# Multicenter Study of Noninvasive Radiofrequency for Periorbital Tissue Tightening

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# Multicenter Study of Noninvasive Radiofrequency for Periorbital Tissue Tightening

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**Background and Objectives:** This 6-month study evaluated the efficacy and safety of treatment with a nonablative radiofrequency (RF) device. **Study Design/Materials and Methods:** Eighty-six subjects received a single treatment with the ThermaCool TC™ System (Thermage, Inc., Hayward, CA) and were evaluated for 6 months after treatment. **Results:** Independent scoring of blinded photographs resulted in Fitzpatrick wrinkle score improvements of at least 1 point in 83.2% (99/119) of treated periorbital areas. Treating physicians, without reference to pre-treatment photographs, noted improvements in 28.9% (48/166) of treatment areas. Fifty percent (41/82) of subjects reported being satisfied or very satisfied with periorbital wrinkle reductions. Objective photographic analysis showed that 61.5% (40/65) of eyebrows were lifted by at least 0.5 mm. Rates and duration of edema/erythema were very low (e.g., vs. ablative procedures). Overall 2nd-degree burn incidence was 0.36% (21 per 5,858 RF applications). Three patients had small areas of residual scarring at 6 months. **Conclusions:** A single treatment with this RF tissue tightening (RFTT) device produces objective and subjective reductions in periorbital wrinkles, measurable changes in brow position, and acceptable epidermal safety. These changes were indicative of a thermally induced early tissue-tightening effect followed by additional tightening over a time course consistent with a thermal wound healing response. Lasers Surg. Med. 33:232-242, 2003. © 2003 Wiley-Liss, Inc.

**Key words:** nonablative; noninvasive; rhytids; ThermaCool; radiofrequency; skin tightening; skin contraction; tissue contraction; tissue tightening

## INTRODUCTION

Over the past several years, laser technologies have replaced chemical peels and dermabrasion as the treatment of choice to improve photodamaged skin. Resurfacing of the facial skin with $CO_2$ or erbium:yttrium-aluminum-garnet (Er:YAG) lasers effectively heats and ablates damaged tissue, causing underlying collagen contraction and new collagen formation that is critical for tissue tightening and wrinkle reduction [1-3]. Although the ablative laser techniques are associated with impressive efficacy in reducing periorbital wrinkles and tightening sagging skin, dermabrasion-type side effects following laser surgery are common [4]. Erythema occurs in practically all patients undergoing $CO_2$ procedures; the healing time usually lasts 3 months but may persist up to 12 months after some procedures. Risk of pigmentary alteration, infection, dermatitis, and scarring are other well-known drawbacks [4-6].

Enhancements in laser design and experience of the aesthetic procedure specialist can somewhat minimize the risk of injury with the ablative techniques [7]. Nonablative technologies have been developed in an effort to reduce complications, minimize perioperative pain, and shorten the healing time by creating a dermal wound without ablating the epidermis [8]. Examples of these newer noninvasive technologies include CoolTouch infrared laser (1,320 nm), pulsed dye laser (585, 595 nm), intense pulsed light sources (585-1,100 nm), Nd:YAG (1,064 nm), Smoothbeam infrared laser (1,450 nm diode), ultrasound, and microdermabrasion [9,10]. While the incidence of adverse effects is unquestionably lower with nonablative techniques, the cosmetic improvement is subtle and/or inconsistent, and often requires serial treatments over a 6- to 12-month period [9-13].

Radiofrequency tissue tightening (RFTT) is a recently introduced alternative to nonablative laser technology. Early low-energy modifications of traditional ablative RF electrosurgery units have been used with limited success for cosmetic purposes to achieve superficial dermatological changes [14,15]. More recently, a nonablative RFTT device

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(ThermaCool TC™ System [Thermage, Inc., Hayward, CA]) was developed especially for tightening deeper dermal structures without epidermal damage [10,16]. This new device uses a proprietary capacitive coupling method to transfer higher energy fluences through skin to a greater volume of dermal tissue than do nonablative lasers, while protecting the epidermis. Unlike lasers, which convert light to heat and target specific superficial structures or chromophores (selective photothermolysis), RF produces heat when the tissue's electrical resistance converts the electric current to thermal energy deeper within the dermis [10]. Moreover, unlike standard RF devices that concentrate energy at single-dimension points or along two-dimension edges, this new RFTT device uniformly disperses the energy to three-dimensional volumes of tissue at controllable depths. Initial collagen denaturation within these thermally modified deep tissues is thought to be the mechanism for immediate tissue contraction; subsequent neocollagenesis then further tightens the dermal tissue and reduces wrinkles [17]. The epidermis is protected with controlled cryogen cooling before, during, and after volumetric RF tissue heating.

Animal studies have documented that this RFTT device can achieve dermal heating as shallow as the papillary dermis or as deep as the subcutaneous fat [10]. Safety evaluations of this RF device on human abdominal skin have demonstrated a low incidence of transient side effects; histological analysis of the tissue verified minimal signs of scarring as well as preservation of the epidermis with fibroplasia and other indicators of increased collagen formation [16]. Skin tightening is also thought to be the main mechanism of action leading to the eyelid elevation that has been reported with this RF technology in a small series of patients [9]. Preliminary reports on the use of this device for tightening of facial skin (including periorbital wrinkles and acne scars) have been promising, with only 2 of 45 subjects (4.4%) presenting with transient 2nd-degree burns (edema and/or erythema) in 6 of 4,147 total applications (0.1%) [18].

The primary purpose of this multicenter clinical study was to evaluate the efficacy and safety of a single treatment with the RFTT device for the reduction of periorbital wrinkles in order to achieve FDA clearance for an established aesthetic indication. An additional interest of the investigators and the sponsoring company was to characterize the objective and subjective clinical effects of both short-term tissue tightening and subsequent additional tightening due to wound healing over the full course of the study. The study integrated a variety of evaluations (e.g., subjective investigator assessment, a patient questionnaire, and blinded photograph review) in an attempt to assess even subtle clinical changes over the 6-month study period.

## MATERIALS AND METHODS Study

### Design

This blinded, multicenter (IRB-approved) study evaluated the efficacy and safety of a nonablative nonlaser RF based device for the treatment of periorbital wrinkles or skin laxity. Each subject received a single course of RF treatment with a standardized algorithm. Investigators evaluated treatment efficacy with the Fitzpatrick Wrinkle Classification System (FWCS), and subjects reported on their overall satisfaction and perceptions at 2, 4, and 6 months. Assessment of wrinkle improvement also included review of a series of baseline and 2-, 4-, and 6-month photographs for each subject; these blinded photographs were separately scored with the FWCS by three independent clinicians, including two facial plastic surgeons and a dermatologic surgeon. In addition, 4- and 6-month photographs were compared with baseline photographs using an objective technique to measure eyebrow lift. During their clinic visits (within 24-72 hours and at 1, 2, 4, and 6 months), subjects were also evaluated for potential adverse effects.

### Study Population

To ensure a diverse mix of subject demographics and clinician experience, the study enrollment goal was set at approximately 80-100 subjects from six separate and geographically diverse practice settings. Enrollment criteria called for subjects of any skin type to be between the ages of 35 and 70 years and to have a desire for improved appearance of periorbital wrinkles or skin laxity in the periorbital area. All surgeons were in private practice and had extensive experience with laser treatments for skin lesion removal or skin resurfacing. Major exclusion criteria included blepharoplasty or chemical peel treatments within 1 year, collagen implants or usage of botulinum toxin type A within 6 months, or recent usage of retinoid either orally (6 months) or topically (2 weeks). Subjects with previous laser surgery were eligible only if the procedure had occurred at least 1 year prior to enrollment.

### RF Device

The ThermaCool TC System heats tissue using a proprietary method of coupling RF to skin by a thin capacitive membrane that distributes RF energy over a volume of tissue beneath the membrane surface. A cryogen system simultaneously cools the epidermal surface for protection. This combination of deep volumetric tissue heating and surface cooling allows sustained delivery of higher energy fluences in a single treatment. The prototype device used in this clinical trial is functionally similar to the device currently marketed as the ThermaCool TC system, but lacks many of the sophisticated features and controls that greatly enhance the usefulness and simplicity of the commercial unit.

The major components of the device include (1) an RF generator producing a 6-MHz alternating-current RF signal, the energy level of which is set by the clinician; (2) a handpiece for directing the RF energy to the skin, delivering cooling cryogen spray, and monitoring temperature, pressure, and RF feedback; (3) an electrode treatment tip, for transferring RF energy to skin and serving as a membrane for contact cooling; and (4) a cooling module that feeds cryogen through a controlled valve on the handpiece

to the tip's contact cooling membrane. The system components are integrated with an imbedded Pentium"-based computer. User controls and a video screen for read-out of procedure data are located on the generator panel. Like conventional RF tissue heating devices, tissue heat is generated based on tissue's natural resistance to the movement of electrons within an RF field (Ohm's law), rather than photon absorption. As with lasers, the energy output can be stated in terms of joules as calculated by: impedance Z (ohms (S2)) to the movement of electrons creates heat (joules (J)) relative to the amount of current I (amps (A)), and time t (seconds) that current is delivered to tissue.

Energy (J) = $7^2$ x Z x t.

The distinguishing tissue-heating feature of the test device is the method of coupling of RF to the skin with a capacitive coupling membrane instead of a standard RF conducting electrode. This capacitive coupling method transforms RF to a volumetric or tissue "zone" heating device, rather than a concentrated "point" heating source as characterized by standard RF electrode heating devices such as a bovie. This unique volumetric heating method allows large amounts of energy (up to 220 J per $cm^2$) to be distributed in a volume of tissue beneath the skin, without coagulation or burning at the electrode-to-skin interface, though the upper limit for facial skin is about 140 J. It is this novel method of distributing large energy deliveries evenly over a three-dimensional volume of tissue that differentiates the test device from standard RF devices and available light-based devices. In addition, the uniform electrical field distribution present at depths of at least 2.5-mm potentially heats deeper structures to higher temperatures than other tissue heating sources.

**Treatment Procedure**

Before the treatment session, each subject submitted to a series of photographs and a baseline wrinkle evaluation. The periorbital region extending from the wrinkled area at the outer canthus to the area above the eyebrow was targeted for treatment [4]. Topical anesthetic (5% lidocaine) was applied to the designated treatment area, which was then occluded with clear dressing for at least 45 minutes before treatment. After the anesthetic was thoroughly and completely wiped off with a dry gauze, the treatment area was marked in ink with a grid pattern of contiguous squares, each square slightly larger than the selected RF treatment tip (0.25 or 1 $cm^2$). The area of the grid and the planned number of RF applications depended on the size of the targeted treatment area in each subject. At the discretion of the investigator, some subjects received nerve blocks into the forehead area just superior to the eyebrow; this was administered either before or during the procedure. A RF return pad was adhered to the subject's back to create a return path for RF travel. A proprietary coupling fluid was spread over the treatment area to enhance thermal and electrical contact with the treatment tip.

Clinicians treated each ink-grid square of the target area with a separate application from the RF tip, resulting in approximately 40-80 RF applications per patient. Each application consisted of three continuous and automatic phases: (1) cryogen pre-cooling, (2) simultaneous RF heating and cryogen cooling, and (3) cryogen post-cooling. A specific combination of treatment parameters that included the RF energy level, energy "on" time, and cooling rate for each application was initially set by the clinician by choosing 1 of 9 possible treatment level settings; the settings correlate with a range of 52-220 J delivered through the 1 $cm^2$ treatment tip surface. The choice of setting was determined mostly by the location and thickness of the skin directly within each targeted grid square. Lower fluences were used for areas directly over thinner wrinkled skin while higher fluences were selected for all other areas where a maximal tightening effect was desired. In addition, clinicians adjusted RF levels or upper limits according to subject pain tolerance during the procedure.

**Efficacy Outcomes**

For objective wrinkle evaluations, photographs obtained at baseline were compared with photographs taken at the 2-, 4-, and 6-month follow-up visits. Five views of the face were taken at each photographic session: front, 3/4 left, 3/4 right, full left, and full right. All photographs were masked to block investigator name, treatment settings, and treatment time. For each subject, sets of the masked photographs taken from the side angles but at different timepoints were then arranged in random (i.e., nonchronological) side-by-side fashion on a storyboard, and the three independent reviewers rated the periorbital wrinkles on each photograph according to the FWCS. After unblinding, the scores were compared to determine inter-rater reliability. Patient effect (outcome) was classified as improved or not on the left and right sides at different timepoints.

Investigator in-clinic evaluations of treatment outcome were assessed using the FWCS (Table 1). Wrinkles were classified into the nine Fitzpatrick subgroups by the investigator at baseline and then again during the posttreatment clinic visits at 2, 4, and 6 months. Clinicians did not refer to pre-treatment photographs while making posttreatment wrinkle assessments. For each subject, wrinkle improvement (reduction of subgroup score > 1), no change, or worsening was calculated for each eye separately for each post-treatment clinical evaluation.

In accord with a post-hoc addendum to the study protocol, frontal photographs were also assessed objectively to determine the amount of forehead tissue tightening as evidenced by eyebrow lift above each eye. This assessment method was developed by clinical photographers and a research scientist at Thermage, Inc. One of the clinical photographers used Adobe PhotoShop 6.0 software to draw a horizontal reference line that intersected the apex of the inner canthus on each eye. On each side of the face, four measurements (at intervals of 1.5, 2.0, 2.5, and 3.0 cm outward from the inner canthus) were then made from this line up to the superior margin of the eyebrow. The average pre-treatment eyebrow values on each side were compared to the average post-treatment values at various timepoints. Measurements were recorded in 0.1 mm increments. Based

**TABLE 1. The Fitzpatrick Wrinkle Classification System (FWCS)**

| Class | Wrinkling | Score | Degree of elastosis |
|---|---|---|---|
| I | Fine wrinkles | 1–3 | Mild (fine textural changes with subtly accentuated skin lines) |
| II | Fine to moderate depth wrinkles<br>Moderate number of lines | 4–6 | Moderate (distinct popular elastosis [individual papules with yellow translucency under direct lighting] and dyschromia) |
| III | Fine to deep wrinkles<br>Numerous lines<br>With or without redundant skin folds | 7–9 | Severe (multipapular and confluent elastosis [thickened yellow and pallid] approaching or consistent with cutis rhomboidalis) |

on pre-trial sensitivity testing, the margin of measurement error in detecting any objective change in brow position was determined to be +/- 0.5 mm. Thus, patients whose average post-treatment eyebrow lift value was above the 0.5 mm sensitivity cutoff were classified as having objective evidence of tissue tightening. The average absolute value of lift was also reported. To meet the specifications of this validated methodology for measuring brow position, precise photographic conditions (including identical head positions and precise camera setup) were required. It was anticipated that many photographs would not be evaluable due to these procedural demands.

Subjects rated their overall satisfaction with the outcome at 2, 4, and 6 months after treatment by assigning a ranking of unsatisfied, neutral, satisfied, or very satisfied at each timepoint. They also rated their perception of skin tightness (looser, same, or tighter) and appearance (worse, same, or better) at 6 months after treatment. The RF browlifting effect was not specifically queried and, thus, was not captured in the patient satisfaction scoring.

### Safety Outcomes

With each RF application, the subject called out the level of procedural pain (on a 5-point scale where 0 = no pain and 4 = intolerable pain). Adverse events were also noted. Thermal injuries were classified by investigators as 1st degree (involving only the epidermis, and characterized by transient erythema and edema without blisters or a break in the skin); 2nd degree superficial or deep (involving destruction of epidermis as well as a variable portion of the dermis [superficial or deep], and characterized by blistering and scabbing that resolved in 1 month [superficial] or longer [deep]); or 3rd degree (involving destruction of the entire thickness of the skin resulting in scarring that did not spontaneously resolve). Investigators documented observations of signs and symptoms related to the treatment area immediately after and within 72 hours of treatment, and then again at 1, 2, 4, and 6 months post-treatment. The photographs used in the efficacy evaluation also provided documentation of reported adverse events.

## RESULTS

### Study Population

Of the 87 subjects enrolled into the study, 86 completed the RF treatment course. One subject dropped out just minutes after initiating RF treatment, citing extreme nervousness. Two subjects were lost to follow-up after 1 month, and another subject was lost to follow-up after 4 months. The number of subjects per clinic ranged from 9 to 20. The study population was fairly diverse in terms of age (mean 54 years) and skin type on the Fitzpatrick scale [19] (Table 2). Skin types were pre-dominantly Type II but ranged from Type I to Type IV. All nine subclasses of wrinkle classifications were represented in the study population at baseline, with an average investigator-assigned FWCS score of 4.7 (Table 3). There were 13 violations of protocol, including eight involving subjects who were enrolled and treated despite being over age 70 years. However, all 86 patients who completed treatment were the basis for all safety evaluations, and all 83 patients who completed 6 months of follow-up were the basis for all efficacy evaluations; full data were not available for all patients at all timepoints due to missing data on case report forms, missing or unevaluable photographs, or missed patient visits.

**TABLE 2. Subject Demographics**

| | Category | Number of subjects | Percentage of subjects evaluated |
|---|---|---|---|
| Gender | Female | 79 | 92 |
| | Male | 7 | 8 |
| Age group | <40 | 6 | 7 |
| | 41–50 | 28 | 33 |
| | 51–60 | 33 | 38 |
| | >60 | 19 | 22 |
| Ethnicity | Caucasian | 72 | 84 |
| | Hispanic | 13 | 15 |
| | Asian | 1 | 1 |
| Sun-reactive skin type | I | 7 | 8 |
| | II | 48 | 56 |
| | III | 23 | 27 |
| | IV | 8 | 9 |
| Prior treatments | Yes | 4 | 5 |
| | No | 82 | 95 |
| Smoking history | Yes | 16 | 19 |
| | No | 70 | 81 |

**TABLE 3. Fitzpatrick Wrinkle Classifications Assigned by Investigator for 86 Subjects at Baseline Clinical Visit**

| Classifications | | Assigned at baseline | |
|---|---|---|---|
| Class | Scores | Right | Left |
| I | 1 | 4 | 4 |
| | 2 | 7 | 7 |
| | 3 | 5 | 5 |
| II | 4 | 30 | 30 |
| | 5 | 13 | 12 |
| | 6 | 10 | 11 |
| III | 7 | 10 | 10 |
| | 8 | 5 | 5 |
| | 9 | 2 | 2 |

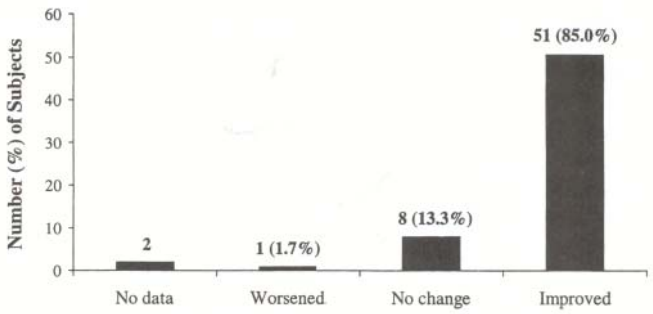


Fig. 2. Number of subjects showing improvement, no change, or worsening 6 months after a single RF treatment based on blinded independent review of photos: right side of face.

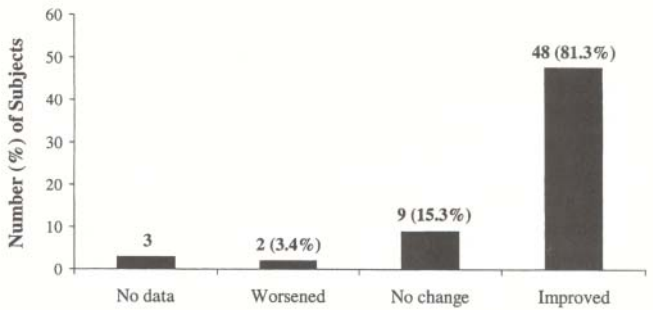


Fig. 3. Number of subjects showing improvement, no change, or worsening 6 months after a single RF treatment based on blinded independent review of photos: left side of face.

### RF Treatments

The average number of RF treatment applications per subject was 68 (range=23-114). The average energy setting for these applications was 16 (range =11-21) (Fig. 1). The amount of energy delivered at these settings was equivalent to approximately 58-140 J/cm$^2$ area of skin. The 1 cm$^2$ treatment tip was employed for almost all RF applications; two subjects received a few applications with the 1/4 cm$^2$ tip in addition to their main treatment with the standard-size tip. Of the 86 subjects completing an RF treatment course, 22 received a nerve block just superior to the eyebrows immediately prior to or shortly after initiation of RF treatment. The average RF setting for these 22 patients was similar to that of the overall patient population.

### Efficacy

At least one evaluable photograph was available for 62 of the 83 subjects at 6 months. The 6-month photographs were of poor technical quality or unavailable in 21 patients; only a single left or right side photograph was evaluable in five patients. The independent and blinded review of evaluable photographic results documented consistent and, in many patients, progressively increasing improvements in wrinkle scores over the full 6-month study period. At the interim 4-month timepoint, 79.1% (76/96) of treated periorbital areas showed >1 FWCS score improvement from baseline. A representative photograph of a subject with objective signs of wrinkle diminution after the single RF treatment is shown in Figure 4. Between the 4- and 6month photographic review, wrinkle improvements were maintained and, in several more subjects, became noticeable for the first time. In the 62 subjects for whom at least one evaluable photograph was available at 6 months, 83.2% (99/119) of treated periorbital areas showed a baseline-to-6month improvement in wrinkle scores. Results for the left and right sides are shown in Figures 2 and 3. Over this same half-year period, 14.3% (17/119) of treated areas had no change and 2.5% (3/119) worsened. Of the 99 areas showing objective improvement, 64.6% (64/99) of the left and right treated areas improved by one Fitzpatrick point, 31.3% (31/99) improved by two Fitzpatrick points, and 4.0% (4/99) improved by three or more Fitzpatrick points.

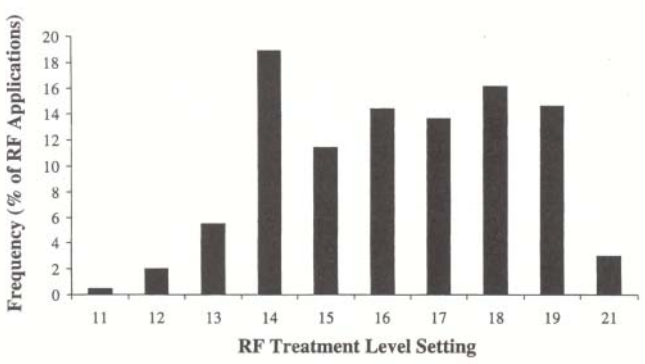


Fig. 1. Distribution of radiofrequency (RF) treatment levels in 86 subjects (1 cm$^2$ treatment tip only).

Investigator-assigned wrinkle scores were based on inclinic examinations at baseline, 2, 4, and 6 months; the investigators did not have access to photographs from previous visits. This subjective evaluation of treated left and right periorbital areas at 6 months showed that 92.8% (154/166) had either improved (i.e., by a decrease of at least one Fitzpatrick point) or remained the same (Table 4). Improvements of at least one Fitzpatrick point (e.g., from score 6 at baseline to score 5) were seen in 25.0% (37/148) of treated areas at 2 months, increasing to 28.9% (48/166) at

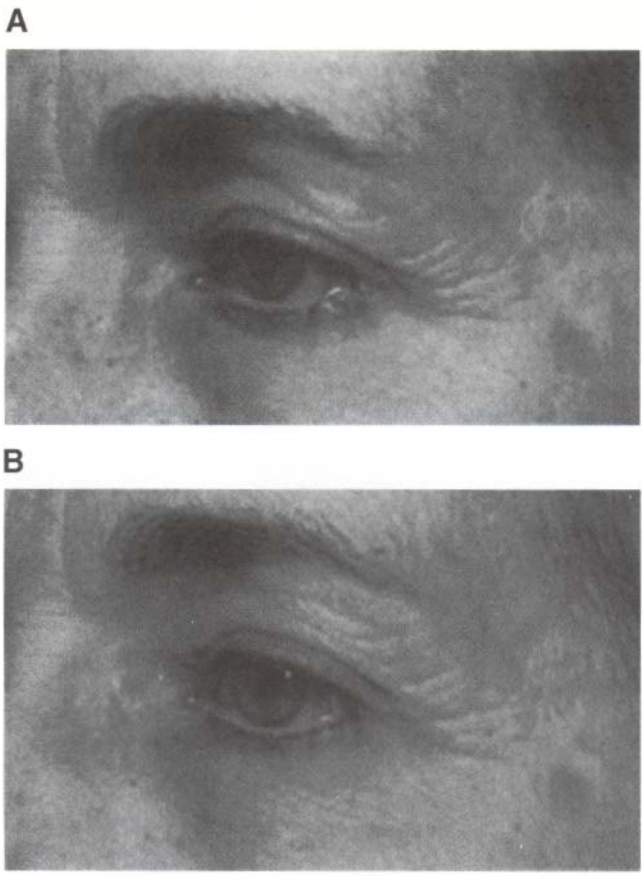


Fig. 4. Example of wrinkle reduction after RF treatment. A: Pre-treatment; (B) 4 months post-treatment. [Figure can be viewed in color online via www.interscience.wiley.com.]

6 months. Wrinkles had worsened in 7.2% (12/106) of the periorbital areas.

Computer-aided measurement of evaluable photographs for post-treatment eyebrow lift was conducted. To meet the specifications of this validated methodology for measuring brow position, precise photographic conditions (including identical head positions and precise camera setup) were required. As a result, only 60 subjects had paired beforeand-after pictures that qualified as evaluable for purposes of the brow measurement, 27 subjects with a 1- to 4-month photograph and 33 subjects with a 6-month photograph. Left and right sides were measured separately and in one subject, only one side of the photograph was suitable for computer analysis. Overall, 66.4% (79/119) of left or right eyebrows had an average lift that was greater than the predetermined minimum threshold for tissue tightening detection (>0.5 mm) from baseline to the time of the follow-up photograph. Average lift was 1.49 mm in all the right sides and 1.30 mm in all the left sides. Representative photographs of a subject with measurable eyebrow lift are shown in Figure 5. Overall, in those subjects with 6-month post-treatment photographs, 61.5% (40/65) of measured eyebrows were raised above the threshold of detection.

Treatment satisfaction data were available from 82 subjects at 6 months (Table 5). Overall, 50% (41/82) of these subjects reported they were satisfied or very satisfied with the treatment outcome, and similar percentages rated their skin to be tighter and their appearance as better. No data on patient satisfaction with the RF brow-lifting effect were collected.

**Safety**

Each subject's application-related pain scores (typically for about 34 applications per side) were averaged. The average pain score on each side was mild or moderate for most patients (Table 6). In those cases when early RF applications produced an uncomfortable level, the clinician could reduce the RF energy level for subsequent applications. Those subjects receiving nerve blocks reported no pain in almost all instances.

The most frequently noted treatment-related events were erythema (36.0% incidence immediately and 16.7% within 72 hours) and edema (13.9% immediately and 6.4% within 72 hours) (Table 7). By 1 month, no subject had signs of edema, and only 3 (3.9%) had lingering signs of erythema. These early and transient 1st degree burns were not unexpected. Scabbing was the next most frequent procedure-related adverse event, seen in 7.7% of subjects at the early clinic visit, in 1.4% at 2 months, and in no subjects at 6 months.

There were no 3rd degree burns, but 15 subjects were reported to have at least one grid-spot of 2nd degree

TABLE 4. **Wrinkle Improvement After a Single Radiofrequency (RF) Treatment: Investigator Clinical Assessments Over Time**

| | Fitzpatrick classification scores over time | | | | | |
|---|---|---|---|---|---|---|
| | Baseline to 2 months | | Baseline to 4 months | | Baseline to 6 months | |
| | Right | Left | Right | Left | Right | Left |
| Eyes with data | 74 | 74 | 80 | 80 | 83 | 83 |
| Number of eyes (%) with improvement | 19 (25.7%) | 18 (24.3%) | 22 (28.6%) | 21 (26.2%) | 24 (28.9%) | 24 (28.9%) |
| Number of eyes (%) remaining the same | 49 (66.2%) | 51 (68.9%) | 51 (66.2%) | 53 (66.3%) | 53 (63.9%) | 53 (63.9%) |
| Number of eyes (%) with worsening | 6 (8.1%) | 5 (6.8%) | 7 (9.1%) | 6 (7.5%) | 6 (7.2%) | 6 (7.2%) |


Fig. 5. Example of eyebrow lift after RF treatment, as described in text. A: Pre-treatment; (B) 6 months post-treatment: average lift =1.7 mm (right) and 2.0 mm (left). {Figure can be viewed in color online via www.interscience.wiley.com. I

**TABLE 5. Subject Evaluation of Treatment Outcome**

| Visit interval | 2 Month (N = 70) | 4 Month (N = 74) | 6 Month (N = 82) |
|---|---|---|---|
| Satisfaction | | | |
| Very satisfied | 8 (11%) | 11 (15%) | 10 (12%) |
| Satisfied | 24 (34%) | 24 (32%) | 31 (38%) |
| Neutral | 28 (40%) | 29 (39%) | 25 (30%) |
| Unsatisfied | 10 (14%) | 10 (14%) | 16 (20%) |
| Skin tightness | | | |
| Looser | 0 | 2 (3%) | 2 (2%) |
| Same | 48 (69%) | 44 (59%) | 43 (52%) |
| Tighter | 22 (31%) | 28 (38%) | 37 (45%) |
| Appearance | | | |
| Worse | 2 (3%) | 1 (1%) | 3 (4%) |
| Same | 36 (51%) | 38 (51%) | 38 (46%) |
| Better | 31 (44%) | 35 (47%) | 40 (49%) |

burning, accounting for 15 burns that were classified as superficial and six as deep. The 21 2nd degree burns resulting from a total of 5,858 RF exposures represented an overall observed burn risk of 0.36% per application. Three clinic sites accounted for all but one of the 2nd degree burns.

**TABLE 6. Subject Comfort Level During RF Treatment**

| | Average pain score (N = 86) | | | |
|---|---|---|---|---|
| Pain (score) | Right side | Percentage | Left side | Percentage |
| No pain (0) | 10 | 12 | 3 | 3 |
| Mild pain (1) | 34 | 40 | 39 | 45 |
| Moderate pain (2) | 33 | 38 | 30 | 35 |
| Severe pain (3) | 8 | 9 | 11 | 13 |
| Intolerable pain (4) | 1 | 1 | 3 | 3 |

The areas of epidermal interruption ranged from 4 to 9 mm in length. Three of the five subjects with deep 2nd degree burns developed residual scars and were offered laser treatment. Another subject developed mild, focal textural changes, and the fifth subject had complete resolution of scarring by 6 months. A representative photographic sequence of a subject with early burning and resolution is shown in Figure 6.

Other adverse events were reported by five subjects. Forehead bruising resolving in 3-4 weeks (three subjects) and altered sensation (two subjects) were both thought to be

**TABLE 7. Clinical Observations After RF Treatment**

| | Time intervals | | | | | |
|---|---|---|---|---|---|---|
| Clinical observation | Immediate | Early | 1 Month | 2 Months | 4 Months | 6 Months |
| Clinical signs | N = 86 | N = 78 | N = 76 | N = 74 | N = 80 | N = 83 |
| Abrasion | 2 (2.3%) | 4 (5.1%) | 0 | 0 | 0 | 0 |
| Edema | 12 (13.9%) | 5 (6.4%) | 0 | 0 | 0 | 0 |
| Erythema | 31 (36.0%) | 13 (16.7%) | 3 (3.9%) | 1 (1.4%) | 0 | 0 |
| Blistering | 2 (2.3%) | 3 (3.8%) | 0 | 0 | 0 | 0 |
| Blanching | 1 (1.2%) | 0 | 0 | 0 | 0 | 0 |
| Bruising | 0 | 3 (3.8%) | 0 | 0 | 0 | 0 |
| Crusting | 0 | 2 (2.6%) | 0 | 0 | 0 | 0 |
| Hyperpigmentation | 0 | 0 | 1 (1.3%) | 1 (1.4%) | 1 (1.2%) | 0 |
| Oozing | 0 | 1 (1.3%) | 0 | 0 | 0 | 0 |
| Purpura | 1 (1.2%) | 2 (2.6%) | 0 | 0 | 0 | 0 |
| Scabbing | 0 | 6 (7.7%) | 2 (2.6%) | 1 (1.4%) | 0 | 0 |
| Ulcer | 1 (1.2%) | 4 (5.1%) | 1 (1.3%) | 0 | 0 | 0 |
| Scarring | 0 | 0 | 1 (1.3%) | 1 (1.4%) | 5 (6.3%) | 3 (3.6%) |
| Textural change | 0 | 0 | 1 (1.3%) | 1 (1.4%) | 1 (1.2%) | 2 (2.4%) |
| Other | 1 (1.2%) (white area) | 0 | 1 (1.3%) (tenderness) | 1 (1.4%) (tenderness) | 0 | 1 (1.2%) (poison ivy) |
| Totals | 51 | 43 | 10 | 6 | 7 | 6 |
| Total number (%) of subjects with observations[a] | 36 (41.9%) | 24 (30.8%) | 7 (9.2%) | 4 (5.4%) | 6 (7.5%) | 7 (8.4%) |

[a]Some subjects with multiple clinical signs are listed more than once within given time interval.

related to use of nerve block. There was one case of posttreatment urticarial swelling that appeared in a hatched pattern of red ridges, apparently demarcating the edge of the treatment tip movement over the treatment grid; this urticaria occurred in a patient pre-treated with nerve block and receiving higher joule settings. Headaches lasting less than 24 hours (one subject) or persisting for months following treatment (two subjects) were of unknown relationship to the device. One subject presented at the 6-month visit with an allergic reaction that was deemed related to her history of food allergies.

## DISCUSSION

There is a growing population seeking to minimize signs of aging without the risks or prolonged recovery of laser procedures [11,201 and there are numerous laser and nonlaser technologies being developed and studied to meet this need. This was the first large multicenter evaluation of a new nonablative RFTT device for cosmetic use. This RF method of heating tissue-with controlled volumetric heating of deeper cutaneous tissues resulting in tissue tightening-differs radically from traditional laser methods. In this 6-month trial, the clinical significance of this novel tightening mechanism was demonstrated in subsets of patients evaluated by different techniques: 83% wrinkle improvement was seen in photographic review, 29% by clinical assessment, and 62% of upper eyelids were elevated. While a number of questions remain, this initial study clearly shows the potential for dramatic clinical benefit with RFTT.

A major limitation of this study's design is that it did not attempt to vary treatment factors that are likely to optimize outcome in clinical practice, such as treatment setting titration, patient selection, and treatment algorithm variations. The size and design of this study did not allow, for example, for subgroup analysis of patients receiving lower or higher numbers of RF applications, patients receiving lower or higher fluence levels (especially those receiving high fluences after nerve block), or patients within varying photoaging classes. In future studies, it will be important to correlate such procedural and patient variables with both wrinkle outcome and adverse event frequency. This will be of particular interest to clinicians seeking the best results from this promising technology.

Notwithstanding the nonoptimal study design, the results of this multicenter 6-month clinical study are significant. Most importantly, analysis of photographs showed clear reductions in wrinkles in the majority of the 86 subjects from a single treatment session. The patient questionnaire, which limited patient feedback on efficacy to the periorbital wrinkles revealed that about half of the subjects were very satisfied or satisfied with the wrinkle reduction results at 6 months. This relatively low number is possibly reflective of the narrow scope of the patient questionnaire, which did not capture the changes in brow position or other potential tissue changes, and lack of patient access to the pre-treatment photographs. Further, the modest nature of wrinkle reduction over a 6-month study period may be difficult to discern with daily selfobservation. Similarly, the difference between the results

of the photographic evaluation and the results of the clinician's analysis (again, without reference to the pretreatment photograph) likely reflects the difficulty in registering subtle changes in a dynamic viewing of the patient versus in a side-by-side comparison of static photographs.

With the recent FDA clearance of this device for cosmetic use-an approval based largely on the generally positive results of this large clinical study-more dermatologists, plastic surgeons, and other aesthetic specialists are now evaluating RF for use in a range of tissue tightening procedures. Clinicians should keep in mind several issues as they consider employing this device for aesthetic procedures, including: the unknown contribution of additional treatment sessions, the likely role of treatment setting titration for each patient and even for each tissue area, and the possibility that certain types of laxity and wrinkles are more likely to respond to a deep volumetric heating effect than others. A better understanding of these variables is likely to lead to more impressive outcomes in the future. Quantifying the efficacy of noninvasive cosmetic procedures is notoriously difficult [8,11]. Histologic changes, although interesting and objective, do not always correlate with aesthetic improvements. Although patients and clinicians frequently report subjective improvements in skin tone and texture after procedures with nonablative techniques, the degree of this mild improvement is hard to measure objectively (i.e., via photography or other techniques) [10].

To add scientific rigor in the present study, three blinded observers rated the post-treatment wrinkle improvements seen on photographs, and a computer-aided photoanalysis program was created to measure eyebrow lift. As suspected at the study outset, the strict technical criteria of these photography-based outcome measures led to a high number of patients being deemed unevaluable. Still, by both of these more objective outcome measures, the treatment session produced positive results at 6 months, with 83% of treated areas showing wrinkle improvement and 61% of eyebrows being elevated by at least 0.5 mm. Significantly, the wrinkle improvements increased continuously from 2 to 4 to 6 months after a single treatment session, a clinical pattern reflecting the postulated two-phase mechanism of action with RFTT: a short-term initial tightening effect due to


Fig. 6. Example of adverse event after RF treatment, showing small burn and subsequent resolution. A: Pre-treatment; (B)1 hour post-treatment; (C) 6 months post-treatment. [Figure can be viewed in color online via www.interscience.wiley.com.]


Fig. 6. (Continued)

primary collagen contraction followed by a longer-term (e.g., 6 months or more) remodeling effect with further tightening due to secondary collagen synthesis [1-3,211. The more subjective interpretations of the investigators and the subjects themselves lend support to the objective evidence of a durable and evolving RF efficacy.

The high degree of safety with this technique is impressive. In this study, the device's simultaneous RF heating and cryogen cooling allowed delivery of energy sufficient to produce good efficacy without also causing long-lasting skin damage. There was considerable centerto-center variation in the rates of 2nd-degree burns following RF treatment, with two clinics reporting no such burns and one clinic accounting for 9 of the 21 reports, suggesting some influence of user technique on safety outcome. Such variations are expected, and may reflect differences in clinic populations or in clinician technique, choice of RF settings, use of nerve block, or reporting accuracy. As previously described, the study was not powered to test the potential correlation between RF setting and either wrinkle outcome or burn frequency. However, the investigators did note a general concordance between higher treatment fluence and higher incidence of burns and by the end of the study had begun developing procedures that might eventually result in even higher levels of safety. Specifically, investigators (1) decreased treatment fluence over areas of bony prominence, since these areas receive intensified treatment effects, (2) removed lipid-based skin creams and applied adequate coupling gel to avoid epidermal heating, and (3) applied the treatment tip with uniform four-corner pressure to avoid preferential application of energy to any one tissue contact point (an edge-of-tip effect that may account for the single case of urticaria). Refinement of such protocol issues and identification of individuals at highest risk for burns and other adverse effects will result in a very high level of safety for RFTT.

The documentation of eyebrow lift seems to confirm the early general impressions reported by investigators that RF treatment not only smoothed wrinkles but also, in many subjects, led to a more "open" expression. However, it should be noted that this endpoint was not included in the original protocol, but was instead added post-hoc to the results analysis based on investigator feedback. The principle of tightening tissue to "lift" adjacent structures has long been employed with conventional incisional plastic surgical procedures. The apparent potential of this novel RF device to achieve even a fraction of a similar "lifting" or tightening benefit without an incision is of great interest to the aesthetic practitioner and patient, and may well represent a more important application for this novel technology than these carefully studied, but modest wrinkle reduction effects.

The mechanism for this observation of clinical tightening is unknown, though the relatively deep electrical field depth of at least 2.5 mm suggests the potential to heat both dermal and fascia components. We have previously investigated the etiology of the skin tightening observed immediately following CO2 ablative resurfacing. In this setting, the thermal reactions of the collagen helix provided an explanation, as collagen reacts in a predictable manner to heat, resulting in reconfiguration of the helical structure at specific instantaneous temperature changes 96 C in human collagen). Thermal changes beyond this point (> 70 C) resulted in denaturation of the helical structure and loss of configuration. These clinical and experimental findings with CO2 laser resurfacing provided the impetus for methods that would tighten the skin laxity without ablating the epidermis. A multitude of lasers have been used in attempts to achieve this nonablative resurfacing but these systems are thought to improve skin texture and remove fine lines not via tissue tightening but by induction of minor superficial dermal wounding and subsequent regeneration of new collagen in the papillary dermis. Thus, clinical findings suggesting that a new RF device can induce skin tightening via controlled volumetric heating of the deeper cutaneous tissues are noteworthy. Questions about the exact location, timing, and mechanism of the tissue tightening remain. For example, the pain sensation at the time of treatment suggests deep-plane tightening rather than dermal layer effects; the lack of textural improvement in many patients with tightening also supports the concept of deep tightening. And while the immediate tightening noted in many patients is consistent with collagen helical structural changes secondary to thermal change, the slower and more subtle tightening effects noted over a period of 2-6 months suggest a mechanism related to wound healing and tissue remodeling. More studies are needed to better define the depth of tissue heating and the mechanisms of tissue tightening, and to correlate these actions to clinical findings. As the novel tissue tightening effects of RF are defined, the range of clinical applications may expand. The RFTT device could potentially be useful, for example, not only on the lower face, jowls, and neck but also in other body areas (e.g., abdominal skin, arms, legs) where tissue laxity associated with aging is problematic for patients.

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