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Radiofrequency Treatment of Turbinate Hypertrophy in Subjects Using Continuous Positive Airway Pressure: A Randomized, Double-Blind, Placebo-Controlled Clinical Pilot Trial

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Objectives: **To estimate the treatment effect of temperature-controlled radiofrequency (TCRF) reduction of turbinate hypertrophy in patients with sleep-disordered breathing (SDB) treated with nasal continuous positive airway pressure (CPAP), and to assess the impact of study design on this estimate. *Study Design:* Prospective, randomized, double-blind, placebo-controlled clinical pilot trial. *Methods:* Twenty-two CPAP-treated patients with SDB with turbinate hypertrophy were randomly assigned to either TCRF turbinate treatment (mean energy 415 ± 37 J/turbinate; n = 17) or placebo control (n = 5). Changes in nasal obstruction were evaluated between pretreatment and 4 weeks post-treatment. The *primary* outcome assessed changes in the blinded examiners' findings of nasal obstruction on a visual analogue scale (VAS). *Secondary* outcomes included blinded patients' and unblinded examiner assessments of nasal obstruction (VAS), nightly CPAP use, adherence, and tolerance, along with sleepiness and general health status scales. The treatment group findings were subtracted from the changes in the placebo group to yield treatment effect. *Results:* The primary outcome treatment effect by VAS was -0.9 cm (95% confidence interval [CI], -2.4, 0.7), and beyond the placebo effect of -1.5 cm (95% CI: -3.4, 0.3). The secondary treatment effect of the *unblinded* examiner was -3.0 cm (95% CI, -4.9, -1.1). A beneficial treatment effect was also seen on every *secondary* outcome except general health status, but only self-reported CPAP adherence (*P* = .03) was statistically significant. *Conclusions:* TCRF turbinate treatment appears to benefit nasal obstruction and CPAP treatment for SDB. Placebo control and double blinding are critical for establishing the true treatment effect. A future definitive trial is feasible to establish statistical significance of these findings. *Key Words:* Temperature-controlled radiofrequency, turbinate hypertrophy, sleep-disordered breathing, CPAP, placebo-controlled, randomized trial, double-blind.**

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INTRODUCTION

Those who use nasal continuous positive airway pressure (CPAP) devices for sleep-disordered breathing (SDB) and experience problems resulting from nasal complaints may benefit from treatment of the shrinkable turbinate tissues in the nose. The anterior inferior turbinates, when enlarged, may create blockage of the nasal passages because they have a variable reactivity to allergens, temperature, humidity, and the increased pressure and airflow from CPAP. Patients using CPAP often experience nasal stuffiness and blockage resulting from this reactive tissue and are commonly on oral decongestant medications, allergic desensitization, or chronic nasal sprays. The currently available treatment modalities for enlarged turbinates (hypertrophy) range from conservative non-invasive medical management to surgical management.[1–6] Although surgical turbinectomy is an acceptable remedy to open the nasal airway, it may require nasal packing. In addition, there are risks of bleeding, infection, adverse airflow patterns, and the onerous problems of atrophic rhinitis. Conservative medical therapies such as steroid injections, nasal sprays, decongestants, and desensitization procedures are not always effective in controlling turbinate enlargement in the patient with sleep-

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disordered breathing on CPAP. An alternative in this patient population may be temperature-controlled radiofrequency (TCRF) shrinkage of a portion of the inferior turbinate tissue. Hence, this pilot study was designed to investigate and estimate the treatment effect of TCRF, assess the impact of study design on the estimate of treatment effects, and determine the feasibility of conducting a future definitive study.

MATERIALS AND METHODS

Study Design

This investigation was designed as a prospective, randomized, double-blind, placebo-controlled clinical pilot trial that adheres to Sackett's level II rules of evidence.[7,8] In addition, for comparison, an unblinded investigator evaluated outcomes but did not communicate with blinded investigators. The university institutional review board approved this protocol, and all subjects provided informed consent.

Eligibility Criteria

General inclusion required an age range of 18 to 60 years and a clinical history of bilateral turbinate hypertrophy causing nasal obstruction interfering with the nightly use of CPAP, a desire for treatment, and otherwise good health (ASA class I–II). Further *inclusion criteria* required a history of incomplete or failed treatment by conventional medical methods and the ability to discontinue all nasal medication for the duration of the study (2 weeks before "treatment" until 4 weeks post-treatment). *Exclusion criteria* included previous nasal surgery, recurrent epistaxis, olfactory abnormalities, and septal or bony deformity affecting the nasal airway. Excluded also were subjects with a history of upper respiratory tract cancer, radiation therapy, active respiratory infections, labile or uncontrolled hypertension, and coagulopathy. Further exclusions were the inability to give informed consent or the inability to complete the study protocol, psychiatric instability, drug or alcohol abuse, pregnancy, or classification as an ASA class III–V. All prospective subjects underwent evaluation and assessment for nasal obstruction, which included a detailed history and physical examination with objective rhinoscopy and photography. The specific evaluation criteria reviewed the patients' complaint of nasal obstruction, which covered frequency, length, and severity of occurrences. This was used to establish that the subject suffered from a chronic, unremitting problem interfering with the use of nightly CPAP. This group then proceeded to clinical screening and rhinoscopy to assess intranasal airway pathology or anatomic deformities, and to evaluate the extent of nasal airway obstruction of the inferior turbinates. Each examiner to independently and serially grade these anatomic findings over the course of the study scored their findings on a 10-cm visual analogue scale (VAS). VAS anchors were 0 = no obstruction and 10 = complete obstruction.

Subjects and investigators did not receive any compensation for participation in this study, and no subject incurred treatment fees.

Subjects

Sixty-two subjects were interviewed from the Stanford Sleep and Research Center and 40 did not meet eligibility criteria. Twenty-two were declined over the phone and 18 were rejected after the clinical and fiberoptic examination. Of these, there were anatomic abnormalities, polyps, unilateral turbinate obstruction, and an unwillingness to be randomized. Twenty-two eligible subjects (22 of 62) were enrolled and were randomly assigned to either the TCRF active treatment or placebo control groups. Randomization was performed with the use of sealed envelopes just before treatment. This sample size was chosen to allow estimations of TCRF treatment effects and variance, to evaluate the influence of placebo control and blinding, and to determine the feasibility of a future study.

Examiners

Blinding to treatment was achieved with a realistic placebo "treatment" and was *identical* to the active treatment protocol, except that a separate unblinded investigator used a covert radiofrequency (RF) energy cut-off switch. The RF device was programmed to mock treatment feedback (audio indicators) to maintain blinding of the patient and treating physician. Patients, as well as treating and examining physicians (R.T. and K.L.), were all blinded to treatment groups for the duration of the study. In addition, an unblinded physician (A.Z.) also examined patients before treatment and after treatment to estimate the effect of blinding on outcome assessment. The unblinded physician did not deliver any treatments or discuss the findings with the subjects or blinded physicians. The subjects were unaware of the unblinded status of this examiner. Examiners did not, at any time, share results during the study.

Study Procedures

Two weeks before randomization and treatment, 20 subjects were switched to new loaner CPAP devices with *overt* electronic metered time/pressure counters: 10 ResMed (ResMed Corp., San Diego, CA) and 10 Nelcor (Nelcor Puritan Bennet, Pleasanton, CA). Two subjects continued their own BiPAP devices (Respironics) already with counters. All subjects continued on their prior pressure settings and used their usual mask apparatus. Each subject kept a sleep diary, which included sleep time and CPAP use starting 2 weeks before and ending at 4 weeks after treatment. All subjects completed data questionnaires and nasal examination (independently by blinded and unblinded physicians) just before treatment and at 1, 2, and 4 weeks after treatment. The patients and blinded physicians remained blinded to treatment groups for the duration of the study.

Treatment (TCRF)

Outpatient treatment intervention consisted of application of topical anesthetic to the turbinate mucosa bilaterally, followed by injection of 2.0 mL of 0.5% lidocaine into the anterior inferior turbinate. Placement of a TCRF electrode (Somnus Medical Technologies Inc., Mountain View, CA) into the anterior inferior turbinate under direct visualization was made, and 350 to 500 J of RF energy was delivered over 25 to 70 seconds at 80°C. One treatment was delivered for each turbinate. The subject was then discharged from the office within 5 minutes of treatment. Each subject was instructed to continue nightly use of CPAP. No sedative medications, steroids, or antibiotics were used. Patients were advised to use 500 to 1000 mg acetaminophen if needed for pain. The subjects were seen for post-treatment clinical follow-up at 1 day, and at 1, 2, and 4 weeks.

Outcome Measures

The primary outcome variable was the change in the blinded examiners' assessment of nasal obstruction from pretreatment to 4 weeks post-treatment. Obstruction was quantified on a 10-cm visual analogue scale (VAS) with anchors of 0 indicating no obstruction and 10 indicating complete obstruction. This outcome metric was chosen because it was relatively standardized and specific to the primary problem of nasal obstruction. A change of 0.7 cm was considered the minimal *clinically* important change from baseline based on previous standards with other subjective measures,[9–11] including other visual analogue scales.[12]

Secondary outcomes, in order of specificity to the problem being treated, included changes in each patient's assessment of nasal obstruction and unblinded examiner assessment of nasal obstruction using the same 10-cm VAS as was used by the blinded physicians. A change in CPAP use from the 2-week period before treatment up to 4 weeks after treatment (objectively measured with an embedded counter), as well as CPAP adherence (mean CPAP time per night/mean sleep time per night), were reported by patients' diaries over the same time periods as CPAP meter readings. Subjective CPAP tolerance (VAS) and sleep propensity changes were measured by the Epworth Sleepiness Scale.[13–15] Health status changes were measured by the SF-36 domain scores pre- and post-treatment. All VAS used a standard 10-cm scale with anchors described in Table I.

Statistical Analyses

Baseline, treatment, and outcome variables of the two groups were compared with Student *t* test for continuous normal variables, the Mann-Whitney test for continuous nonparametric variables, and the Fisher's Exact Test for dichotomous variables. The paired *t* test for continuous normal variables and the sign test for continuous nonparametric variables were used to test the hypothesis that changes within groups were equal to zero. For nasal obstruction, right and left sides were scored separately and averaged for each patient's overall nasal obstruction score, which was then used for analyses.

All results regarding continuous variables are expressed as mean ± standard deviation. The data were analyzed with Intercooled Stata 6.0 software (Stata Corp., College Station, TX). All statistical tests used a two-tailed significance level because it was plausible that treatment could worsen symptoms in the 4-week post-treatment period. P value $<.05$ was considered statistically significant.

RESULTS

All subjects who entered the protocol (N = 22) completed the study. There were no complications or untoward reactions to treatment. Table II contains baseline data and Table III displays treatment data of the two groups. The subjects were middle-aged, overweight, and had moderate to severe SDB by respiratory disturbance index (RDI).[16] The groups were statistically different only with respect to baseline nasal obstruction assessed by the unblinded examiner and treatment energy delivered.

Table IV summarizes the nasal obstruction data (VAS) before and after treatment in the control and intervention groups. Tabulations are presented for the patient, blinded physicians, and unblinded physician assessments. The negative values for all tabulations in the columns headed "change" indicate there was an observed mean improvement by all assessors in both the control group and the intervention group. These VAS improvements in the control group represent the *placebo effect*: -1.7 cm (95% confidence interval [CI], -4.1, 0.6) for patient, -1.5 cm (95% CI, -3.4, 0.3) for blinded examiners, and -0.8 cm (95% CI, -2.7, 1.2) for unblinded examiner assessments. The true treatment effect is the *difference* in improvement between the intervention group and control group (placebo effect) shown in Table IV. Only the *unblinded* physician assessment demonstrated a statistically significant improvement in treated patients over control subjects.

The effects of turbinate treatment on CPAP measures (objective use, self-reported adherence, and subjective tolerance) are displayed in Table V. For all CPAP measures, a negative change indicates a decrease in CPAP use, adherence, or tolerance. The treatment effect is estimated by the difference in these mean changes between the intervention and placebo groups. CPAP adherence had a statistically significant improvement in treated patients over control subjects. The effects of turbinate treatment on daytime sleep propensity (ESS) and the vitality domain of the SF-36 (most pertinent to SDB) are summarized in Table VI. No statistically significant improvements were noted with these measures or with any of the other SF-36 domain scores.

DISCUSSION

Our primary hypothesis was that TCRF turbinate treatment would improve nasal obstruction and thus the effectiveness of CPAP for patients with SDB having problems with nasal congestion secondary to turbinate hypertrophy. This study was by design, a pilot study, hence, not powered with sufficient patient numbers to be a definitive study. As a pilot study it was designed to control for key biases, most importantly the placebo effect and examiner bias, to estimate the *real* effect of TCRF treatment. The three main results from this pilot study are: 1) TCRF treatment of turbinates appears to have a beneficial effect, 2) appropriate study design is critical in assessing treatment, and 3) a future definitive study is feasible.

Effect of TCRF Treatment

The point estimates consistently suggest a beneficial treatment effect from TCRF turbinate treatment. Table IV summarizes the degree of nasal obstruction, and all three assessors consistently found greater improvement in the treatment group over the placebo group. Similarly, the point estimates of the CPAP measures all suggest improvements in the treatment group over the placebo

TABLE I.
Visual Analog Scale Anchors*.

Measure	Minimum Anchor (0)	Maximum Anchor (10)
Nasal obstruction†	No obstruction	Complete obstruction
CPAP tolerance	Unable to tolerate or use	Easily tolerated and use all 7 nights per week
Pain	No pain	Intense pain

*All scales on a 10-cm unmarked line.
†Same scale for patient, blinded examiner, and unblinded examiner assessments.
CPAP = continuous positive airway pressure.

TABLE II.
Baseline Data.

Variable	Control Group (N = 5)	Intervention Group (N = 17)	*P* value*
Demographic variables			
Gender (% female)	60%	41%	.62
Age (y)	51 ± 7	55 ± 12	.46
Clinical variables			
Body mass index (kg/m^2)	31 ± 6	29 ± 4	.39
Polysomnography variables			
Apnea-hypopnea index (events/hr)	25 ± 18	35 ± 26	.39
Apnea index (events/hr)	6.2 ± 7.8	17 ± 21	.46
Minimum oxygen saturation (%)	83 ± 11	80 ± 8	.55
Awake oxygen saturation (%)	94 ± 2	95 ± 2	.51
Sleep & CPAP variables†			
CPAP duration			
Total (mo)	6.0 ± 3.3	14 ± 19	.87
New, w/counter (days)	15 ± 2	15 ± 2	.48
CPAP pressure (cm H_2O)	8.8 ± 1.3	8.0 ± 2.2	.45
CPAP use (min/night): diary	234 ± 133	318 ± 93	.12
Mean sleep time (min/night): diary	382 ± 30	390 ± 62	.78
Blocked nose on CPAP‡ (% Yes)	100%	88%	1.00
Outcome variables before intervention			
Nasal obstruction (VAS§), assessed by			
Patient	5.6 ± 0.8	5.1 ± 1.8	.52
Blinded examiner	6.8 ± 2.2	7.0 ± 2.1	.88
Unblinded examiner	7.3 ± 0.7	8.5 ± 0.8	.01
CPAP use (min/night): counter	259 ± 146	346 ± 125	.20
CPAP adherence (CPAP min per night/sleep min per night): diary	0.61 ± 0.35	0.82 ± 0.20	.41
CPAP tolerance (VAS§)	4.3 ± 3.6	4.9 ± 2.8	.72
Epworth Sleepiness Scale	8.8 ± 2.8	10.5 ± 4.8	.47
SF-36 Vitality Domain	29 ± 13	41 ± 20	.23

**P* value based on two-tailed *t* test (normal) or Mann-Whitney test (nonparametric) for equality of means, or Fisher exact test for homogeneity (gender, blocked nose on CPAP).
†All sleep and CPAP baseline summaries pertain to the 2-week period before treatment, except where specified otherwise.
‡At initiation of CPAP.
§See Table I for details of visual analog scales.
CPAP = continuous positive airway pressure; VAS = visual analog scale.

group (Table V). Small improvements in sleepiness were also noted (Table VI). Furthermore, the magnitude of the clinical treatment effects were approximately 10% for nasal obstruction (0.8–0.9 on VAS), an increase in CPAP use by 32 minutes, 10% for CPAP adherence (0.10), and >20% for CPAP tolerance (2.4 cm by VAS).

These small but positive findings may be far more relevant in patients with SDB than previously appreciated. Support for this is seen in Poiseuille's law which states that flow through a tube is proportional to the fourth power of the radius or to the square of the cross-sectional area of the tube.[17] Thus, a 10% increase in the cross-sectional area of the nasal passage would result in a 21% increase in airflow through the nose. In this study, the blinded and unblinded examiners' assessment of nasal obstruction was based only on visual examination and rhinoscopy, thus roughly estimating cross-sectional area. Resistance in a tube is also inversely proportional to the fourth power of the radius. King et al.[18] recently reported on 12 normal healthy, non-obese subjects who were restricted to nasal breathing (through a nasal CPAP mask) at a subatmospheric pressure of -10 cm H_20 while sleeping

TABLE III.
Treatment Data: Temperature-Controlled Radiofrequency Energy.

Variable	Control Group (N = 5)	Intervention Group (N = 17)	*P* value*
Energy per turbinate (J)	0 ± 0	415 ± 37	<.001
Time per turbinate (sec)	31 ± 3	39 ± 12	.24
Pain (VAS†)	2.3 ± 1.7	1.9 ± 1.7	.62

**P* value based on two-tailed *t* test (normal) or Mann-Whitney test (nonparametric) for equality of means.
†Visual analog scale (10 cm) with anchors "no pain" and "intense pain."
VAS = visual analog scale.

TABLE IV.
Nasal Obstruction*: Comparison of Patient, Blinded Examiner, and Unblinded Examiner.

Assessor	Control Group (N = 5)				Intervention Group (N = 17)				Comparison of Changes Between Groups		
	Pre-Tx†	Post-Tx‡	Change§	*P* Value‖	Pre-Tx†	Post-Tx‡	Change§	*P* Value¶	Treatment Effect§#	95% CI**	*P* Value**
Patient	5.6 ± 0.8	3.9 ± 1.6	−1.7 ± 1.9	.11	5.1 ± 1.8	2.6 ± 1.8	−2.5 ± 2.5	.001	−0.8	(−3.3, 1.8)	.55
Blinded MD	6.8 ± 2.2	5.3 ± 1.6	−1.5 ± 1.5	.08	7.0 ± 2.1	4.6 ± 2.1	−2.4 ± 1.5	<.001	−0.9	(−2.4, 0.7)	.28
Unblinded MD	7.3 ± 0.7	6.5 ± 1.2	−0.8 ± 1.6	.32	8.5 ± 0.8	4.7 ± 1.8	−3.8 ± 1.8	<.001	−3.0	(−4.9, −1.1)	.004

*Nasal obstruction: visual analog scale (10 cm) with anchors "no obstruction" and "complete obstruction."
†Pre-Tx = immediately before treatment.
‡Post-Tx = 4 weeks after treatment.
§Negative value denotes improved nasal obstruction.
‖*P* value tests the (null) hypothesis: the change in the control group equals zero (paired *t* test, two-tailed).
¶*P* value tests the (null) hypothesis: the change in the intervention group equals zero (paired *t* test, two-tailed).
#Treatment effect = change in intervention group—change in control group (placebo effect).
***P* value tests the (null) hypothesis: the change in the control group equals the change in the intervention group (two sample *t* test, two-tailed).
Tx = treatment; CI = confidence interval; MD = physician.

for 2 nights (-10 cm H_20 is the upper limits of *normal* during sleep[19]). During 2 nights restricted to this negative nasal pressure, subjects developed obstructive respiratory events, associated oxyhemoglobin desaturations, sleep stage disruption, frequent arousals, and a mean RDI of 32.6 and 37.8, respectively. During control nights before and after the test nights, their mean RDI was 0.4 and 0.0, respectively. Thus, it appears that a small increase in negative nasal pressure may contribute significantly to the severity of SDB.

Most of the benefits seen in our study do not reach statistical significance because this study was not powered for that purpose. This study had just 20% power to detect a statistically significant effect with our primary outcome (i.e., 20% probability of achieving statistical significance if there was a real effect) (Table VII). While a *P* value of .28 for treatment effect on primary outcome (Table IV) does not achieve our statistical standard to reject the null hypothesis, this *P* value still (weakly) supports rejection of the null hypothesis.[20] This is especially true in light of the biologic plausibility of effect,[21] case series suggesting an effect,[22–26] and the consistency of effect among our primary and secondary outcomes (Tables IV–VI). The bottom line is that a study to confirm definitively (statistically) a treatment effect would require a greater sample size than was recruited for this pilot study (see *Future Definitive Study Is Feasible* below). To reject the existence of a real treatment effect because the *P* value is >.05 may risk misinterpretation of the statistics (type II error).

Finally, the effect of TCRF turbinate treatment may be greater than we report. We began this study early in our experience with TCRF turbinate treatment and, hence, used a conservative RF dose (mean, 415 J/turbinate). Additional treatment sessions and slightly higher RF energy levels may have enhanced the clinical out-

TABLE V.
CPAP: Comparison of Objective Use, Self-reported Adherence, and Subjective Tolerance.

CPAP Measure	Control Group (N = 5)				Intervention Group (N = 17)				Comparison of Changes Between Groups		
	Pre-Tx[a]	Post-Tx[b]	Change[c]	*P* Value[d]	Pre-Tx[a]	Post-Tx[b]	Change[c]	*P* Value[e]	Treatment Effect[cf]	95% CI	*P* Value[g]
Use[h]	259 ± 146	239 ± 149	−20 ± 33	.25	346 ± 125	358 ± 86	12 ± 82	.57	32	(−21, 84)	.22
Adherence[i]	0.61 ± 0.35	0.57 ± 0.36	−0.04 ± 0.05	.38	0.82 ± 0.20	0.88 ± 0.13	0.06 ± 0.12	.007	0.10	[j]	.03
Tolerance[k]	4.3 ± 3.6	3.3 ± 1.6	−1.0 ± 3.2	.51	4.9 ± 2.8	6.3 ± 2.7	1.4 ± 4.0	.17	2.4	(−1.7, 6.6)	.23

[a]Pre-Tx = the time period 2 weeks before treatment for use and adherence. Pre-Tx = immediately before treatment for tolerance.
[b]Post-Tx = the time period 2–4 weeks after treatment for use and adherence. Post-Tx = 4 weeks after treatment for tolerance.
[c]Negative value denotes less CPAP use, adherence, or tolerance.
[d]*P* value tests the (null) hypothesis: the change in the control group equals zero (paired *t* test or sign test, two-tailed).
[e]*P* value tests the (null) hypothesis: the change in the intervention group equals zero (paired *t* test or sign test, two-tailed).
[f]Treatment effect = change in intervention group—change in control group (placebo effect).
[g]CI: confidence interval.
[g]*P* value tests the (null) hypothesis: the change in the control group equals the change in the intervention group (two sample *t* test or Mann-Whitney test, two-tailed).
[h]Use: objective meter (min/night).
[i]Adherence: self-reported log of CPAP min per night/sleep minutes per night.
[j]Nonparametric test of comparison does not yield confidence interval.
[k]Tolerance: visual analog scale (10 cm) with anchors "unable to tolerate or use" and "easily tolerated and use all 7 nights per week."
CPAP = continuous positive airway pressure; Tx = treatment; CI = confidence interval.

TABLE VI.
Subjective Sleep Disordered-Breathing Outcomes.

	Control Group (N = 5)				Intervention Group (N = 17)				Comparison of Changes Between Groups		
Outcome Measure	Pre-Tx*	Post-Tx†	Change‡	*P* Value§	Pre-Tx*	Post-Tx†	Change‡	*P* Value‖	Treatment Effect‡¶	95% CI	*P* Value#
ESS**	8.8 ± 2.8	8.6 ± 1.8	−0.2 ± 1.3	.75	10.5 ± 4.8	9.3 ± 4.6	−1.2 ± 3.6	.18	−1.0	(−3.2, 1.2)	.34
SF-36 Vitality††	29 ± 13	40 ± 10	11 ± 12	.11	41 ± 20	44 ± 23	3 ± 20	.60	−8	(−23, 7)	.45

*Pre-Tx = immediately before treatment.
†Post-Tx = 4 weeks after treatment.
‡Negative value denotes improved ESS or worse SF-36.
§*P* value tests the (null) hypothesis: the change in the control group equals zero (paired *t* test, two-tailed).
‖*P* value tests the (null) hypothesis: the change in the intervention group equals zero (paired *t* test, two-tailed).
¶Treatment effect = change in intervention group—change in control group (placebo effect).
#*P* value tests the (null) hypothesis: the change in the control group equals the change in the intervention group (two sample *t* tests, two-tailed).
**Epworth Sleepiness Scale (0–24 scale).
††SF-36 Vitality Domain Score (0–100).
Tx = treatment; CI = confidence interval; ESS = Epworth Sleepiness Scale.

comes. In addition, the full benefit may not have been realized at a 4-week end point.

Study Design Is Critical

Several study design elements that are critical for evaluating treatment outcomes were used in this study. While a case series can only generate a hypothesis about treatment effect, a controlled trial is necessary to test this hypothesis.[7] Placebo control neutralizes a key bias, namely the placebo effect, which is the effect attributable to the expectation that the treatment will succeed. Double-blinding controls for unintentional bias introduced by the investigator, a potentially profound source of misleading data, and prevents either the patient or investigator from unblinding the other (as may happen in a single-blinded study). Randomization controls for known and unknown confounders of the treatment effect by preventing preferential selection (intentionally or unintentionally) of subjects into one group or the other. Lastly, the choice of outcome measure influences the assessment of treatment effect.

This pilot study highlights the importance of placebo control, blinding, and outcomes measurement selection. In this study, the placebo was identical to active treatment in all respects except that it did not include actual delivery of RF energy (Table III). Table IV reveals the placebo effect. Placebo patients rated a mean improvement by VAS of 1.7 cm (-1.7 cm; 95% CI, -3.4, 0.3) on nasal obstruction. This placebo effect accounts for more than half of the total improvement of 2.5 cm seen in the intervention group. This finding highlights the importance of a placebo control: without it, we would have falsely ascribed a much greater improvement and statistical significance to treatment. Even the blinded examiners' assessment of nasal obstruction demonstrated a significant placebo effect of 1.5 cm (VAS). There is a subjective element to the examiners' estimation of visible obstruction, and with most of the patients (N = 17) having received active treatment, blinded examiners may have had a tendency (bias) to see improvement in everyone. This explanation is supported by the fact that the unblinded examiner, who knew these patients received no active treatment, found less placebo effect of 0.8 cm (VAS). Although it is possible that there is a real effect with the placebo (i.e., the turbinate actually shrinks), it is less plausible biologically. In addition, the only truly objective measure (CPAP use recorded by meter) showed no improvement in the placebo group (Table V).

Table IV also reveals the effect of investigator blinding. The unblinded investigator found more than a threefold greater treatment effect of 3.0 cm (VAS) than the blinded investigators of 0.9 cm (VAS). The subconscious

TABLE VII.
Power of Pilot Study (N = 22).

Outcome	Measure	Observed Effect Size*	Power†
Nasal obstruction: blinded examiner	VAS (cm)	0.9	20%
Nasal obstruction: patient	VAS (cm)	0.8	11%
CPAP use	Objective meter (min)	32	24%
CPAP adherence	Diary (CPAP min/sleep min)	0.10	76%
CPAP tolerance	VAS (cm)	2.4	29%
Epworth Sleepiness Scale	Scale (0–24)	1.0	17%

*All listed effects sizes represent magnitude of improvement in intervention group over control group.
†Power to detect the observed effect size for each outcome variable at $\alpha = 0.05$ (two-tailed) significance level.
VAS = visual analog scale; CPAP = continuous positive airway pressure.

bias resulting from expectation of treatment effect can be profound. These results indicate the importance of blinding the examiner or outcomes assessor to treatment group. Even if double blinding cannot be used because treatment is obvious (e.g., because of surgical changes), single-blinding of the outcomes assessor may still be feasible.

Comparison of our outcomes measures demonstrates the importance of defining an appropriate primary outcome. While TCRF treatment appears to have a positive clinical effect on nasal obstruction, CPAP use, and SDB symptoms (sleepiness), we saw no meaningful beneficial effect on general health status. The SF-36 inquires about health status and function deficits over the previous 4 weeks, so the 4-week post-treatment questionnaire covered the time from *right after* treatment to the time of the questionnaire. Because we expect increased obstruction (swelling) for 1 to 2 weeks post-treatment, the SF-36 may be measuring the transient acute undesirable effects of treatment rather than the expected benefit thereafter. Furthermore, the SF-36 is a general instrument that probes issues not likely affected directly by nasal obstruction (e.g., measures include mobility, physical function, emotional function, bodily pain, and so on). Dramatic improvement in sleep-disordered breathing symptoms by improving CPAP use could improve health and functional status, but one would be more likely to detect these benefits with an SDB-specific instrument that focuses on issues important to patients with SDB (vitality, concentration, mood, productivity, and so on) rather than a generic instrument. As noted, the timing of assessment will also influence the results.

Future Definitive Study Is Feasible

Unlike many invasive procedures, TCRF turbinate treatment offers a unique opportunity to perform randomized, double-blind, placebo-controlled clinical trials. First of all, randomization is ethical. TCRF treatment creates minimal morbidity, so randomization to this treatment is acceptable. In fact, some may argue that it is unethical to treat patients with unproven therapy when a definitive trial is feasible to establish treatment efficacy.[27] Because TCRF treatment is not yet the standard of care, placebo assignment does not deny patients standard treatment. Although there are case series to suggest that TCRF treatment improves nasal congestion, there are no studies demonstrating its effectiveness in improving CPAP adherence and SDB outcomes. This lack of data leaves clinical equipoise[28] on whether the potential treatment benefit is worth the risk of side effects, although minimal, and the costs of TCRF treatment.

It is feasible to create an excellent placebo of TCRF treatment and maintain double-blinding (see *Methods and Materials*). Every step of the TCRF procedure can be performed with only the "active ingredient" (the actual RF energy) withheld unbeknownst to the patient and treating physician. TCRF treatment effect is subtle, so there are no obvious distinguishing characteristics of treated patients. It is helpful to blind the treating physicians, even if they are not assessing outcomes, because they may inadvertently inform patients of their treatment group, thus spoiling the *placebo* control.

These pilot data suggest that it would be feasible to conduct a future definitive study with adequate power to rule in or rule out an important treatment effect. Thirty-eight subjects in each group (total N = 76) will provide 90% power to test the hypothesis that TCRF treatment would improve nasal obstruction by 10% on the VAS as assessed by a blinded examiner, testing at a one-tailed significance level of $\alpha = 0.05$ (Table VIII). Because this pilot study suggests a beneficial treatment effect, it justifies one-tailed significance testing in the future. This sample size would also provide adequate power to detect important changes in CPAP measures and ESS (Table VIII).

In addition to sample size, there are other limitations to this pilot study that could be improved in a future definitive follow up study. It will be preferable to provide more complete treatment with additional RF energy or more sessions. Ideally, all subjects would get identical CPAP devices with mask adjustments optimized individually. Outcomes assessment could be improved by including a validated objective measure of nasal obstruction (e.g., acoustic rhinometry[29,30] or rhinomanometry[31,32]), a covert CPAP meter, CPAP pressures, and SDB-specific quality-of-life measures. Ideally, longer follow-up is

TABLE VIII.
Power of Proposed Study (N = 76*).

Outcome	Proposed Effect Size	Power to Detect Proposed Effect Size†	Effect Size Detectable With 80% Power‡
Nasal obstruction: blinded examiner (VAS cm)	1.0	90%	0.9
Nasal obstruction: patient (VAS cm)	1.0	62%	1.3
CPAP use (meter min)	30 min	67%	36 min
CPAP adherence (diary CPAP min/sleep min)	0.10	99%	0.05
CPAP tolerance (VAS cm)	2.0	77%	2.1
Epworth Sleepiness Scale (0–24 scale)	2.5	99%	1.6

*Sample size required to have 90% power to detect proposed effect size (1.0 cm on 10-cm VAS) of the primary outcome (nasal obstruction assessed by blinded examiner) at $\alpha = 0.05$ (one-tailed) significance level.

†Power to detect proposed effect size for each outcome variable at $\alpha = 0.05$ (one-tailed) significance level. Future one-tailed significance testing justified in Tables IV–VI.

‡Effect size detectable with 80% Power at $\alpha = 0.05$ (one-tailed) significance level.

VAS = visual analog scale; CPAP = continuous positive airway pressure.

needed to more accurately assess the outcomes and changes resulting from healing. Evaluation at 3, 6, and 12 months with long-term reassessments at 2 and 3 years would help to establish long-term treatment effects.

CONCLUSION

TCRF treatment appears to have benefit for nasal obstruction in patients with CPAP, as assessed by a randomized, double-blind, placebo-controlled clinical pilot trial. Definitive results will depend on a study with adequate power to confirm this result statistically. TCRF treatment provides a rare opportunity to conduct a well-designed rigorous study of a surgical treatment. This pilot study demonstrates that a future definitive study is feasible.

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