paresis [374].

Conclusions and recommendations

MLS cannot be recommended as a substitute for CPAP but as a salvage procedure for OSA patients in whom CPAP and other conservative therapies have failed. Surgical success of MLS for OSA is often unpredictable and less effective than CPAP. MLS seems to be more effective in mild to moderate REM-associated OSA, in patients aged <60 yrs, and with BMI <30 $kg \cdot m^{-2}$, pharyngeal narrowing in the basal lingual area, retrognathia or dolichofacial appearance and without significant comorbidity. Success depends on appropriate patient selection, the type of surgical procedure performed and the experience of the surgeon. Most studies are retrospective and observational case series, and therefore do not provide high-level evidence (C). Further research should include larger, higher level studies that compare surgical procedures and identify factors associated with outcomes.

STATEMENT OF INTEREST

Statements of interest for S. Andreas, I. Smith, B.A. Stuck, J.T. Maurer and T. Verse can be found at www.erj.ersjournals.com/site/misc/statements.xhtml

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