

# A randomized trial of temperature-controlled radiofrequency, continuous positive airway pressure, and placebo for obstructive sleep apnea syndrome

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**OBJECTIVE:** The study goal was to determine the effectiveness of (1) multilevel temperature-controlled radiofrequency tissue ablation (TCRFTA) or (2) continuous positive airway pressure (CPAP) for the treatment of mild to moderate obstructive sleep apnea syndrome (OSAS).

**STUDY DESIGN AND METHODS:** We conducted a randomized, placebo-controlled, 2-site trial, comparing TCRFTA (n = 30) and CPAP (n = 30) with sham-placebo (n = 30) using intention-to-treat analysis.

**RESULTS:** Compared with pretreatment baseline, TCRFTA improved reaction time, OSAS-specific quality of life (QOL), and subjective sleepiness (all  $P < 0.05$ ). Compared with sham-placebo, TCRFTA improved QOL, airway volume, apnea index, and respiratory arousal index (all  $P < 0.05$ ). TCRFTA side effects and complications were mild, temporary, and similar to sham-placebo. CPAP improved QOL and sleepiness compared with baseline and QOL when compared with sham-placebo (all  $P < 0.05$ ).

Significant differences were not seen between TCRFTA and CPAP outcomes.

**CONCLUSION:** TCRFTA and CPAP each improve QOL for mild-moderate OSAS patients. TCRFTA improvements may result from changes in airway volume, apnea index, and respiratory arousal index. (Otolaryngol Head Neck Surg 2003;128:848-61.)

**S**leep disordered breathing defined by an Apnea-Hypopnea Index (AHI) of 5 or more events per hour is estimated to affect 9% to 24% of middle-aged adults.<sup>1</sup> Obstructive sleep apnea syndrome (OSAS) includes both sleep disordered breathing and excessive daytime somnolence<sup>2</sup> and affects 2% to 4% of adults.<sup>1</sup> It is associated with cardiovascular disease, quality of life and performance deficits, and motor vehicle accidents.<sup>3-6</sup> Within the OSAS population, a large proportion of the patients manifest mild or moderate disease (AHI < 30 events per hour).<sup>1</sup>

First-line treatment for many OSAS patients is nasal continuous positive airway pressure (CPAP). When used adequately, CPAP improves sleepiness, performance, quality of life, and cardiovascular risk.<sup>4,7,8</sup> However, the effectiveness of CPAP in patients with milder OSAS remains unclear.<sup>9-11</sup>

Temperature-controlled radiofrequency tissue ablation (TCRFTA) applied to the tongue base and palate have been described to treat OSAS. Several case series and one large multicenter clinical trial have demonstrated improvement in polysomnographic parameters and in clinically important outcomes, with low morbidity and complication rates.<sup>12-14</sup> Studies have also demonstrated TCRFTA successfully reduces soft tissue volume of the tongue.<sup>12</sup> However, none of these studies included control subjects. Thus, this study was undertaken to evaluate the effects of multilevel (tongue and palate) TCRFTA on clinically important outcomes in patients with mild to moderate

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OSAS. Sham-placebo and nasal CPAP arms were included for controlled comparison.

## METHODS

### Study Design and Objectives

A 2-institution randomized placebo-controlled trial was performed to test the hypothesis that multilevel (tongue base and palate) TCRFTA is more effective than sham-placebo for improvement of clinically important outcomes in patients with mild to moderate OSAS. This trial was also performed to test the hypothesis that nasal CPAP is more effective than sham-placebo.

### Participants

Eligibility criteria included (1) age 18 to 65 years, (2) self-reports of daytime somnolence, (3) body mass index (BMI)  $\leq 34$  kg/m<sup>2</sup>, (4) no prior surgical or CPAP treatment for OSAS, and (5) mild to moderate OSAS defined by an AHI of 10 to 30 on screening sleep study. Exclusion criteria included (1) another significant sleep disorder (eg, insomnia, periodic limb movement), (2) tonsillar hypertrophy, (3) nasal or supraglottic obstruction on examination, (4) ASA class IV/V, (5) claustrophobia, (6) Latex allergy, (7) pregnancy or plans to become pregnant, (8) major depression or non-stabilized psychiatric disorder, (9) drug or alcohol abuse, (10) history of an accident secondary to sleepiness, or (11) participation in another study. Eligible subjects passing all exclusion criteria then had a baseline full polysomnography (PSG) and were included if AHI was 5 to 40 (Fig 1).

Subjects were recruited directly from the academic otolaryngology practices and from poster and newspaper advertisements. This study was designed, performed, and reported according to the Revised CONSORT Statement<sup>15</sup> and with approval from local institutional review boards. All patients gave informed consent. Subject flow is summarized in Figure 1.

### Polysomnography/Sleep Studies

Screening sleep studies included home Autoset PDS (ResMed Inc, Poway, CA) or full in-laboratory PSG (if performed within 1 year of enrollment). All subjects underwent a subsequent baseline full PSG (unless full in-laboratory PSG performed within 6 months of enrollment), which

included an electroencephalogram ( $\geq 2$  channels), electrooculogram, chin and leg muscle electromyograms, electrocardiogram, measures of oronasal airflow, thoracic and abdominal efforts, body position, and pulse oximetry. *Apnea* was defined as cessation of inspiratory airflow of at least 10 seconds. *Hypopnea* was defined as a reduction of inspiratory airflow of at least 10 seconds, with an associated 4% decrease in oxyhemoglobin saturation or an electroencephalographic arousal. Respiratory arousals were quantified on PSGs at University of Cincinnati and were defined as arousals associated with an apnea or hypopnea. AHI, apnea index (AI), total arousal index, and respiratory arousal index were calculated as the number of events, respectively, per hour of sleep. For CPAP subjects, treatment AHI and AI were downloaded from Autoset T (ResMed Inc).

### Interventions

Nasal CPAP therapy was titrated unattended over 3 or more nights with the AutoSet T device.<sup>16</sup> Final constant CPAP pressure was set as the 95 percentile pressure and was continued for 8 weeks. Subjects were seen at 1, 2, and 4 weeks to troubleshoot and optimize compliance. Side effects were identified by questionnaire at each visit and were treated appropriately (eg, nasal medication, heated humidifier, etc). Side effects recorded on the final (8-week) questionnaire is reported (see Table 3). Objective pressure-on time was acquired from usage software within the CPAP device, and self-reported use was recorded at each visit.

Active temperature-controlled radiofrequency tissue ablation (TCRFTA) was performed with the Somnoplasty radiofrequency generator (Gyrus-ENT, Memphis, TN). Five tongue and 2 palate sessions were planned for each active subject. Subjects were treated perioperatively with oral antibiotics, prednisone, antiseptic oral rinse, analgesic (as needed), and nonsteroidal anti-inflammatory medication (as needed). A local anesthetic mixture (2.5 mL of 2% lidocaine with 1:100,000 epinephrine, 2.0 mL of normal saline, and 0.5 mL of 8.4% sodium bicarbonate) was injected into each tongue treatment site, and 1% lidocaine with 1:100,000 epinephrine (1 to 2 mL) was injected into each palate site. Radiofrequency energy was delivered to create nonoverlapping lesions in 2 or

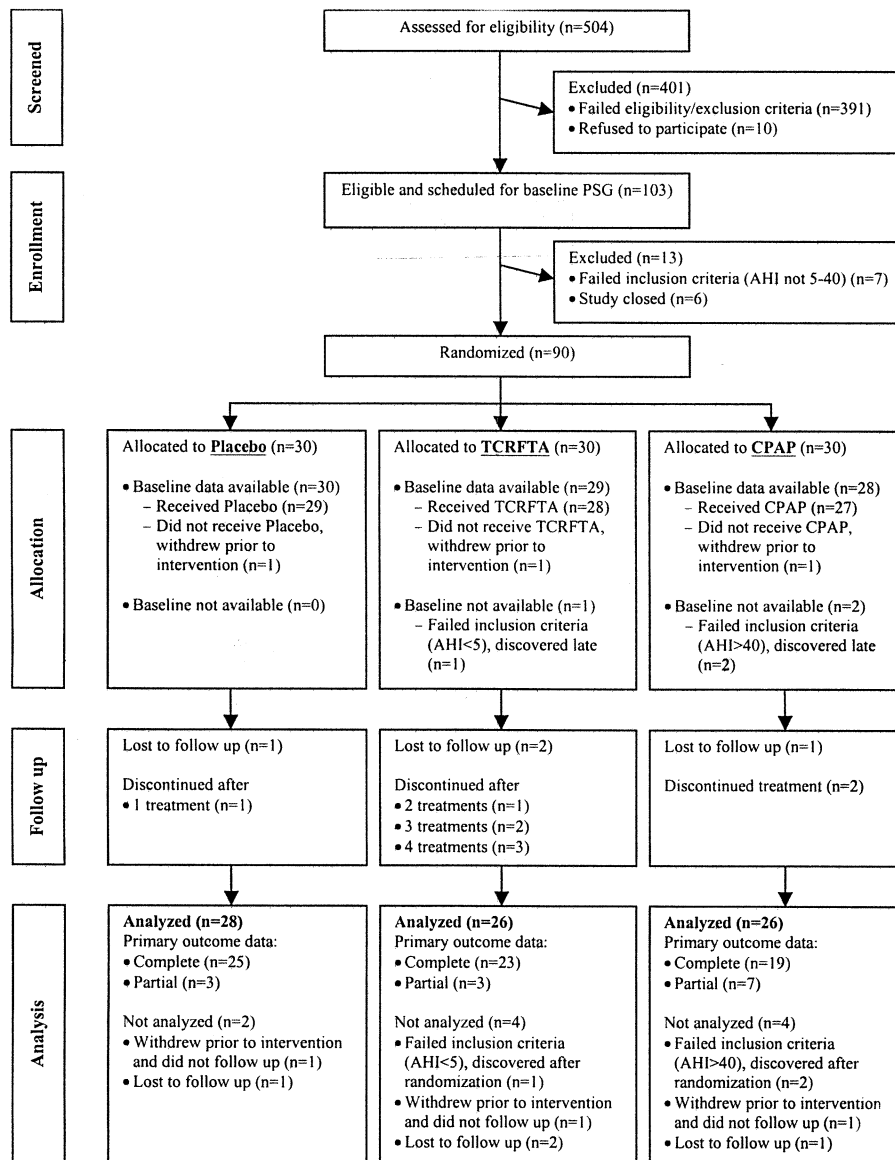


Fig 1. Flow diagram of subject progress through trial. Flow diagram of subjects' progress through the screening, enrollment, allocation, follow-up, and analysis.

3 tongue sites (1000 or 750 J, respectively, per site; target temperature 85° C; maximum power 10 W) per tongue treatment session, which occurred at 4-week intervals. Radiofrequency energy was delivered to create 1 midline and 2 lateral lesions (nonoverlapping) to the soft palate (650 J and 325 J, respectively) in each palate treatment session. Investigators were instructed to adjust lesion numbers per treatment session based on clinical judgment and patient tolerance. When tongue and palate sessions were combined, the subject was offered overnight hospital admission. Investiga-

tors were instructed to perform sequential and not simultaneous tongue and palate treatments if there were concerns about airway edema or patient tolerance. Attempts were made to apply similar levels of energy in all patients irrespective of the timing of sessions.

Sham-placebo TCRFTA was performed as described above for tongue TCRFTA except that a blocking control box on the radiofrequency generator was set to "off" to prevent delivery of energy. Three tongue sessions were planned for each sham-placebo subject at 4-week intervals,

with 3 tongue lesions created per session. Subjects were anesthetized and medicated as described for active tongue TCRFTA. The sham treatment sessions were limited to 3 to balance the risk of hematoma, edema, or abscess formation at the site of anesthetic injection or TCRFTA probe insertion versus the goal of providing a realistic placebo.

## Outcomes

The primary outcome measures were chosen a priori to represent meaningful measurements of patient function and quality of life. The primary outcome measures are changes in slowest reaction time (SRT) and OSAS-specific quality of life. Slowest reaction time was measured as the mean of the slowest 10% of reaction times on the Psychomotor Vigilance Task (PVT-192; Ambulatory Monitoring Inc, Ardsley, NY) with a total test time of 10 minutes and stimulus interval of 2 to 10 seconds. SRT was analyzed as the reciprocal ( $1/\text{SRT}$ ) to minimize the contribution of very long lapses.<sup>17</sup> OSAS-specific quality of life was measured with 2 validated questionnaires: (1) Functional Outcomes of Sleep Questionnaire (FOSQ)<sup>18</sup> and (2) Symptoms of Nocturnal Obstruction and Related Events (SNORE25), formerly the OSA Patient Oriented Severity Index.<sup>19</sup>

The secondary outcome measures include changes in (1) median reaction time (RT) and fastest reaction time (mean of fastest 10% reaction times, FRT) measurements, using the Psychomotor Vigilance Task as described above<sup>17</sup>; (2) daytime sleepiness using the Epworth Sleepiness Scale (ESS); (3) general health status measured with the SF36 (version 1) Mental Component Summary (MCS) and Physical Component Summary (PCS) scales; (4) total upper airway volume (incisors to epiglottis) using acoustic pharyngometry (SensorMedics, Yorba Linda, CA); and (5) in sham-placebo and TCRFTA subjects, PSG parameters (AHI, AI, lowest oxyhemoglobin saturation [LSAT], total arousal index, and respiratory arousal index). Pain and swallowing side effects were assessed 1 and 3 weeks after each TCRFTA and sham-placebo treatment session, using 10-cm visual analog scales (pain: 0 = "no pain" and 10 = "severe pain"; swallowing: 0 = "normal swallow" and 10 = "unable to swallow without pain, even with medication"). Adverse events were re-

corded with a description, course of action, and sequelae and were reported to local institutional review boards. Adverse event rates are reported as events per treatment session.

## Randomization and Blinding

Random treatment assignment was made with block randomization by site, using a computer-generated random number table. Randomization was concealed before assignment using sealed envelopes. Those responsible for randomization were not involved in enrollment or treatment assignment.

Patients were blinded to active versus placebo TCRFTA treatment. Subjects were blinded to the difference in treatment schedule between placebo and active TCRFTA groups. CPAP patients were not blinded. Treating investigators and study coordinators were not blinded to intervention group; however, medical assistants delivering self-administered subjective questionnaires were blinded. Furthermore, sleep laboratory staff including those scoring the PSGs were blinded to active or placebo TCRFTA treatment as well as to baseline or posttreatment status. Last, as treatment assignment was performed after baseline evaluations, all involved were blinded to treatment group for baseline assessments.

## Data Management and Statistical Methods

Data were collected on case report forms at each site. Copies were mailed to the sponsor's data coordinators, who entered the data and visually checked for accuracy. The principal investigator at each treatment site verified data accuracy. Data were also checked statistically and inconsistencies were resolved with the raw data at each site.

The sample size was calculated as 30 patients per treatment group, based on the primary outcome  $1/\text{SRT}$ , using the 2-sample  $t$  test with  $\alpha = 0.05$ , power = 90%, standard deviation  $1/\text{SRT} = 0.3$ ,<sup>17</sup> the minimal clinically important treatment effect (difference) =  $0.27$ ,<sup>17</sup> and accounting for a 10% dropout rate.

Subjects were analyzed according to their original group assignment (intention-to-treat analysis). For all analyses of continuous variables, normality was tested with the Shapiro-Wilk  $W$  test, Shapiro-

**Table 1.** Baseline Characteristics

Variable	Norm	Placebo* (n = 30)	TCRFTA* (n = 29)	CPAP* (n = 28)	P value†
Demographics					
Age (yr)		46.0 ± 8.1	49.4 ± 9.2	51.7 ± 8.6	0.04‡
Male gender (%)		70.0	89.7	75.0	0.17
Anatomy					
Body mass index (kg/m <sup>2</sup> )	<25	28.5 ± 4.2	27.7 ± 3.6	29.1 ± 3.7	0.36
Neck circumference (cm)	<43	40.6 ± 3.6 (29)	40.9 ± 3.3 (28)	41.4 ± 3.3 (27)	0.69
Upper airway volume (cm <sup>3</sup> )		77.1 ± 18.0 (28)	73.6 ± 19.8 (27)	69.3 ± 15.4 (22)	0.31
Polysomnography parameters					
Apnea-Hypopnea Index (events/hr)	<5 <sup>2</sup>	15.4 ± 7.8	21.3 ± 11.1	19.8 ± 9.9 (27)	0.06
Apnea Index (events/hr)	<5	3.9 ± 4.1	7.5 ± 10.9	6.2 ± 7.5 (27)	0.21
Lowest saturation (%)	>90	88.3 ± 3.9	86.3 ± 7.6	86.0 ± 6.4 (27)	0.32
Symptoms and quality of life					
Epworth Sleepiness Scale	<10	11.6 ± 3.5	11.9 ± 4.6	12.6 ± 5.0 (27)	0.68
Functional Outcomes of Sleep questionnaire	>17.8 <sup>18</sup>	16.8 ± 2.1	16.5 ± 2.0	16.0 ± 2.6 (27)	0.38
Symptoms of Nocturnal Obstruction and Related Events Questionnaire		1.6 ± 0.7	1.6 ± 0.7 (28)	1.5 ± 0.6 (27)	0.51
SF36 Mental Component Summary	50	46.7 ± 9.8	46.4 ± 9.4 (28)	47.2 ± 10.5 (27)	0.95
SF36 Physical Component Summary	50	49.9 ± 8.0	50.1 ± 8.3 (28)	50.7 ± 6.7 (27)	0.92
Psychomotor vigilance					
1/Slowest reaction time (1/msec)	≥2.88 <sup>17</sup>	2.88 ± 0.55 (29)	2.71 ± 0.69	2.77 ± 0.66	0.60
Median reaction time (msec)	≤231 <sup>17</sup>	227 ± 35 (29)	236 ± 41 (28)	226 ± 34	0.55
Fastest reaction time (msec)	≤191 <sup>17</sup>	184 ± 18 (29)	192 ± 26	183 ± 24	0.31

TCRFTA, temperature-controlled radiofrequency tissue ablation group; CPAP, continuous positive airway pressure group.

\*Values given in mean ± SD. n indicated in parentheses if less than the whole group.

†ANOVA ( $\chi^2$  for gender variable). For nonnormal distributions, normal transformations (Box-Cox, logarithmic, or square root) revealed similar results (not shown).

‡P-value <0.05 is significant.

Francia W' test, and combined skewness and kurtosis tests. For non-normality by any one of these tests, non-parametric tests or normal transformations (Box-Cox, logarithmic, or square root) were used to confirm parametric test results.

Baseline characteristics between groups were compared using ANOVA for continuous variables and the  $\chi^2$  test for the categorical variable (sex) (Table 1). Objective versus self-reported CPAP treatment data were compared with the paired *t* test (normal continuous variable), Wilcoxon sign-rank test (non-normal continuous variable), and Fisher's exact test (proportions) (see Table 3). The paired *t* test for continuous normal variables and the sign test for continuous nonnormal variables were used to test the null hypothesis that changes within groups were equal to zero (see Table 5). One-tailed tests were used for TCRFTA and

CPAP groups because an effect was expected a priori. Two-tailed tests were used for the placebo group because an effect was not expected a priori. The unpaired 2-sample *t* test (1-tailed) was used to test the null hypothesis that TCRFTA and CPAP were no different from-placebo (see Table 6). Statistical results were confirmed adjusting for study site (ANCOVA) (not shown). Normal transformations and/or the Mann-Whitney *U* test were used to confirm the statistical testing for non-normal variables (not shown). The unpaired 2-sample *t* test (2-tailed) was used to test the null hypothesis that TCRFTA was no different from CPAP (see Table 7), confirming with study site-adjusted ANCOVA (not shown) and with normal transformations or Mann-Whitney *U* test for nonnormal variables (not shown). Fisher's exact test (2-sided) was used to test the null hypothesis that TCRFTA

**Table 2.** Placebo and TCRFTA treatment data

Variable	Placebo (n = 28)	TCRFTA (n = 26)
Tongue		
No. of sessions	2.9 ± 0.4	4.5 ± 0.8
No. of lesions/session	2.7 ± 0.5	2.8 ± 0.5
Time/lesion (sec)	96 ± 12	219 ± 62
Energy/lesion (J)	0	770 ± 118
Energy/session (J)	0	2144 ± 375
Total energy (J)	0	9700 ± 2000
Palate		
No. of sessions	0	1.5 ± 0.7
No. of lesions/session		2.7 ± 0.8
Time/midline lesion (sec)		129 ± 43
Time/lateral lesion (sec)		59 ± 10
Energy/midline lesion (J)		624 ± 74
Energy/lateral lesion (J)		309 ± 29
Energy/session (J)		1129 ± 330
Total energy (J)		1785 ± 904

TCRFTA, temperature-controlled radiofrequency tissue ablation group.

success was no different from CPAP success, and logistic regression (Wald test) was used to test the null hypothesis adjusting for study site (not shown). Success was defined as achieving an effect size  $\geq 0.50$  over placebo.

All results of continuous variables are expressed as mean  $\pm$  SD. Within-group effect size was calculated as (posttreatment mean – baseline mean)/(baseline SD) as per Kazis et al.<sup>20</sup> Positive sign denotes improvement; negative sign denotes worsening. Between group effect size was calculated as (active treatment mean change – placebo mean change)/(placebo change SD). Positive sign denotes improvement in active treatment group over placebo; negative sign denotes worsening. The data were analyzed with Intercooled Stata 7.0 software (Stata Corp, College Station, TX).  $P < 0.05$  was considered statistically significant. Corrections for multiple comparisons were not made because the primary outcomes were limited to 3.

## RESULTS

Details of subject recruitment and the final sample of study participants are outlined in Figure 1. The dropout rate was 12% (Fig 1). Data were not complete on all follow-up subjects, but all available data were analyzed.

The 3 treatment groups were not significantly different with respect to all baseline variables except age, which was not considered a clinically

relevant difference (Table 1). On average, subjects had moderate OSA by AHI criteria,<sup>2</sup> and evidence of OSAS with excessive daytime sleepiness and deficits in OSAS-specific quality of life. BMI did not change significantly within groups (overall mean increase  $0.2 \pm 0.7$  kg/m<sup>2</sup>,  $P > 0.10$  for each group) or between groups ( $P = 0.64$ ).

Sham-placebo and TCRFTA treatment data are shown in Table 2, and CPAP treatment data are shown in Table 3. Subjects overestimated their actual CPAP use. Built-in CPAP apnea/hypopnea monitors demonstrate efficacy of prescribed pressures (Table 3). Between CPAP users ( $\geq 4$  hr/night and  $\geq 5$  nights/wk<sup>21</sup>) and nonusers, there were no significant differences in prescribed pressure ( $8.4 \pm 1.2$  versus  $7.6 \pm 1.8$  cm water,  $p = 0.24$ ) or residual AHI ( $5.1 \pm 2.1$  versus  $4.6 \pm 2.9$  events/hr,  $P = 0.59$ ).

Adverse events were mild and temporary in all cases, and the frequency was comparable between sham-placebo and TCRFTA groups (Table 4). No adverse events were seen with palate TCRFTA. Three subjects received additional medication (prednisone and/or prophylactic amoxicillin/clavulanate). Pain and swallowing difficulty increased mildly 1 week after treatment for both the placebo and TCRFTA groups but returned to baseline by 3 weeks with no significant differences noted between groups. After simultaneous tongue

**Table 3.** CPAP treatment data

Variable	Objective measure*	Self-report*†	P value‡ objective versus self-report
Use (hrs/night used)	4.2 ± 2.5 (24)	4.9 ± 2.5 (22)	0.09 (19)
Use (nights/wk)	4.0 ± 2.5 (25)	5.7 ± 2.1 (22)	0.002 (20)
No. of nights recorded	63.0 ± 29.7 (27)		
Adequate use§	9/24, 37.5%	17/22, 77.3%	0.007
CPAP (cm H <sub>2</sub> O)	7.9 ± 1.6 (24)		
Apnea-Hypopnea Index on CPAP   (events/hr)	4.6 ± 2.7 (24)		
Apnea Index on CPAP   (events/hr)	0.5 ± 1.0 (24)		

CPAP, continuous positive airway pressure.

\*\*Values given in mean ± SD. n indicated in parentheses if less than the whole group.

†Self-report based on report at final follow up (8 weeks after CPAP started).

‡P value based on paired *t* test (use hr/night, normal distribution), Wilcoxon sign-rank test (use nights/wk, nonnormal distribution), and Fisher's exact test (adequate use, proportions). *P* < 0.05 is significant.

§Adequate use: ≥4 hr/night used and ≥5 nights/wk.<sup>21</sup>

||Apnea-Hypopnea Index and Apnea Index readings from built-in CPAP monitor (not polysomnography).

**Table 4.** Adverse events and side effects

Event	Placebo (n = 28)	TCRFTA (n = 26)	Event	CPAP (n = 21)
Adverse events				
No. of hematomas (% of sessions)	3 (3.5%)	3 (2.3%)		
No. of ulcerations (% of sessions)	0 (0%)	1 (0.8%)		
No. of infections (% of sessions)	0 (0%)	0 (0%)		
Side effects*				
Pain pretreatment	0.37 ± 0.78 (17)	0.64 ± 1.46 (19)	Nasal	8 (38%)
Pain 1 wk†	1.84 ± 2.35 (81)	1.64 ± 2.19 (75)	Sleep	9 (43%)
Pain 3 wk†	0.33 ± 0.65 (58)	0.71 ± 1.13 (68)	Inconvenience	7 (33%)
Swallow pretreatment	1.32 ± 2.08 (17)	0.85 ± 1.63 (19)	Air mechanics	7 (33%)
Swallow 1 wk††	1.73 ± 2.44 (81)	2.14 ± 2.52 (76)	Skin or eyes	8 (38%)
Swallow 3 wk†	0.57 ± 0.99 (59)	0.85 ± 1.36 (68)	Subjects affected	20 (95%)

TCRFTA, temperature-controlled radiofrequency tissue ablation group; CPAP, continuous positive airway pressure group.

\*Pain and swallow side effects measured in placebo and TCRFTA patients at baseline and after tongue treatments, presented as mean ± SD of 10-cm visual analog scale (pain: 0 = "no pain" and 10 = "severe pain"; swallowing: 0 = "normal swallow" and 10 = "unable to swallow without pain, even with medication"). n indicated in parentheses if less than the whole group. CPAP side effects measured in CPAP patients only, presented as number (percentage) of patients. Nasal = dryness, congestion, bleeding, and/or sinusitis; sleep = delayed sleep and/or subjective sleep fragmentation; inconvenience = noise and/or spouse objection; air mechanics = aerophagia, chest wall discomfort, and/or mouth breathing.

†1 wk = mean at 1 wk for all 3 tongue-only treatments; 3 wk = mean at 3 wk for all 3 tongue-only treatments.

and palate TCRFTA, mean pain scores were 2.8 ± 2.5 at 1 week and 0.7 ± 1.2 at 3 weeks, and mean swallowing scores were 2.6 ± 2.6 at 1 week and 1.0 ± 1.4 at 3 weeks. Most CPAP subjects experienced at least one side effect but none were serious (Table 4).

Table 5 and Figure 2 display the absolute changes and effect sizes for most outcome variables in each group compared with their pretreatment baseline. The placebo effects were small and not statistically significant. TCRFTA subjects improved on all primary outcome measures. CPAP

subjects improved on all primary outcome measures, but without statistical significance on the objective primary outcome (1/SRT). Among secondary outcomes, CPAP subjects had a large improvement on AHI measured by AutoSet (effect size 1.5, *P* < 0.001). Compared with the entire CPAP group, CPAP users (n = 9, use ≥4 hr/night on ≥5 nights/wk) had larger improvements on FOSQ, SNORE25, and ESS, but similar improvements on all 3 reaction time outcomes, SF36 MCS, SF36 PCS, and total airway volume (data not shown).

**Table 5.** Treatment effects for each group

Outcome	Placebo				TCRFTA				CPAP			
	n	Change*	P value†	Effect size‡	n	Change*	P value†	Effect size‡	n	Change*	P value†	Effect size‡
Primary												
1/SRT (1/msec)	25	0.05 ± 0.66	0.68	0.09	23	0.32 ± 0.57	<b>0.006</b>	0.42	19	0.18 ± 0.60	0.11	0.30
FOSQ	28	0.4 ± 2.0	0.18	0.18	26	1.2 ± 1.6	<b>0.005</b>	<b>0.66</b>	25	1.5 ± 2.1	<b>0.02</b>	<b>0.61</b>
SNORE25	28	-0.21 ± 0.56	0.06	0.31	25	-0.43 ± 0.56	<b>&lt;0.001</b>	<b>0.65</b>	24	-0.30 ± 0.52	<b>0.005</b>	0.46
Secondary												
RT (msec)	27	-4.4 ± 22.6	0.32	0.12	23	-10.0 ± 19.5	<b>0.03</b>	0.23	22	-3.1 ± 27.6	0.26	0.09
FRT (msec)	25	-3.1 ± 16.7	0.37	0.14	23	-10.2 ± 21.9	<b>0.02</b>	0.37	19	-0.8 ± 13.0	0.82	0.03
ESS	28	-1.0 ± 3.1	0.11	0.27	26	-2.1 ± 3.9	<b>0.005</b>	<b>0.50</b>	25	-2.3 ± 5.2	<b>0.02</b>	0.44
MCS	27	0.4 ± 6.4	0.70	0.04	24	2.9 ± 7.3	0.08	0.32	24	2.0 ± 6.1	0.73	0.22
PCS	27	1.5 ± 7.8	0.44	0.18	24	0.5 ± 6.8	0.42	0.06	24	0.1 ± 7.7	0.08	0.02
AHI (events/hr)	28	-1.8 ± 11.5	0.34	0.24	24	-4.5 ± 13.8	0.34	0.38				
AI (events/hr)	28	1.7 ± 5.4	1.00	-0.54	24	-3.1 ± 9.5	0.25	0.27				
LSAT (%)	28	0.6 ± 4.7	0.54	0.15	24	-0.6 ± 4.6	0.81	-0.08				
Total Vol (cm <sup>3</sup> )	26	-3.7 ± 15.7	0.17	-0.20	22	6.6 ± 19.5	0.14	0.27				

TCRFTA, temperature-controlled radiofrequency tissue ablation group; CPAP, continuous positive airway pressure group; 1/SRT, slowest reaction time (reciprocal); FOSQ, functional Outcomes of sleep questionnaire; SNORE25, symptoms of Nocturnal Obstruction and Related Events questionnaire; RT, reaction time; FRT, fastest reaction time; ESS, Epworth Sleepiness Scale; MCS, SF36 Mental Component Summary; PCS, SF36 Physical Component Summary; AHI, Apnea-Hypopnea Index; AI, Apnea Index; LSAT, lowest oxyhemoglobin saturation; Total Vol, volume of upper airway.

\*Change = posttreatment mean - baseline mean. Values given in mean ± SD.

†P value based on paired t test for comparison of means for normally distributed variables or sign test for comparison of medians for nonnormally distributed variables. Two-sided tests used for placebo (no effect expected a priori), one-sided tests used for TCRFTA and CPAP groups (effect expected a priori). P < 0.05 is significant (**bold**).

‡Effect size = (posttreatment mean - baseline mean)/(baseline standard deviation). Positive indicates improvement, negative indicates worsening. Subject not included in effect size calculation if baseline or posttreatment data missing. Effect size ≥0.50 is at least moderate (**bold**).

Table 6 and Figure 3 display the absolute differences and effect sizes for most outcome variables in the treatment groups compared with sham-placebo. TCRFTA subjects had clinically important improvement on all primary outcomes, with statistical significance or a statistical trend. TCRFTA subjects also improved on most secondary outcomes compared with sham-placebo, but only AI and total airway volume were statistically significant. TCRFTA also improved the respiratory arousal index over sham-placebo (effect size 0.95, P < 0.04), but data were available from only one site (n = 11). Other standard PSG parameters (HI, percent sleep time with oxyhemoglobin saturation <90%, and total arousal index) were not significantly different between TCRFTA and sham-placebo groups (data not shown). CPAP subjects had a statistically significant moderate improvement in FOSQ but no statistically significant improvement over sham-placebo on the other outcomes measured (Table 6 and Fig 3).

Statistical significance did not change with adjustment for study site (not shown).

The primary and many of the secondary outcomes were comparable between TCRFTA and CPAP groups with no significant differences noted between treatments (Table 7). However, a significantly greater proportion of TCRFTA subjects achieved a moderate improvement over placebo on the SNORE25 questionnaire compared with CPAP subjects (52% versus 21%, P = 0.04) (Table 8). As expected, TCRFTA subjects experienced a statistically significantly greater enlargement of the upper airway volume than CPAP subjects, consistent with this mode of therapy (P = 0.02). The CPAP group experienced a statistically significantly greater reduction in AHI during CPAP use (measured by AutoSet) than the TCRFTA group experienced after treatment (measured on PSG) (P = 0.004). However, average CPAP use was only 16.8 hr/wk (4.2 hr/CPAP-night × 4.0 nights/wk, Table 3), which translates

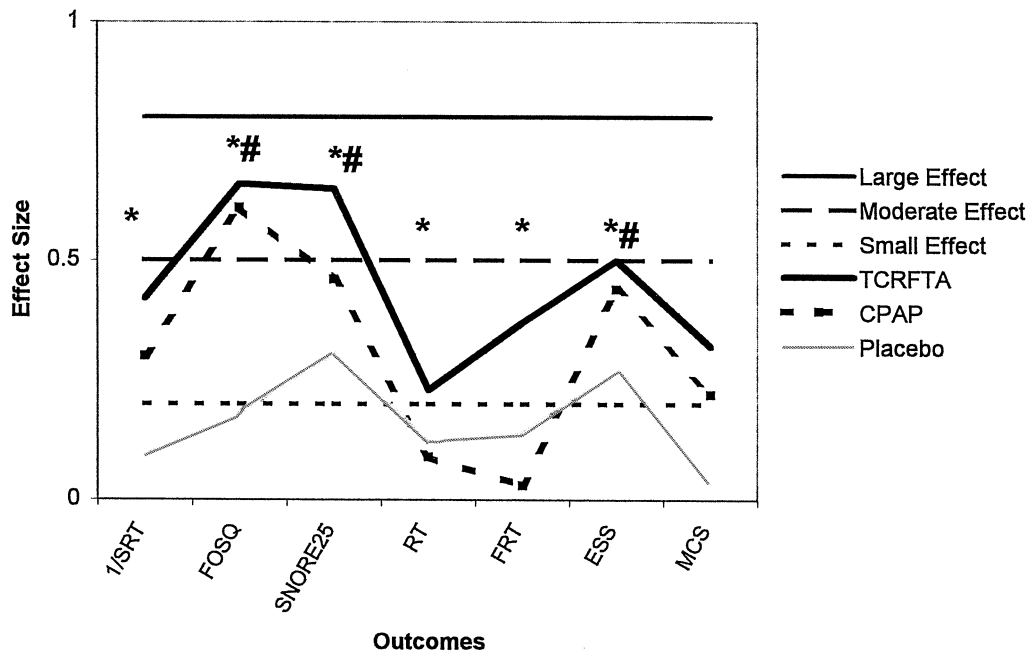


Fig 2. Effect sizes (before–after). Posttreatment effect sizes over baseline measures for all primary and several secondary outcome measures in each treatment group. TCRFTA, temperature-controlled radiofrequency tissue ablation group; CPAP, nasal continuous positive airway pressure group; 1/SRT, slowest reaction time (reciprocal); FOSQ, Functional Outcomes of Sleep Questionnaire; SNORE25, Symptoms of Nocturnal Obstruction and Related Events questionnaire; RT, median reaction time; FRT, fastest reaction time; ESS, Epworth Sleepiness Scale; MCS, SF36 Mental Component Summary. Statistically significant ( $P < 0.05$ ) effects are indicated by \* (TCRFTA) and # (CPAP).

into 30% of the 56 hr/wk (8 hours nightly) of recommended sleep time.

## DISCUSSION

### Treatment Effects and Outcome Measures

These results suggest that either multilevel (tongue and palate) TCRFTA or nasal CPAP significantly improves sleep apnea quality of life for patients with mild to moderate OSAS compared with pretreatment baseline (Table 5) or a sham-placebo treatment (Table 6). Compared with pretreatment baseline, TCRFTA but not nasal CPAP significantly improves reaction time testing, an objective measurement of patient function. TCRFTA appears to enlarge the airway and improve some PSG parameters (AI and respiratory arousal index), which may represent the mechanism by which this treatment improves function and OSAS quality of life.

The clinical importance of therapeutic effect may be inferred from analyses of effect sizes (small = 0.2, moderate = 0.5, and large = 0.8).<sup>20</sup> These data suggest a very consistent small to moderate therapeutic effect of TCRFTA across both

subjective and objective outcome measures compared with baseline or sham-placebo (Figs 2 and 3). Analysis of CPAP effect sizes suggests a small to moderate therapeutic effect for subjective measures compared with pretreatment baseline or sham-placebo (Figs 2 and 3).

CPAP is efficacious in improving respiratory parameters while it is actually used; however, its effectiveness in improving clinically important outcomes is limited by inadequate usage. Despite all efforts to optimize CPAP use in our patients and despite normalization of AHI with CPAP use, only 38% demonstrated adequate use by objective measurement. Similar patterns of use are reported in other randomized trials.<sup>9,11</sup> Thus, it is important to distinguish CPAP efficacy (ie, effect when actually used) from effectiveness (ie, effect in everyday life).<sup>22</sup> Respiratory parameters measured while using the CPAP device inherently represent efficacy measures. Because compliance is moot after surgical treatment, use of respiratory parameters as outcome measures unfairly compare CPAP efficacy to

**Table 6.** Outcomes comparison: Active treatments versus placebo

Outcome	Placebo (n)	TCRFTA					CPAP				
		n	Diff*	95% CL†	P value‡	Effect size§	n	Diff*	95% CL†	P value‡	Effect size§
Primary											
1/SRT (1/msec)	25	23	0.27	-0.09, 0.62	0.07	0.41	19	0.12	-0.26, 0.51	0.26	0.18
FOSQ	28	26	0.9	-0.1, 1.9	<b>0.04</b>	0.45	25	1.2	0.1, 2.3	<b>0.02</b>	<b>0.60</b>
SNORE25	28	25	-0.22	-0.53, 0.09	0.08	0.39	24	-0.09	-0.39, 0.21	0.28	0.16
Secondary											
RT (msec)	27	23	-5.6	-17.5, 6.4	0.18	0.25	22	1.4	-13.4, 16.2	0.57	-0.06
FRT (msec)	25	23	-7.1	-18.5, 4.3	0.11	0.43	19	2.3	-6.8, 11.3	0.69	-0.14
ESS	28	26	-1.2	-3.1, 0.8	0.12	0.39	25	-1.4	-3.8, 1.1	0.13	0.45
MCS	27	24	2.5	-1.4, 6.4	0.10	0.39	24	1.7	-1.8, 5.2	0.17	0.27
PCS	27	24	-1.0	-5.1, 3.1	0.69	-0.13	24	-1.4	-5.8, 3.0	0.74	-0.18
AHI (events/hr)	28	24	-2.7	-9.9, 4.5	0.23	0.23					
AI (events/hr)	28	24	-4.8	-9.3, 0.4	<b>0.02</b>	<b>0.89</b>					
LSAT (%)	28	24	-1.2	-3.8, 1.4	0.83	-0.26					
Total Vol (cm <sup>3</sup> )	26	22	9.3	-1.1, 19.8	<b>0.04</b>	<b>0.59</b>					

TCRFTA, temperature-controlled radiofrequency tissue ablation group; CPAP, continuous positive airway pressure group; CL, confidence limits; 1/SRT, slowest reaction time (reciprocal); FOSQ, Functional Outcomes of Sleep Questionnaire; SNORE25, Symptoms of Nocturnal Obstruction and Related Events questionnaire; RT, reaction time; FRT, fastest reaction time; ESS, Epworth Sleepiness Scale; MCS, SF36 Mental Component Summary; PCS, SF36 Physical Component Summary; AHI, Apnea-Hypopnea Index; AI, Apnea Index; LSAT, lowest oxyhemoglobin saturation; Total Vol, volume of upper airway.

\*\*Diff = active treatment change - placebo change.

†95% CL may include 0 with a one-sided  $P < 0.05$ .

‡P value based on two-sample Student's  $t$  test (one-sided) for comparison of mean diffs displayed. For nonnormal variables,  $P$  values were confirmed with normal transformations (not shown) or when adequate transformation not available by nonparametric (Mann-Whitney  $U$ ) test.  $P$  values not changed significantly after adjusting for study site (ANCOVA) (not shown). One-sided tests used because a net effect was expected a priori for each group over placebo.  $P$  value  $< 0.05$  is significant (**bold**). One-sided  $t$  test shown, but two-sided non-parametric test was not statistically significant.

§Effect size = (active treatment mean change - placebo mean change)/(placebo change standard deviation). Positive indicates improvement in active group over placebo, negative indicates worsening. Effect size  $\geq 0.50$  is at least moderate (**bold**).

surgical effectiveness. In contrast, reaction time tests and quality of life questionnaires measure CPAP effectiveness.

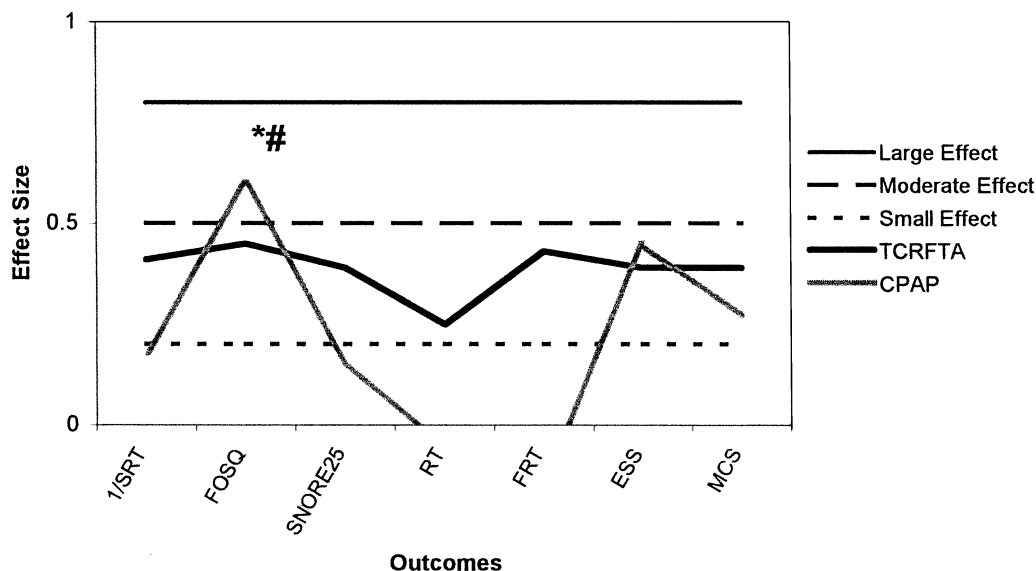
Reaction time and quality of life represent clinically important outcomes. The day-to-day effects of untreated OSAS manifest as compromised function and poor quality of life. Patients seek treatment to improve these problems. PSG parameters, on the other hand, are surrogate measures of clinically important outcomes. They appear to predict cardiovascular risk, which is clinically important; however, they are not clinically important per se. Thus we chose to study reaction time and OSAS quality of life as our primary outcomes.

### Role for TCRFTA in the Treatment of OSAS

These findings suggest an important role for TCRFTA in the treatment of OSAS. Because

CPAP therapy poses no risks and CPAP users achieve good outcomes, CPAP continues to represent a primary therapeutic option for patients with mild to moderate OSAS. TCRFTA may represent an alternative treatment in mild to moderate OSAS patients that refuse CPAP, demonstrate inadequate use, or experience insufficient improvement. TCRFTA may represent an alternative treatment in mild to moderate OSAS patients that refuse CPAP, demonstrate inadequate use, or experience insufficient improvement. Surgical treatment offers the major advantage of not depending on nightly compliance to achieve an adequate treatment effect. TCRFTA may also represent an adjunctive therapy to other surgical or non-surgical treatments of OSAS.

The low morbidity with TCRFTA is a major benefit over traditional OSAS surgery. Our find-



**Fig 3.** Effect sizes: active treatments versus placebo. Active treatment effect sizes over placebo for all primary and several secondary outcome measures. TCRFTA, temperature-controlled radiofrequency tissue ablation group; CPAP, nasal continuous positive airway pressure group; 1/SRT, slowest reaction time (reciprocal); FOSQ, Functional Outcomes of Sleep Questionnaire; SNORE25, Symptoms of Nocturnal Obstruction and Related Events questionnaire; RT, median reaction time; FRT, fastest reaction time; ESS, Epworth Sleepiness Scale; MCS, SF36 Mental Component Summary. Statistically significant ( $P < 0.05$ ) effects are indicated by \* (TCRFTA) and # (CPAP).

**Table 7.** Outcomes comparison: TCRFTA versus CPAP

Outcome	n (TCRFTA)	n (CPAP)	Difference*	95% CL	P value†	Effect size‡
Primary						
1/SRT (1/msec)	23	19	-0.15	-0.22, 0.52	0.43	-0.26
FOSQ	26	25	-0.29	-1.35, 0.77	0.58	-0.16
SNORE25	25	24	-0.13	-0.44, 0.18	0.41	0.24
Secondary						
RT (msec)	23	22	-6.9	-21.4, 7.6	0.34	0.29
FRT (msec)	23	19	-9.4	-20.4, 1.6	0.09	0.50
ESS	26	25	0.20	-2.39, 2.80	0.87	-0.04
MCS	24	24	0.83	-3.07, 4.74	0.67	0.12
PCS	24	24	0.38	-3.86, 4.62	0.86	0.05

TCRFTA, temperature-controlled radiofrequency tissue ablation group; CPAP, continuous positive airway pressure group; CL, confidence limits; 1/SRT, slowest reaction time (reciprocal); FOSQ, Functional Outcomes of Sleep Questionnaire; SNORE25, Symptoms of Nocturnal Obstruction and Related Events questionnaire; RT, reaction time; FRT, fastest reaction time; ESS, Epworth Sleepiness Scale; MCS, SF36 Mental component Summary; PCS, SF36 Physical Component Summary.

\*Difference = TCRFTA change - CPAP change.

†P value based on two-sample Student's *t* test (two-sided) for comparison of mean differences displayed. For nonnormal variables, p-values were confirmed with normal transformations (not shown) or when adequate transformation not available by nonparametric (Mann-Whitney *U*) test. P values not changed significantly after adjusting for study site (ANCOVA) (not shown). Two-sided tests used because a difference between TCRFTA and CPAP was not expected a priori. P value < 0.05 is significant.

‡Effect size = (TCRFTA mean change - CPAP mean change)/(combined standard deviation). Positive indicates TCRFTA better than CPAP; negative indicates TCRFTA worse than CPAP. Effect size  $\geq 0.50$  is at least moderate.

ings demonstrate mild, transient side effects (pain and swallowing difficulty) and low complication rates. The most common complication (hematoma) appears not to result from the radiofrequency

energy, because sham-placebo subjects had a similar rate of hematoma. Nonsteroidal anti-inflammatory medication can inhibit platelet activity and may have contributed to the occurrence of hema-

**Table 8.** Outcomes success (effect size  $\geq 0.50$ ) comparison: TCRFTA versus CPAP

Outcome	Success criteria*	TCRFTA success†	CPAP success†
Primary			
1/Slowest reaction time (1/msec)	0.383	10/23,43%	6/19,32%
Functional Outcomes of Sleep Questionnaire	1.34	12/26,46%	10/25,40%
Symptoms of Nocturnal Obstruction and Related Events Questionnaire	-0.486	13/25,52%	5/24,21%
Secondary			
Reaction time (msec)	-15.73	6/23,26%	5/22,23%
Fastest reaction time (msec)	-11.39	7/23,30%	5/19,26%
Epworth Sleepiness Scale	-2.50	11/26,42%	8/25,32%
SF36 Mental Component Summary	3.55	7/24,29%	7/24,29%
SF36 Physical Component Summary	5.40	3/21,13%	3/21,13%
Upper airway volume (cm <sup>3</sup> )	4.11	12/22,55%	
Apnea-Hypopnea Index (events/hr)	-7.50	9/15,38%	
Apnea Index (events/hr)	-0.96	11/24,46%	
Lowest saturation (%)	2.95	5/24,21%	

TCRFTA, temperature-controlled radiofrequency tissue ablation group; CPAP, continuous positive airway pressure group; 1/SRT, slowest reaction time (reciprocal).

\*Success criteria = change in each outcome measure required for active treatment to have an effects size  $\geq 0.50$  over placebo. Effect size = (active treatment mean change - placebo mean change)/(placebo change standard deviation); positive indicates improvement over placebo, negative indicates worsening.

†Proportion of subjects in each treatment group achieving treatment success criteria (effect size  $\geq 0.50$  over placebo).

tomas. Other investigators have found similar low morbidity associated with TCRFTA, with significantly less pain than other surgical therapies for OSAS.<sup>12,23</sup> Major complications from TCRFTA include tongue base abscess or airway obstruction, seen in approximately 1% to 8% of treatment sessions in previous case series.<sup>14,24,25</sup> We observed no major complications, possibly related to perioperative antiseptic rinse, antibiotics, and steroids. All complications were mild, without airway compromise, and resolved completely.

### Study Limitations and Strengths

Limitations to these results include limited statistical power, a sham-placebo schedule that was not identical to active treatment, a nonstandard CPAP titration method, incomplete follow-up data, risk of type I error due to multiple testing, and the lack of long-term outcomes assessment. The study had adequate power to achieve statistical significance for moderate effect sizes but insufficient power to achieve statistical significance for small clinically important effect sizes (possible type II errors). Ideally, the sham-placebo schedule would have been identical to the active TCRFTA schedule; however, ethical concerns regarding unnecessary potential complications from repeated

placebo treatment superseded this study design concern. Multilevel treatment was used in the active group because it was an a priori opinion that we could not rely consistently on pretreatment examination to eliminate the need for multilevel treatment. Preliminary analysis of pretreatment examination data has confirmed this assumption (data not shown). Furthermore, both active and sham-placebo TCRFTA groups remained blind to treatment group. Ideally, CPAP would have been titrated with overnight, in-laboratory polysomnography. Expense precluded this titration method, and autotitrating CPAP has been shown to reduce PSG parameters to levels comparable to in-laboratory titrations.<sup>16</sup> Titration was performed over several nights to optimize CPAP pressures, which were documented to dramatically improve AHI and AI (Table 3).

Twelve percent of randomized subjects were lost to follow-up, and only partial follow-up data were available on others. The follow-up rates were similar between treatment groups. All baseline variables except FOSQ and SNORE25 were similar between those with complete follow-up data and those with incomplete follow-up data. Baseline OSAS quality of life (FOSQ and SNORE25)

was worse in subjects with incomplete follow-up data compared with those with complete follow-up data (both  $P < 0.05$ ); however, this discrepancy was no different between treatment groups (all  $P > 0.3$ ). This study includes multiple outcome measures. We defined 3 primary outcomes a priori to reduce the risk of type I error caused by multiple testing. The consistency of improvement across all primary and most secondary outcomes in the TCRFTA group suggests that statistically significant improvements were not by chance alone.

Ideally, long-term outcomes would be assessed; however, long-term outcomes were not studied for several reasons. First, short-term improvements in quality of life and sleepiness appear to persist greater than 2 years after TCRFTA,<sup>13</sup> and short-term CPAP use reflects long-term use.<sup>26</sup> Second, long-term outcomes are particularly difficult to justify in a randomized, placebo-controlled trial where placebo patients' treatment is deferred. Third, we will follow TCRFTA patients (and sham-placebo or CPAP subjects who subsequently underwent active TCRFTA) to assess long-term outcomes.

The methodologic rigor (randomized, placebo-controlled, blinded, analyzed by intention-to-treat) is a major strength for these results. Some of the other strengths include the measurement of clinically important outcomes (both subjective and objective) rather than just surrogate outcomes, consistency of treatment effect observed, separate screening and baseline measurements, and a low dropout rate. This study is the first conclusive, placebo-controlled OSAS surgery trial to achieve level I evidence according to Sackett's criteria.<sup>27</sup>

## CONCLUSION

The results of this study suggest that both TCRFTA and nasal CPAP improve quality of life for mild to moderate OSAS patients compared with sham-placebo TCRFTA. The treatment effect sizes of both therapies over sham-placebo are small to moderate, but clinically important, for most outcomes. TCRFTA improvements may result from an increase in upper airway volume and a reduction in apnea and respiratory arousal indices; however, these hypotheses require independent testing in a separate sample of patients.

TCRFTA is a low morbidity procedure. Side effects of CPAP were mild but common.

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