What Is Nonablative Photorejuvenation of Human Skin?

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Nonablative photorejuvenation has become an integral procedure in the emerging discipline of laser dermatologic surgery. The objective is to confine selectively, without any epidermal damage, thermal injury to the papillary, and upper reticular dermis leading to fibroblast activation and synthesis of new collagen and extracellular matrix material. The procedure results in minimal patient morbidity, no interference with lifestyle, and a low risk of complications, while providing a satisfying degree of rhytides reduction. Multiple devices have been studied and marketed for nonablative photorejuvenation of human skin. However, currently, nonablative photorejuvenation should not be considered an alternative to laser skin resurfacing. The skin surface is not removed or modified. What really occurs may be more accurately referred to as dermal "remodeling" or "toning" as a wound healing response is initiated and collagen regenerated. The narrow "therapeutic window" of laser-induced dermal heating and epidermal cooling must still be optimized so that effective treatments can be obtained routinely. Clinical verification of effective treatment parameters (irradiation wavelength, pulse structure, radiant exposure, cooling time) will be obtained through further human studies. Most importantly, understanding the relationship between the degree of dermal thermal injury and synthesis of new collagen and extracellular matrix material will be fundamental to predicting the clinical efficacy and limitations of nonablative photorejuvenation.

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THE TREATMENT OF PHOTODAMAGE and/or facial rhytides has been the concern of physicians and patients for many centuries. Popular approaches have historically included dermabrasion and chemical peeling. Topical applications of tretinoin (all-trans-retinoic acid), vitamin C (ascorbic acid), and α-hydroxy acids (eg, glycolic acid) are widely used. Although these methods have been described and used, no single method has become the dominant one. More recently, laser skin resurfacing (LSR) has emerged as a widely used aesthetic treatment modality that may have the advantages of improved reproducibility and control when compared to dermabrasion and chemical peeling.[1]

The carbon dioxide (CO_2) and erbium:yttrium-aluminum-garnet (Er:YAG) lasers are currently the devices of choice for human LSR. In practice, superficial layers of human skin are removed through a primarily ablative process, driven by intense infrared (IR) radiation. If used properly, the procedure is clinically similar to dermabrasion because the laser gradually removes cell layer after cell layer through volatilization of water present in human skin. Because IR radiation is absorbed so intensely by water, optical penetration depths are very shallow. Deposition of laser energy in a shallow tissue layer produces a rapid rise in local skin temperature. As more energy is added, water is raised to its boiling point. Internal vapor pressure builds up until a microexplosion occurs. The rapid expansion created by this excitation gives rise to ejection of microscopic tissue fragments at high velocities. Since most of the energy of the laser pulse goes into the thermal phase change associated with tissue vaporization, ablated fragments ejected from the skin surface carry most of the energy with them, leaving little energy in the form of heat to damage surrounding tissue. Because of the significantly higher absorption of the Er:YAG wavelength (2.94 μm), as compared to

the CO_2 wavelength (10.6 μm), the depth of thermal damage in subjacent tissue is much less (10-30 μm for the Er:YAG as opposed to 80-150 μm for the CO_2).[2]

Although both the CO_2 and Er:YAG lasers are quite effective in terms of photodamage removal and rhytides reduction, epidermal disruption and removal results in an open wound that places the patient at risk for bacterial, viral, and fungal infections. Patients also experience edema, drainage and burning discomfort during, typically, the first week after LSR. The wound resolves with significant erythema, which often persists for several months. Although erythema is of shorter duration when the Er:YAG laser is used, virtually all patients undergoing LSR procedures experience this side effect. Finally, delayed or abnormal wound healing often results in complications such as dyspigmentation and/or scarring.

Although several details remain incompletely understood, 3 main processes are involved in LSR of human skin: 1) ablation of the epidermis and upper dermis; 2) acute shrinkage of dermal collagen; and 3) long-term wound healing that leads to dermal remodeling as new collagen and extracellular matrix are synthesized over a period of months after treatment.

Epidermal and dermal ablation may be useful to remove superficial textural irregularities and the dyschromia associated with photodamage (and acne scars), but may not be a major contributor to rhytides reduction. Dermal collagen shrinkage induced by LSR may contribute to acute wound contraction, but may be only incidental to long-term rhytides reduction. Therefore, it seems that long-term wound healing, including dermal remodeling and collagen and extracellular matrix synthesis, is the most likely process responsible for rhytides reduction.

Fisher et al[3] found that ultraviolet irradiation induces metalloproteinases in the skin including collagenase, gelatinase, and stromelysin, which subsequently degrade dermal collagen. Free radicals, induced by ultraviolet radiation, further damage collagen. Histologic evaluation of photodamaged human skin shows increased glycosaminoglycans, which replace damaged and disorganized collagen fibrils in the dermis. Elastic fibers are abundant, thickened, and tortuous (solar elastosis).[4,5]

A histologic study by Thomsen et al,[6] involving polarization sensitive light microscopy of rodent skin irradiated with parameters derived from human CO_2 LSR, indicated thermal alteration of collagen fibrils in the dermis at depths up to 300 μm. In another histological study, Cotton et al[7] noted that reduction of human facial rhytides after CO_2 LSR corresponded to the formation of a new band of dense, compact collagen bundles in the papillary dermis. Moreover, the degree of thermally denatured dermal collagen strongly correlated with bundle thickness.

Long-term studies have documented that CO_2 and Er:YAG LSR results in acute dermal collagen denaturation.[8-11] During the first 3 days after LSR, injured papillary dermal fibroblasts proliferate and migrate into the wound site where they are activated to synthesize type I procollagen (the most abundant dermal protein and synthetic precursor to collagen I) and other matrix molecules. Partial collagen denaturation also stimulates a wound healing reaction, accelerating collagen synthesis by fibroblasts and reabsorption of elastotic material. Thirty days after LSR, new deposition of dense, compact, collagen fibers oriented parallel to the skin surface is visible in the papillary dermis. Ninety days after treatment, there is an even more highly organized network of collagen and elastic fibers in the upper dermis.

In conclusion, because these histologic changes occur primarily in the dermis, epidermal removal may not be required to provoke a dermal wound healing response leading to remodeling and collagen and extracellular matrix synthesis.

WHAT IS NONABLATIVE PHOTOREJUVENATION?

Nonablative photorejuvenation of human skin is a procedure designed to confine selectively, without any epidermal damage, thermal injury to the papillary, and upper reticular dermis leading to fibroblast activation and synthesis of new collagen and extracellular matrix material. The skin surface is not removed or modified. What really occurs may be more accurately referred to as dermal "remodeling" or "toning" as a wound healing response is initiated to regenerate subsurface collagen. Laser-induced thermal injury should be

confined to a zone 100 to 500 μm below the skin surface where the majority of the aforementioned histologic changes associated with photoaging, occur. More superficial injury may be ineffective for rhytides reduction; deeper injury may result in scarring.

Nonablative photorejuvenation potentially meets the following consumer demands: 1) low risk of complications; 2) little or no interference with life style; 3) rapid, simple, and affordable; 4) not obvious that a "procedure" has been done; and 5) offers the possibility of long-term clinical improvement. Most patients and physicians are willing to accept subtle, incremental improvements if the procedure is associated with significantly reduced discomfort and fewer complications such as prolonged erythema and dyspigmentation. The procedure is also more efficient than the traditional LSR procedures, in which most of the costly laser energy is wasted on epidermal ablation.

Favorable treatment outcome with nonablative photorejuvenation requires that the: 1) laser irradiation wavelength, pulse structure, and radiant exposure must be selected to produce sufficient injury in the papillary and upper reticular dermis thereby activating a long-term wound healing response; and 2) epidermis must be protected by, for example, cooling before, during and/or after laser exposure.

ROLE OF THE LASER

Before discussing the various approaches to nonablative photorejuvenation, the first and intuitively simple question that should be addressed is—do we need a laser? In the case of nonablative photorejuvenation, the answer is emphatically no! According to current understanding of the processes involved, any radiant source (eg, filtered noncoherent light source, micro- or radio-frequency-waves) should work just as well, provided: 1) sufficient energy is delivered to the skin; 2) energy is deposited in the upper 100 to 500 μm of human skin; and 3) the skin surface can be spared by selective energy deposition in the dermis and/or application of active cooling.

DERMAL HEATING

The primary goal of successful nonablative photorejuvenation of human skin is a sufficient degree of rhytid reduction. To recapitulate, the most important mechanism of rhytid improvement after traditional LSR is believed to be dermal thermal injury, resulting in collagen denaturation, fibroblast activation and synthesis of new collagen, and extracellular matrix material. To develop nonablative photorejuvenation procedures with results comparable to traditional LSR, neo-collagen formation needs to be induced in (and, most likely, confined to) a zone approximately 100 to 500 μm below the skin surface, which contains the majority of solar elastoses in photodamaged skin.

Despite recent advances achieved in understanding the important cellular and biochemical processes involved in the dermal wound healing response, one must not expect, however, that the degree of dermal thermal injury may be arbitrarily increased (leading to increased dermal remodeling and collagen and extracellular matrix synthesis) without increasing the risk of complications. For example, increased levels of dermal thermal injury might temporarily occlude or irreversibly damage the microvasculature in the papillary and upper reticular dermis resulting in a layer of compromised or necrotic tissue that cannot be regenerated or salvaged. Clearly, potential accompanying damage to the cutaneous microvasculature warrants further study.

Absorption by Water

Thermal injury during laser or light treatment results from heat generated by absorption of laser radiation. The depth of thermal injury depends primarily on the light-tissue interaction, which dictates the induced temperature distribution through absorption and scattering of laser radiation. In the near- and mid-IR spectral regions, where light-tissue interaction is absorption-dominated, the radiation intensity will decrease exponentially with depth, according to Beer's law. As a result, the optical penetration depth (l_{opt}) is equal to the reciprocal of the absorption coefficient (μ_a) at the selected optical wavelength:

$$l_{opt} = 1/\mu_a \quad (1)$$

Because local conversion of laser energy to heat will follow the same depth profile, it is useful to

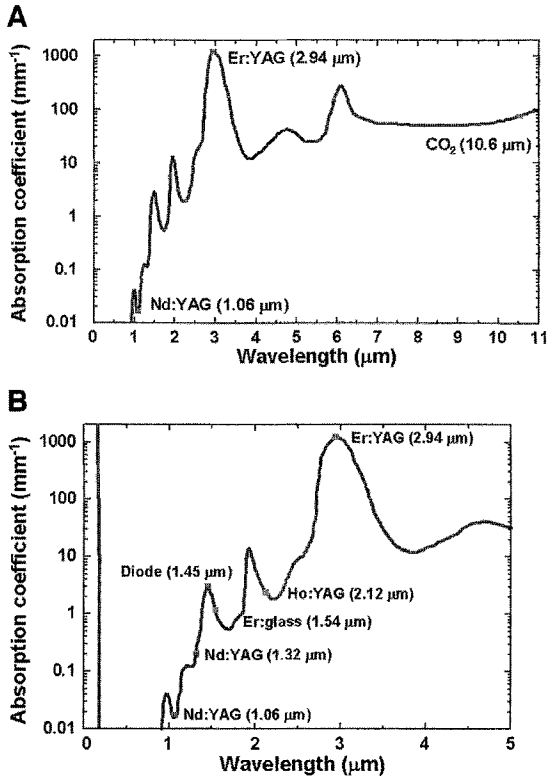

Fig 1. Absorption coefficient of water as a function of radiation wavelength: (A) λ = 1-10 μm; and (B) λ = 1-5 μm.

select a wavelength with a l_{opt} that matches the targeted tissue depth. If the optical penetration depth is too great, a minor fraction of incident energy will be absorbed in the target layer, and transmitted energy may well cause unwanted thermal damage in deeper structures. Alternatively, if l_{opt} is too small, intense local heating in the superficial layers (epidermis, basal layer) may induce adverse effects, with a reduced amount of heat available for deposition in deeper parts of the target layer.

In the near- and mid-IR spectral regions, dermal absorption is dominated by tissue water (Fig 1). Therefore, μ_a can be calculated as a product of the water absorption coefficient (μ_{water}) and the hydration level (w) of the dermis,

$$\mu_a = \mu_{water} w \tag{2}$$

whereby,

$$l_{opt} = 1/(\mu_{water} w) \tag{3}$$

If the targeted dermal depth is 100 to 500 μm below the skin surface, values in Table 1 indicate that the optimal light source would be the recently developed 1.45 μm diode laser.

However, tissue scattering significantly affects the penetration of laser radiation in both epidermis and dermis, particularly at shorter wavelengths. The so-called reduced scattering coefficient (μ_s'), related to the axial dimension over which a considerable amount of laser radiation will be scattered from its initial direction, exceeds the absorption coefficient of water at wavelengths below 1.5 μm. Under such conditions, depth profiles of the fluence rate (accounting for radiance in all directions) do not follow Beer's law. The theory of such radiation transport for specific geometrical and spectroscopic configurations are complicated and far exceed the scope of this chapter. Nevertheless, the characteristic length of the fluence rate profile under such conditions is indicated by the so-called reduced mean free path (z_0),

$$z_0 = 1/(\mu_a + \mu_s') \tag{4}$$

Table 1. Optical Penetration (l_{opt}) and Reduced Mean Free Path (z_0) in Human Skin as a Function of Radiation Wavelength

Laser	Wavelength (μm)	μ_{water} (mm^{-1})	l_{opt} (μm)	z_0 (μm)
Diode	0.980	0.0448	32,000	1,100
Nd:YAG	1.064	0.0177	81,000	1,300
Nd:YAG	1.32	0.204	7,000	1,600
Diode	1.45	3.04	470	390
Er:glass	1.54	1.18	1,200	840
Ho:YAG	2.12	2.39	600	530
Er:YAG	2.94	1220	1.2	1.2
CO_2	10.6	84.4	17	17

The values in Table 1 show that z_0 depths are much more realistic as compared to l_{opt}, in particular for wavelengths below 1.5 μm. It should be stressed, however, that z_0 provides a rough indication of the fluence rate depth profile, and the corresponding heat deposition. Three-dimensional numerical calculations are usually required to determine reliably the optical transport under such conditions, to account properly for the lateral and axial distribution of fluence rate inside the scattering tissue.

The deposited heat is redistributed within tissue by the process of heat diffusion during and following laser irradiation. As a result, the ultimate depth of thermal injury is influenced not only by optical properties of the dermis at the selected wavelength, but also by several other factors including pulse duration and, if multiple pulses are used, the repetition rate and number of pulses. In addition, because the deposited energy must exceed a certain threshold to induce the desired thermal effects, the delivered light dosage (radiant exposure) will obviously affect the extent of dermal thermal injury.

While a detailed discussion of such a multitude of variables is beyond the scope of this chapter, their influence must be considered in the development of novel approaches to nonablative skin photorejuvenation. However, in general, with longer irradiation times and/or higher light dosages, heat diffusion will tend to increase the extent of thermal injury beyond that suggested by the characteristic depth of the fluence rate profile. Finally, utilization of active skin cooling may affect not only the extent of epidermal, but also the depth of dermal thermal injury.

Absorption by Hemoglobin and Melanin

Hemoglobin has significant light absorption in the violet, blue/green, and yellow portions of the spectrum. In the case of laser treatment of cutaneous blood vessels, the wavelengths suitable for consideration are the hemoglobin Soret absorption band at 418 nm and the absorption bands at 542 and 577-595 nm. Despite the higher extinction coefficient of the Soret band, this wavelength can be rejected for clinical use because penetration of radiation into the dermis is insufficient. However, if one takes advantage of the longer wavelength hemoglobin absorption bands, where tissue penetration is increased and melanin absorption reduced, less heating of the epidermis should occur and more incident light energy is transmitted to dermal blood vessels.

Wavelengths that target oxyhemoglobin, such as 577-595 nm produced by the pulsed dye laser (PDL), can be used to heat dermal blood vessels. Subsequent heat conduction to adjacent perivascular collagen may result in the desired histologic changes described above.

Epidermal melanin is the dominant chromophore in human skin. Although distributed throughout the epidermis, melanin is particularly concentrated in the 10-μm thick basal layer located typically 50 to 100 μm below the skin surface. Although highest in the ultraviolet portion of the spectrum, melanin absorption is also significant in the visible and near-IR wavelengths. Subsequent heat conduction to subjacent dermal collagen may result in the desired histologic changes necessary for nonablative photorejuvenation of human skin.

EPIDERMAL PROTECTION

A second objective of nonablative photorejuvenation of human skin is to minimize epidermal injury. Except for treatment of epidermal melanoses, melanin absorption is unwanted because it reduces the effective light dosage and decreases the amount of heat produced in the targeted papillary and upper reticular dermis. Moreover, the associated epidermal temperature rise, if not controlled, can lead to blistering, dyspigmentation, or scarring, which limits the radiant exposure that can be safely applied. In the near- and mid-IR portions of the spectrum (700 nm-5 μm), melanin absorption is reduced. At longer laser wavelengths, less epidermal heating will occur at the same incident radiant exposure, and more light energy will be transmitted to the targeted papillary and upper reticular dermis.

However, although melanin absorption is minimal at wavelengths longer than 1.5 μm, active skin cooling may required because, even in a homogeneously absorbing medium, the fluence, and, therefore, heat deposition will always be highest at the skin surface. Moreover, the damage threshold for the basement membrane may be

lower than the light dosage required to induce significant dermal collagen remodeling.

A valuable method to overcome the problem of epidermal heating is to cool selectively the superficial layers of the skin before, during, and after laser irradiation—so long as the epidermis is prevented from reaching a temperature that is above its threshold for denaturation (60-65°C), the epidermis can be preserved.[12]

Several different methods have been developed for active cooling of human skin in conjunction with laser therapy. All methods use a precooled medium brought in contact with the skin surface. Deeper skin layers are cooled by heat diffusion toward the cooled surface with subsequent transfer to the cooling medium. The rate of heat transfer across the interface between the skin and cooling medium depends primarily on the temperature difference between the 2 adjacent materials, as well as other parameters, specific to each cooling method. Cooling efficiency using any method can be characterized approximately by a proportionality constant, termed "heat transfer coefficient" (h), regardless of the physical mechanism involved.

Contact cooling (CC) exploits conduction of heat from human skin into an adjacent solid body, usually an optically transparent plate, kept at a low temperature (−10 to 4°C) by an external cooling system. Laser exposure is typically delivered through the plate, which is pressed against the patient's skin. CC can be efficient when a highly conductive material, such as sapphire, is used for the cooling plate and relatively long cooling times are permitted. However, in practice, air, bubbles, hair, or other substances impede the thermal contact between the skin surface and cooling plate, which impairs the rate of heat extraction achievable with CC.

Human skin can also be cooled by precooled air (at a temperature as low as −30°C), blown onto or across the surface. Despite the low air temperature used, air cooling (AC) is characterized by the lowest cooling rate since the heat transfer coefficient for forced convection in gas is very low. As a result, very long cooling times (on the order of several seconds) are necessary to induce significant temperature reductions in the basal layer. As a result, the outcome is inevitably general ("bulk") cooling of the entire skin with minimal spatial selectivity. The latter is required for nonablative photorejuvenation.

The most rapid and spatially selective cooling can be achieved by cryogen spray cooling (CSC).[13] Tetrafluoroethane (TFE) is the only cryogenic compound currently FDA approved for use in dermatologic laser surgery. TFE is a nonflammable, nontoxic, environmentally compatible freon substitute that does not deplete atmospheric ozone or contribute to global warming.[14]

CSC's main cooling mechanism is rapid evaporation of cryogen, which extracts the required latent heat from the skin. Liquid cryogen is dispersed into a fine spray and directed toward the skin surface by a suitable nozzle, connected to an electronically controlled valve. During flight, spray droplets cool rapidly due to cryogen evaporation, typically reaching between −40°C and −60°C when impinging onto the skin surface. As a result, CSC provides a rapid, large and spatially selective epidermal temperature reduction (Fig 2). In some instances, a layer of liquid cryogen can remain on the skin surface after spurt termination, extending the cooling time beyond the actual user-specified spurt duration.

Nonablative photorejuvenation is an example of a clinical entity with a relatively superficial target for laser-induced thermal injury. Therefore, selective epidermal cooling is necessary because the targeted papillary and upper reticular dermis is only 100 to 500 μm below the skin surface. For high spatial selectivity, the following are required: 1) very cold cooling medium; 2) good thermal contact; and 3) very short cooling times (tens of milliseconds) to avoid unwanted cooling of the deeper dermis. These considerations favor use of CSC, which offers precise control of the precooling time and higher heat transfer rates (h = 5,000-10,000 W/m^2 K) as compared to CC ($h \approx$ 2,000 W/m^{2}K) or AC (h = 20-200 W/m^{2}K).[12]

CSC has been incorporated into Candela Laser Corporation's (Wayland, MA) Smooth Beam and ICN Photonics' (Costa Mesa, CA) Cool Touch II devices for nonablative photorejuvenation. Cryogen spurt duration and delay between spurt termination and the laser pulse can be controlled electronically, which results in predictable cooling with reproducible spatial selectivity. CSC provides an unparalleled safety margin with respect

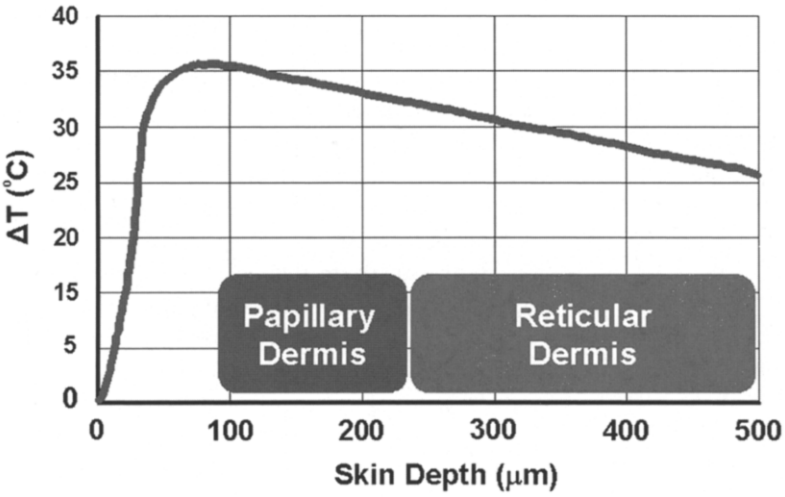

Fig 2. Computed temperature increase as a function of depth in human skin following Nd:YAG laser (λ = 1.32 μm) in conjunction with cryogen spray cooling.

to prevention of undesirable thermal injury by the laser pulse or frostbite due to cooling.

CURRENT APPROACHES TO NONABLATIVE PHOTOREJUVENATION OF HUMAN SKIN

As a result of the above scientific considerations, multiple devices have been studied and marketed for nonablative photorejuvenation of human skin. Although nonablative photorejuvenation is now widely practiced, considerable controversy surrounds this methodology. Variable treatment success has been achieved, but to date an optimal method has not been shown. We present herewith an overview of currently used methods and explore their advantages and disadvantages.

1.32 μm Nd:YAG Laser

One of the first lasers designed and marketed specifically for nonablative photorejuvenation was the 1.32 μm neodymium:yttrium-aluminum-garnet (Nd:YAG) laser (Cool Touch I and Cool Touch II, ICN Photonics, Costa Mesa, CA) used in combination with CSC. An early multicenter study evaluated peri-orbital rhytid improvement in 35 adults after 3 treatments performed at 2-week intervals.[15] Small but statistically significant clinical improvements were noted in the mild, moderate and severe rhytid groups 12 weeks after the last laser treatment. A final assessment performed 24 weeks after the last treatment showed statistically significant clinical improvement only in the severe rhytid group. Epidermal preservation was achieved, eliminating wound care issues. Transient hyperpigmentation was noted on 4 sites (5.6%) and 2 sites (2.8%) developed barely perceptible pinpoint-pitted scars of unknown origin. Subsequent device improvements including features to prevent laser irradiation if the cryogen spray fails to operate and a thermal sensor which rapidly reports skin temperatures allowing optimal fluence adjustment, have improved safety and efficacy and this laser is now one of the most popular non-ablative devices currently available (Fig 3).

Several subsequent studies[16-21] confirmed the real but subtle improvement in rhytides obtained using the 1.32 μm Nd:YAG laser as well as histologic evidence of fibroblast stimulation and new collagen formation.

1.45 μm Diode Laser

Another laser designed and marketed specifically for nonablative photorejuvenation is the 1.45 μm diode laser (Smooth Beam, Candela, Wayland, MA). Hardaway et al,[22] in a phase I clinical trial, investigated several laser parameters that involved postauricular treatment and biopsies performed immediately and 2 months after laser irradiation in 10 patients with Fitzpatrick skin phototypes I-IV. Treatment consisted of 1 or 2 passes with a 4-mm spot, average power of 12 W and heating times of 150 to 500 ms. Not unexpectedly, epidermal whitening and subsequent scar-

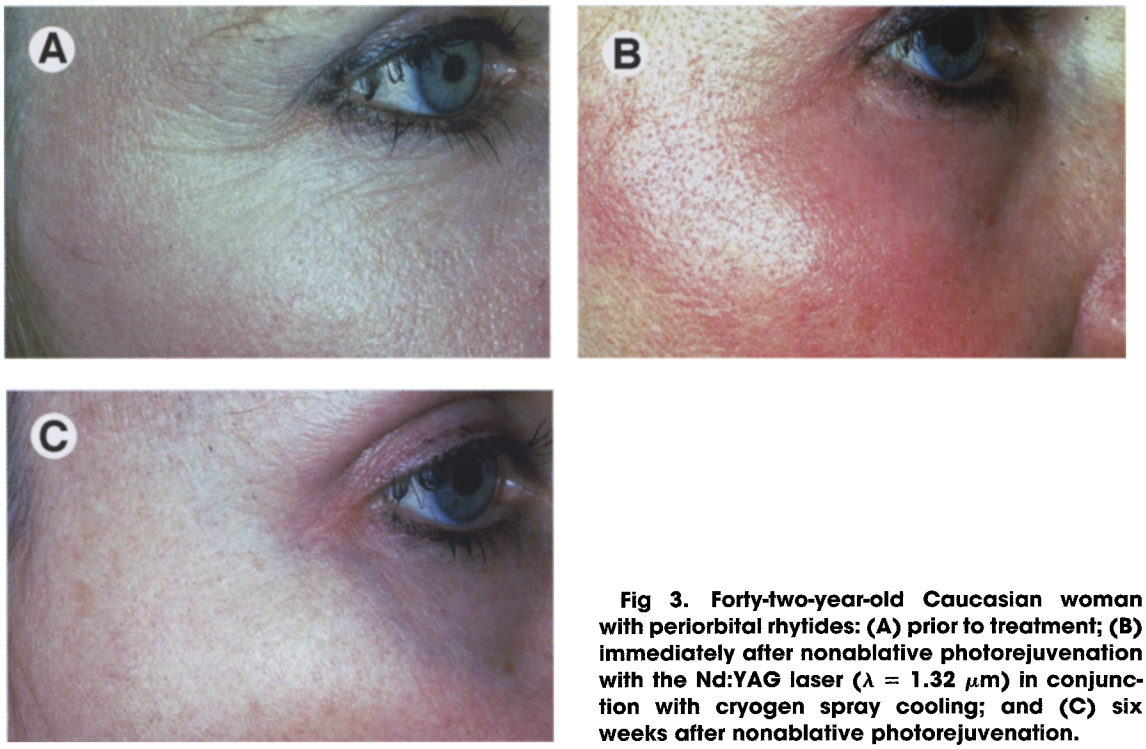

Fig 3. Forty-two-year-old Caucasian woman with periorbital rhytides: (A) prior to treatment; (B) immediately after nonablative photorejuvenation with the Nd:YAG laser (λ = 1.32 μm) in conjunction with cryogen spray cooling; and (C) six weeks after nonablative photorejuvenation.

ring were observed from the use of such long exposure times without concomitant cooling. Immediate postirradiation biopsies of 8 patients showed thermal damage in a zone that ranged from 311 to 644 μm below the skin surface. Biopsies at 2 months showed dermal fibrosis at the desired dermal depth of 148 to 420 μm. Phase II clinical studies evaluated the treatment of individual peri-orbital or peri-oral rhytides in 9 patients[23] by using a sequence of CSC spurts applied before, during and after 1.45 μm laser irradiation. Single rhytides received 3 treatments at 3-week intervals with a 4 or 5 mm spot, average power of 12 W and heating times of 200 to 300 ms. Rhytid scores improved from 2.3 at baseline to 1.8 at 6 months ($P > .05$). The investigators reported no scarring. Branny hyperpigmentation occurred in 6 patients but resolved within 1 week with no residual dyspigmentation. In Phase III clinical studies, the entire peri-orbital or peri-oral cosmetic unit of 25 patients was treated using a 4-mm spot size and power of 13 W. Final results are currently pending but preliminary subjective and objective evaluations indicate modest improvement comparable to that seen in Phase II.[24]

1.54 μm Er:glass Laser

Fournier et al[25] used an Er:glass 1.54 μm laser in combination with contact cooling (Aramis, Quantel Medical, Les Ulis Cedex, France) on periorbital and -oral rhytides in 60 patients with Fitzpatrick skin types I-IV. Patients received 4 treatments at 6-week intervals utilizing a 4-mm spot and fluences of 24 J/cm^2 (3 pulses at 2 Hz) for peri-orbital rhytides and 40 J/cm^2 (5 pulses at 2 Hz) for peri-oral rhytides. No adverse effects were reported and patients experienced minimal discomfort. Independent observers noted mild improvement after the third and fourth treatments. Silicone imprints demonstrated a 40.2% reduction of anisotropy ($P < .001$) 6 weeks after the final treatment and histology demonstrated new collagen formation in the dermis.

PDL

Anecdotal reports of rhytides reduction in patients treated with the PDL for vascular lesions prompted Zelickson et al[26] to explore that device's potential for nonablative photorejuvenation. The investigators used a 585 nm PDL with a pulse

duration of 450 μs (Photogenica V, Cynosure, Chelmsford, MA, or SPTL-1b, Candela, Wayland, MA) and treated 20 patients using a 7 or 10 mm spot size and fluence of 3.0 to 6.5 J/cm^2. Three blinded observers noted clinical improvement in 90% of patients with mild to moderate rhytides and 40% of those with moderate to severe rhytides, 6 months after 1 PDL treatment. However, significant purpura and swelling lasting for 1 to 2 weeks occurred in all patients. Two subjects developed postinflammatory hyperpigmentation.

In an effort to improve efficacy and decrease purpura associated with PDL non-ablative photorejuvenation, Bjerring et al[27] treated the periorbital region of 30 patients with a 585 nm PDL with a shorter pulse duration of 350 μs (Nlite, ICN Photonics, Costa Mesa, CA). With a 5-mm diameter spot size and fluence of 2.4 J/cm^2, the investigators were able to eliminate purpura and skin dyspigmentation. Subsequent histologic studies showed a statistically significant increase in production of type III pro-collagen in the dermis. Rhytid improvement 6 months after 1 treatment was judged by 3 blinded observers to be 52%, 89%, and 79% of that seen in previous CO_2 LSR studies[28] for class I, II, and III rhytides, respectively.

Long-pulse dye lasers (LPDL) have also been investigated for photorejuvenation of human skin. Rostan et al[29] treated 1 cheek of 15 women with moderate to severe photoaging with a series of 4 monthly LPDL (V Beam, Candela Corporation, Wayland, MA) treatments using a wavelength of 595 nm, fluence 6 J/cm^2, pulse duration 6 ms, spot size 10 mm, CSC spurt duration of 20 ms, and a delay time of 30 ms. The contralateral cheek was treated with CSC alone. Eleven patients showed improvement on the LPDL treated cheek, while 3 were judged to have improvement on the CSC cheek. One patient had no improvement on either cheek. Average improvement on the LPDL side in those who improved was 18.1%. No adverse effects were reported.

Frequency Doubled 532 nm Nd:YAG Laser

The frequency doubled potassium-titanyl-phosphate (KTP) 532 nm Nd:YAG laser has also been evaluated for nonablative photorejuvenation potential. This laser is well established as an effective method for reducing superficial photodamage including both telangiectasias and pigmentation.[30,31] More recently, the rhytides reduction capabilities of this laser were investigated by Bernstein et al[32] who treated 1 side of the perioral area of 11 women with mild-to-deep wrinkles using a 532-nm device (VersaPulse-C, Lumenis, Santa Clara, CA). Laser parameters were a 3-mm spot size, 2 ms pulse duration and a fluence range of 4 to 7 J/cm^2. Patients received an average of three treatments at 3- to 6-week intervals. Three months after the final treatment, patients self-assessments of peri-oral rhytides improvement averaged 51.4%. A blinded observer correctly identified the treated side in 8 of 11 patients.

1.06 μm Nd:YAG Laser

Several early attempts at nonablative photorejuvenation investigated the rhytides reduction potential of devices commonly used for other indications and readily available to laser practitioners. Goldberg et al[33] used the Q-switched Nd:YAG laser with a 3-mm spot size and fluence of 5.5 J/cm^2 for treatment of peri-oral or -orbital rhytides in eleven patients. The investigators reported improvement comparable to ablative LSR in 3 patients, some improvement in 6 patients, and no improvement in 2 patients. Because pinpoint bleeding occurred, this technique might be more correctly termed "partially ablative." Erythema persisted in several patients for up to 3 months.

Subsequently, Newman et al[34] combined the use of a topical carbon suspension with Q-switched Nd:YAG laser treatment. Twelve patients received 4 treatments at 7- to 10-day intervals with a 6 to 7 mm spot. The carbon suspension provided the chromophore target, which allowed the use of lower fluences (2.5 J/cm^2) and resulted in an average of 25% rhytid improvement without epidermal disruption. Small areas of transient hypopigmentation were noted in two patients with type VI skin, prompting the use of even lower fluences in those subjects. Goldberg and Metzler[35] evaluated a similar technique using a 7-mm spot size, pulse durations 6 to 20 ns, repetition rate 1 to 10 Hz, and fluence 2.5 J/cm^2. Three treatments were performed at 4-week intervals. Eight months after the final treatment,

97% and 68% of class I and II rhytides, respectively, were at least slightly improved.

Combined Wavelengths

A combination of the 532 and 1064 nm wavelengths has also been studied by Lee[36] using a variable pulse KTP laser (Aura, Laserscope, San Jose, CA) and a long-pulsed Nd:YAG laser (Lyra, Laserscope, San Jose, CA) individually or in combination to treat photodamage in 150 patients with skin types I-IV. Fifty patients received 532 nm treatment (2 mm spot, 7-15 J/cm^2, 7-20 ms pulse duration or 4 mm spot, 6-9 J/cm^2, 30 ms pulse duration), 50 patients received 1064 nm treatment (10 mm spot, 24 J/cm^2, 30 ms pulse duration or 10 mm spot, 30 J/cm^2) with a SmartScan Plus (Laserscope), and 50 patients received 532 nm treatment immediately followed by 1064 nm treatment. Each patient received between 3 and 6 treatments at 4- to 6-week intervals and was followed for 3 to 6 months after the final laser treatment. The 50 patients treated with the 532 nm laser alone showed a 70% to 80% reduction in redness and pigmentation, 40% to 50% improvement in skin tone/tightening, 30% to 40% improvement in skin texture, and 20% to 30% rhytides reduction. The 50 patients treated with the 1064 nm laser alone showed a 10% to 20% reduction in redness, 0% to 10% reduction in pigmentation, 10% to 30% improvement in skin tone/tightening, 20% to 30% improvement in skin texture, and 10% to 30% rhytides reduction. The 50 patients treated with the combined 532 and 1064 nm wavelengths showed a 70% to 80% reduction in redness and pigmentation, 40% to 60% improvement in skin tone/tightening, 40% to 60% improvement in skin texture, and 30% to 40% rhytides reduction.

It appears that all treatment groups achieved reasonably good improvement of superficial photodamage. The improvements in skin texture and rhytides reduction in patients treated with the combined 532 and 1064 nm wavelengths was particularly impressive when compared to CO_2 LSR,[37] which achieves on average a 45% to 60% rhytides reduction. Further research is required but combined wavelength approaches as shown above may offer realistic goals for nonablative photorejuvenation: slow but significant improvement of photoaging (albeit somewhat less than that achieved with ablative LSR) with minimal risk of adverse effects and no prolonged period of wound healing.

980 nm Diode Laser

Diode lasers have also been evaluated for nonablative photorejuvenation potential. Muccini et al[38] tested a 980 nm diode laser in combination with a spherical optical hand-piece, which focused the beam in the dermis. The optic floated in an air bearing, which provided cooling to both the optical train and underlying tissue. The device was evaluated by in vivo testing on the eyelid skin of 2 patients before blepharoplasty in comparison to 3 passes of the scanned CO_2 laser. Treatment parameters were a 400 ms pulse duration and powers ranging from 6 to 24 W delivered at a repetition rate of 1 Hz. This device was able to achieve epidermal preservation with 16% tissue shrinkage as compared to 15% shrinkage noted with the CO_2 laser. Histology showed denatured collagen with subsequent new collagen and elastin formation. The depth of thermal injury averaged 750 μm with the shallow and moderate probes and 1475 μm with the deep probe. Such treatment depths may be deeper than desired and might result in adverse clinical effects such as pitted scarring; obviously, further studies will be necessary to evaluate this device.

Intense Pulsed Light Sources

Intense pulsed light sources are flashlamp devices that emit a broad continuous range of wavelengths from 515 and 1200 nm. Cut-off filters can be used to remove shorter wavelengths. Depending on the filter set used, the light targets hemoglobin, melanin, and water at various levels. Lumenis (Santa Clara, CA) has developed an Intense Pulsed Light Source, which delivers energies of 3-90 J/cm^2 over multiple pulses through an 8 $\times$ 35 mm hand-piece that can be pre-cooled with a cooling collar. Bitter[39] treated 49 patients with 4 to 6 full-face treatments at 3-week intervals. Treatments were performed with cut off filters of 550 or 570 nm and fluences of 30 to 50 J/cm^2. Energy was delivered in double or triple

pulses of 2.4 to 4.7 ms with interpulse delays of 10-60 ms. Overall, 31 patients self-reported 25% improvement in fine rhytides, 22 patients reported 50% improvement, and 9 patients reported 75% improvement. Patients also reported improvements in skin coarseness, irregular pigmentation, pore size, and telangiectasias. Erythema and swelling were common but limited activities in only 2 patients and generally resolved in 12 to 24 hours. Temporary darkening of epidermal hyperpigmentation occurred in 66% of patients but resolved within 7 days. Blistering developed in 16% of patients. No scarring was reported.

Radiofrequency Device

The ThermaCool TC System (Thermage, Inc, Hayward, CA) is the first radio frequency (RF) technology to be deployed for the purpose of nonablative photorejuvenation. The Thermage system utilizes two electrodes on the skin, an active and a return electrode. The active electrode produces an electric field under it as the electrode builds up a charge. The charge is then rapidly changed from positive to negative. To produce a uniform distribution of charge across the electrode face, a dielectric is used to couple capacitively to the skin. The size and strength of the electric field are dependent on the geometry of the electrode and the power delivered through the tip. Ions and charged molecules in the tissue within the electric field move or rotate. The inherent resistance to the movement of these ions and molecules in tissue causes heat. The resistance and the heat produced are tissue-dependent. It is therefore possible to change the depth of treatment by altering the electrode geometry, power delivered, delivery time, and cooling parameters. A cryogen spray inside the cooling tip (not applied directly to the skin) creates a cooling device to protect the epidermis. It has been proposed that this technology may achieve controlled, uniform heating at considerably greater depths than those reported with light-based technologies, with the potential to vary the depth of heating to reach a desired target. In a preliminary report, Ruiz-Esparza et al[40] treated rhytides in the peri-orbital region of 45 patients and found "some degree of improvement" in 60% of patients. This and other clinical studies are on-going and should define the efficacy of this device in the near future.

CONCLUSIONS

The objective of nonablative photorejuvenation is to confine selectively, without any epidermal damage, thermal injury to the papillary, and upper reticular dermis leading to fibroblast activation and synthesis of new collagen and extracellular matrix material. At the present time, nonablative photorejuvenation of human skin should not be considered an alternative to LSR. The skin surface is not removed or modified. What really occurs may be more accurately referred to as dermal "remodeling" or "toning" as a wound healing response is initiated and subsurface collagen regenerated.

Both patients and physicians are willing to accept subtle, incremental, and gradual improvements if the procedure is associated with reduced discomfort, minimal morbidity, no interference with lifestyle, and a low risk of complications such as prolonged erythema and dyspigmentation. Patients should be informed that the collagen remodeling response is delayed and that maximum regeneration occurs 30 to 90 days after treatment.

Improved results are obtained when non-ablative photorejuvenation is combined with other techniques such as Botox (Allergan Inc., Irvine, CA) injections into forehead lines and/or crow's feet, filler injections, superficial chemical peels, microdermabrasion and long-term skin care regimens. Candidates for nonablative photorejuvenation are patients: 1) who decline ablative LSR; 2) willing to accept subtle, incremental, and gradual improvements; and 3) participating in a long-term antiaging rejuvenation and skin maintenance program.

The development of non-ablative rejuvenation of human skin is at an early stage. The narrow "therapeutic window" of laser-induced dermal heating and epidermal cooling must still be optimized so that effective treatments can be obtained routinely. Clinical verification of effective treatment parameters will be obtained through further human studies. Most importantly, understanding the relationship between the degree of dermal thermal injury and synthesis of new colla-

gen and extracellular matrix material will be fundamental to optimizing the clinical efficacy and defining the limitations of nonablative photorejuvenation.

REFERENCES

1. Kelly KM, Nelson JS: Laser skin resurfacing. Lasers Med Sci 13:232-241, 1998
2. Fitzpatrick RE, Rostan EF, Marchell N: Collagen tightening induced by carbon dioxide laser versus erbium:YAG laser. Lasers Surg Med 27:395-403, 2000
3. Fisher GJ, Wang ZQ, Datta SC, et al: Pathophysiology of premature skin aging induced by ultraviolet light. N Engl J Med 337:1419-1428, 1997
4. Kligman AM, Zheng P, Lavker RM: The anatomy and pathogenesis of wrinkles. Br J Dermatol 113:37-42, 1985
5. Bernstein EF, Chen YQ, Kopp JB, et al: Long-term sun exposure alters the collagen of the papillary dermis: comparison of sun-protected and photoaged skin by Northern analysis, immunohistochemical staining, and confocal laser scanning microscopy. J Am Acad Dermatol 34:209-218, 1996
6. Thomsen SL, Ellard J, Schwartz JA, et al: Chronology of healing events in pulsed CO_2 laser skin resurfacing in fuzzy rat, in Anderson RR, Bartels KE, Bass LS, et al (eds): Lasers in Surgery: Advanced Characterization, Therapeutics, and Systems VIII, Proc SPIE 3245:337-343, 1998
7. Cotton J, Hood AF, Gonin R, et al: Histologic evaluation of preauricular and postauricular human skin after high-energy, short-pulse carbon dioxide laser. Arch Dermatol 132: 425-428, 1996
8. Kaufmann R, Hibst R: Pulsed erbium: YAG laser ablation in cutaneous surgery. Lasers Surg Med 19:324-330, 1996
9. Kuo T, Speyer MT, Ries WR, et al: Collagen thermal damage and collagen synthesis after cutaneous laser resurfacing. Lasers Surg Med 23:66-71, 1998
10. Ratner D, Viron A, Puvion E: Pilot ultrastructural evaluation of human pre-auricular skin before and after high-energy pulsed carbon dioxide laser treatment. Arch Dermatol 134:582-587, 1998
11. Mordon S, Capon A, Creusy C, et al: In vivo experimental evaluation of skin remodeling by using an Er:glass laser with contact cooling. Lasers Surg Med 27:1-9, 2000
12. Nelson JS, Majaron B, Kelly KM: Active skin cooling in conjunction with laser dermatologic surgery. Sem Cutan Med Surg 19:253-266, 2000
13. Nelson JS, Milner TE, Anvari B, et al: Dynamic epidermal cooling during pulsed laser treatment of port-wine stain. A new methodology with preliminary clinical evaluation. Arch Dermatol 131:695-700, 1995
14. Nelson JS, Kimel S: Safety of cryogen spray cooling during pulsed laser treatment of selected dermatoses. Lasers Surg Med 26:2-3, 2000
15. Kelly KM, Nelson JS, Lask GP, et al: Cryogen spray cooling in combination with nonablative laser treatment of facial rhytides. Arch Dermatol 135:691-694, 1999
16. Goldberg DJ: Full-face nonablative dermal remodeling with a 1320 nm Nd:YAG laser. Dermatol Surg 26:915-918, 2000
17. Menaker GM, Wrone DA, Williams RM, et al: Treatment of facial rhytides with a nonablative laser: a clinical and histologic study. Dermatol Surg 25:440-444, 1999
18. Goldberg DJ: Non-ablative subsurface remodeling: Clinical and histologic evaluation of a 1320-nm Nd:YAG laser. J Cutan Laser Ther 1:153-157, 1999
19. Trelles MA: Short and long-term follow-up of nonablative 1320 nm Nd:YAG laser facial rejuvenation. Dermatol Surg 27:781-782, 2001
20. Trelles MA, Allones I, Luna R: Facial rejuvenation with a nonablative 1320 nm Nd:YAG laser: a preliminary clinical and histologic evaluation. Dermatol Surg 27:111-116, 2001
21. Levy JL, Trelles MA, Lagarde PJ, et al: Treatment of wrinkles with the nonablative 1320-nm Nd:YAG laser. Ann Plast Surg 47:482-488, 2001
22. Hardaway CA, Ross EV, Barnette DJ, et al: Non-ablative cutaneous remodeling with a 1.45 μm mid-infrared diode laser: phase I. J Cosmet Laser Ther 4:3-8, 2002
23. Hardaway CA, Ross EV, Paithankar DY: Non-ablative cutaneous remodeling with a 1.45 μm mid-infrared diode laser: phase II. J Cosmet Laser Ther 4:9-14, 2002
24. Hardaway CA, Ross EV: Nonablative laser skin remodeling. Derm Clinics 20:97-111, 2002
25. Fournier N, Dahan S, Barneon G, et al: Nonablative remodeling: Clinical, histologic, ultrasound imaging, and profilometric evaluation of a 1540 nm Er:glass laser. Dermatol Surg 27:799-806, 2001
26. Zelickson BD, Kilmer SL, Bernstein EF, et al: Pulsed dye laser therapy for sun damaged skin. Lasers Surg Med 25:229-236, 1999
27. Bjerring P, Clement M, Heickendorff L, et al: Selective non-ablative wrinkle reduction by laser. J Cutan Laser Ther 2:9-15, 2000
28. Fitzpatrick RE, Goldman MP, Satur NM, et al: Pulsed carbon dioxide laser resurfacing of photo-aged facial skin. Arch Dermatol 132:395-402, 1996
29. Rostan E, Bowes LE, Iyer S, et al: A double-blind, side-by-side comparison study of low fluence long pulse dye laser to coolant treatment for wrinkling of the cheeks. J Cosmet Laser Ther 3:129-136, 2001
30. Chan HH, Fung WK, Ying SY, Kono T: An in vivo trial comparing the use of different types of 532 nm Nd:YAG lasers in the treatment of facial lentigines in Oriental patients. Dermatol Surg 26:743-749, 2000
31. Goldberg DJ, Meine JG: A comparison of four frequency-doubled Nd:YAG (532 nm) laser systems for treatment of facial telangiectasias. Dermatol Surg 25:463-467, 1999
32. Bernstein EF, Ferreira M, Anderson D: A pilot investigation to subjectively measure treatment effect and side-effect profile of non-ablative skin remodeling using a 532 nm, 2 ms pulse-duration laser. J Cosmet Laser Ther 3:137-141, 2001
33. Goldberg DJ, Whitworth J: Laser skin resurfacing with the Q-switched Nd:YAG laser. Dermatol Surg 23:903-907, 1997

34. Newman J, Lord J, McDaniel DH: Non-ablative laser therapy in skin types I-VI: Clinical evaluation of facial treatment using QS 1064 nm Nd:YAG laser combined with carbon suspension lotion. Lasers Surg Med Supplement 12:17, 2000

35. Goldberg DJ, Metzler C: Skin resurfacing utilizing a low-fluence Nd:YAG Laser. J Cutan Laser Ther 1:23-27, 1999

36. Lee M-WC: Combination Aura 532 nm and Lyra 1064 nm lasers for non-invasive skin rejuvenation and toning. Lasers Surg Med Supplement 14:32, 2002

37. Lowe NJ, Lask G, Griffin ME, et al: Skin resurfacing with the Ultrapulse® carbon dioxide laser. Dermatol Surg 21: 1025-1029, 1995

38. Muccini JA, O'Donnell FE, Fuller T, et al: Laser treatment of solar elastosis with epithelial preservation. Lasers Surg Med 23:121-127, 1998

39. Bitter PH: Noninvasive rejuvenation of photodamaged skin using serial, full-face intense pulsed light treatments. Dermatol Surg 26:835-843, 2000

40. Ruiz-Esparza J, Barba-Gomez JM, Buckman P, et al: First case reports of a new radio frequency procedure to noninvasively contract facial skin. Poster Presentation American Academy of Dermatology Annual Meeting, New Orleans, LA, 2002