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Cutaneous Effects of Cryogen Spray Cooling on In Vivo Human Skin

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The cryogen spray cooling method described in this article is contained within U.S. Patent 5,814,040-Apparatus and Method for Dynamic Cooling of Biological Tissue for Thermal Mediated Surgery, awarded to J. Stuart Nelson, MD, PhD, Thomas E. Milner, PhD, and Lars O. Svaasand, PhD, and assigned to the Regents of the University of California.

BACKGROUND Despite widespread clinical use of cryogen spray cooling (CSC) in conjunction with laser dermatologic surgery, in vivo cutaneous effects have not been systematically evaluated.

OBJECTIVE The authors characterize the in vivo cutaneous effects for Fitzpatrick skin types I through VI after CSC exposures of varying spurt durations and spurt delivery patterns (single vs. multiple spurts).

METHODS AND MATERIALS Twenty-seven normal human subjects were exposed to single cryogen spurts from 10 to 80 milliseconds, and multiple spurt patterns consisting of two 20-millisecond spurts, four 10-millisecond spurts, and eight 5-millisecond spurts. Subjects were evaluated by clinical observation and photography at 1 hour, 1 day, and 1, 4, 8, and 12 weeks after CSC exposure.

RESULTS Acute erythema and urticaria (1–24 hours) were noted in 14 of 27 and 3 of 27 subjects, respectively. Transient hyperpigmentation occurred in 4 of 27 subjects (skin types III–VI) but resolved spontaneously without medical intervention in all subjects by 8 weeks. No permanent skin changes were noted in any subjects. Skin reactions were more common with longer single-spurt durations (50 milliseconds or greater) and multiple spurt patterns.

CONCLUSION Acute erythema, urticaria, and, less commonly, transient hyperpigmentation were observed after CSC exposure. Permanent skin injury was not observed and is unlikely.

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Cryogen spray cooling (CSC) is a method of epidermal cooling frequently used in conjunction with dermatologic laser therapy. A cryogen spurt with a duration of milliseconds is applied to the skin surface immediately before laser exposure to selectively cool the epidermis. The use of

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epidermal cooling during laser treatment decreases procedural-associated pain, allows safer treatment of darker skin types, and allows use of higher fluences.¹⁻³

CSC has been incorporated into many Food and Drug Administration (FDA)-approved, commercially available laser devices currently used for treatment of vascular lesions, hair removal, and nonablative skin rejuvenation.⁴ 1,1,1,2-Tetrafluoroethane, an environmentally compatible, nontoxic, nonflammable freon substitute,⁵ has been demonstrated in multiple studies to be a safe and effective cooling agent and is the only cryogenic compound currently approved for dermatologic use by the FDA.

Despite the extensive clinical use of CSC, the cutaneous effects of CSC have not been well characterized. Hirsch and colleagues⁶ and Weisberg and Greenbaum⁷ observed arcuate-shaped permanent dyspigmentation after laser hair removal performed in combination with CSC. The cause of the injury was unclear, but the authors hypothesized that the skin discoloration may have been a result of cold injury caused by CSC. In an effort to address this potential issue, preliminary studies were performed in a RAFT tissue culture model to evaluate epidermal and dermal effects of single cryogen spurts (SCS) of 10 to 100 milliseconds.⁸ Minimal if any injury was observed with SCS

of 80 milliseconds or less. Longer spurt durations are rarely used clinically but, in this *in vitro* study, did result in epidermal injury.

A subsequent evaluation⁹ demonstrated that angling of the handpiece during treatment can result in a cryogen/laser spot mismatch and produce arcuate-shaped burn patterns, similar to those observed by Hirsch and colleagues⁶ and Weisberg and Greenbaum.⁷ As such, it was proposed that laser burn and not cryoinjury was the likely cause of the reported permanent dyspigmentation.

In recent years, clinicians and engineers have sought to expand the boundaries of laser dermatologic surgery, using higher fluences to improve therapeutic outcomes in patients of all skin types.¹⁰⁻¹² Several commercially available devices have been designed to deliver multiple intermittent cryogen spurts (MCS) before, after, or alternated with laser exposure in a variety of patterns in an effort to augment epidermal cooling and permit the safe use of higher fluences.¹³ RAFT tissue culture model studies, however, demonstrated that epidermal injury risk increased for MCS patterns compared to SCS of the same total cryogen delivery time when the total cooling time was less than 110 milliseconds.^{14,15}

The RAFT model is a useful evaluation tool but has several limitations including a lack of

blood vessels, an inability to vary melanin content (replicate different Fitzpatrick skin types), and greater sensitivity of the RAFT epidermal cells compared to intact *in vivo* skin.

The specific aim of the current study was to characterize the *in vivo* cutaneous effects for Fitzpatrick skin types I through VI after CSC exposure of varying spurt durations and spurt delivery patterns (single vs. multiple spurts).

Methods and Materials

The protocol was approved by the University of California, Irvine, investigational review board and conformed to the guidelines of the 1975 Declaration of Helsinki, and all subjects were consented before participation.

Subjects

Twenty-seven normal human subjects were recruited from all six Fitzpatrick skin types.¹⁶ On each subject, the deltoid area served as the test site.

CSC Delivery

1,1,1,2-Tetrafluoroethane, also known as R134a ($T_b \approx -26.2^\circ\text{C}$ at atmospheric pressure) was contained at saturation pressure (6.7 bar at 25°C) and delivered through a standard high-pressure hose to a control valve. A commercial cryogen spray nozzle (with an approximate inner diameter of 0.5 mm) was used for laser treatment of vascular

SCS 10 ms	SCS 20 ms	SCS 30 ms
SCS 40 ms	SCS 50 ms	SCS 60 ms
SCS 70 ms	SCS 80 ms	MCS 20 ms × 2
MCS 10 ms × 4	MCS 5 ms × 8	

Figure 1. Replication of grid used in this study during skin application of single cryogen spurts (SCS) and multiple cryogen spurt (MCS) patterns.

lesions, and hair removal was employed to spray the cryogen onto the skin.

The nozzle-to-sprayed surface distance, z , was 31 mm (similar to that currently used in several commercially available CSC devices). The relative humidity was 39% and room temperature was approximately 23°C.

Subjects were exposed to SCS of 10 to 80 milliseconds in 10-millisecond increments (e.g., 10, 20, and 30 milliseconds) and to MCS consisting of two 20-millisecond spurts, four 10-millisecond spurts, and eight 5-millisecond spurts (Figures 1 and 2). The delay time between spurts for all MCS was 10 milliseconds.

Cutaneous Evaluation

Test sites were carefully evaluated before intervention and then monitored by clinical observation for cutaneous change (specifically erythema, urticaria, blistering,

dyspigmentation, and scarring) at 1 hour, 1 day, and 1, 4, 8, and 12 weeks after CSC exposure.

Observable skin changes were graded on the following scale: 0 = absent; 1 = minimal (light pink; barely perceptible skin elevation; whitening of skin, no evident blister); 2 = mild (light red/pink; slight skin elevation; skin wrinkling—no well-formed blister); 3 = moderate (red; clearly visible urticaria; flaccid blisters); and 4 = severe (very red; pronounced urticaria; tense blisters)

Results

Twenty-seven subjects (five of skin types I, II, III, and IV each; 3 of type V; and 4 of type VI) were enrolled. Acute erythema was noted in 14 of 27 subjects (Table 1 and Figure 3). One hour after CSC, 1+ erythema (based on the scale above) was present in 12 of 27 subjects, and 2+ erythema was present in 1 subject with type II skin. One skin type III subject did not develop 1+ erythema until 1 day after CSC. In most of the subjects, the erythema was resolved by 24 hours. In 4 sub-

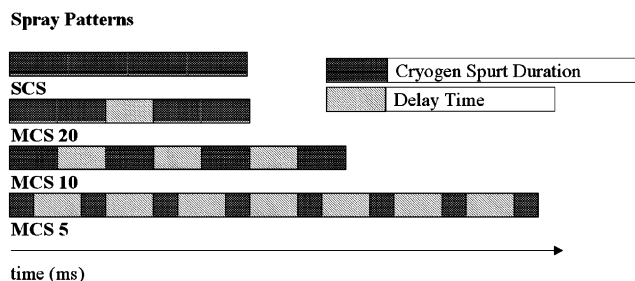


Figure 2. Diagram of multiple cryogen spurt (MCS) patterns evaluated in this study. SCS = single cryogen spurts.

jects, there was still mild erythema at 24 hours, which was resolved at the 1-week follow-up.

Urticaria was noted in 3 of 27 subjects (Table 1 and Figures 3 and 4). One each of skin types I and II developed 1+ urticaria. One type VI subject developed 2+ urticaria. All urticaria was resolved at the day 1 follow-up. No blistering was observed in any subjects.

Transient hyperpigmentation (Table 1 and Figure 4) occurred in 4 of 27 subjects [2 with skin type III (1+), 1 with skin type V (1+), and 1 with skin type VI (2+)]. All hyperpigmentation was resolved by 8 weeks.

No subjects developed hypopigmentation or scarring. Skin reactions were more common with longer single SCS (greater than 50 milliseconds) and MCS patterns.

Discussion

Dermatologists commonly use liquid nitrogen for destruction of benign and malignant skin lesions and, thus, are familiar with the

TABLE 1. Observed Changes for Each Fitzpatrick Skin Type*

Skin Change	Fitzpatrick Skin Type					
	I	II	III	IV	V	VI
Erythema	4/5 (all 1+); SCS 50–80 ms; MCS 5, 10, 20; all resolved at 1 day	3/5 (1+, 2+); SCS 40–80 ms; MCS 5, 10, 20; all resolved at 1 week	4/5 (all 1+); SCS 50–80 ms; MCS 5, 10; all resolved at 1 week	3/5 (all 1+); SCS 60–80 ms; 5,10; MCS all resolved at 1 week	0/3	0/4
Urticaria	1/5 (1+); SCS 80 ms; MCS 5; resolved at 1 day	1/5 (1+); SCS 50–80 ms; MCS 5, 10, 20; resolved at 1 day	0/5	0/5	0/3	1/4 (2+); SCS 40–80 ms MCS 5, 10, 20; all resolved at 1 hr
Blistering	0/5	0/5	0/5	0/5	0/3	0/4
Hyperpigmentation	0/5	0/5	2/5 (1+); SCS 60–80 ms MCS 5, 10, 20; all resolved at 4 weeks	0/5	1/3 (1+); SCS 70, 80 ms; MCS 5, 10; resolved at 8 weeks	1/4 (2+); SCS 50–80 ms; MCS 5, 10; resolved at 8 weeks
Hypopigmentation/scarring	0/5	0/5	0/5	0/5	0/3	0/4

*Note: 1+ = minimal change (light pink; barely perceptible skin elevation); 2+ = mild (light red/pink; slight skin elevation). SCS, single cryogen spurts; MCS, multiple intermittent cryogen spurts.



Figure 3. Type II subject with erythema and urticaria at 1 hour after cryogen spray cooling (CSC) exposure at 50, 60, 70, and 80 milliseconds and all multiple cryogen spurt (MCS) pattern test spots. After CSC exposure day 1, mild erythema was still present at the 80-millisecond and MCS test spots. No erythema or pigmentary change was noted at 1 week after CSC or later.

destructive effects that can be induced on skin by cryogen application. Liquid nitrogen is generally applied to the skin for several seconds resulting in rapid tissue temperature decrease to -50 or -60°C . Significant skin injury generally results and is the intended goal in an effort to remove an unwanted lesion.

CSC differs significantly from liquid nitrogen dermatologic cryosurgery. CSC utilizes SCS of 10 to 80 milliseconds or MCS patterns of tetrafluoroethane applied to the skin as a fine mist, resulting in a thin layer of cryogen on the skin surface that is rapidly evaporated. The much abbreviated (millisecond) applications expose the skin surface to sub-zero temperatures for less than

2 seconds. Cryogen-induced skin response depends on both the degree and the time of skin temperature alteration. As such, the tissue response to CSC is greatly different from that observed with liquid nitrogen cryosurgery.

In this study, cryogen exposure alone was evaluated. Of course in clinical practice, CSC is always used in conjunction with laser heating, and this may minimize cryoinjury. As such, it could be stated that our study evaluates an extreme situation, and clinicians are likely to note even less skin response than the authors observed. Of the 27 subjects who were tested in this study, 14 developed mild to moderate erythema and 3 developed mild

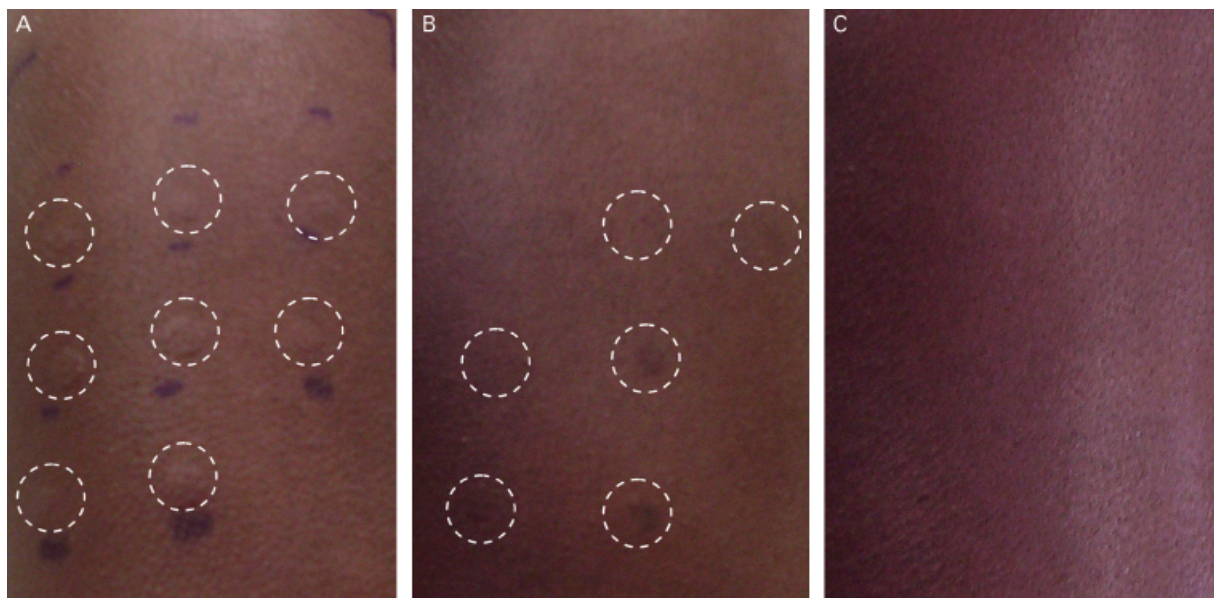


Figure 4. Type VI subject with (A) urticaria immediately after cryogen spray cooling (CSC) exposure at 40, 50, 60, 70, and 80 milliseconds and all multiple cryogen spurt (MCS) pattern test spots. This was resolved by the 1-hour evaluation. (B) Hyperpigmentation developed at 1 week after CSC at 50, 60, 70, and 80 milliseconds, and MCS 5 and MCS 10 spots. (C) Hyperpigmentation was completely resolved at 8 weeks after CSC.

urticaria. In all cases, these reactions were well tolerated, required no treatment, and in most cases resolved within 1 day. Four subjects developed mild transient hyperpigmentation, which again was well tolerated and required no treatment and was resolved by 8 weeks. Cryogen-induced hyperpigmentation can be minimized by careful selection of cryogen parameters and potentially with use of bleaching agents and sun protection after treatment. The authors did not find any permanent skin changes.

Transient (1 week or less) scabbing or crusting was not observed in this study but has been noted very rarely by the authors (KMK) in clinical practice. The cause of such changes is not known, but it is possible it was a cutaneous

cryogen response; alternatively, such injury could result from laser heating with inadequate epidermal cooling.

Although the CSC exposures evaluated in this study resulted in minimum tissue response, significantly longer SCS applications or MCS patterns that result in prolonged skin temperature depressions (as a result of longer spurts or possibly longer delay times) could result in an enhanced potential for injury. This should be kept in mind as industry develops new devices, especially those with the potential to deliver high energies that require enhanced epidermal cooling.

As noted in the introduction, skin injury has been associated with laser procedures performed in conjunction with CSC.^{6,7} The current

study demonstrates that cryogen is unlikely to be the cause of permanent skin injury, and other etiologies should be sought. Laser-induced burn injury can result from operator angling of the handpiece during treatment or handpiece misalignment.⁹ Failure of the cryogen to fire resulting in exposure of the skin to high laser energies without epidermal protection can also result in laser burn.

In summary, at the evaluated commonly utilized cryogen parameters, CSC may cause acute erythema and more rarely urticaria and transient hyperpigmentation. No evidence of cryogen-induced permanent skin dyspigmentation or scarring was found. CSC offers a safe method of selective epidermal cooling with minimal risk of cryoinjury.

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