

Ablative Fractional Versus Nonablative Fractional Lasers—Where Are We and How Do We Compare Differing Products?

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Abstract The concept of nonablative fractional photothermolysis was introduced almost a decade ago to address the main shortcomings of non-fractionated, nonablative devices available at that time. By delivering laser light as a series of fractionated columns, the 1550 nm Er:doped laser was able to achieve greater penetration depths and spare areas of normal intervening skin, allowing epidermal contribution to a more rapid healing process. Yet these devices, despite their more predictable outcomes, were felt to lack the efficacy of complete epidermal ablation, spawning the expansion of fractionated devices to include ablative wavelengths, which have proven more consistent and safer than pre-existing pulsed ablative devices. This article will summarize an ever-expanding literature to facilitate the application of both nonablative and ablative fractional technologies in clinical practice, and establishes grounds by which varying fractional lasers can be compared.

Keywords Fractional · Ablative · Nonablative · Laser · Cosmetic · Scar

Abbreviations

NAFL Nonablative Fractional Laser
AFL Ablative Fractional Laser

Introduction to Fractional Photothermolysis

A basic understanding of laser principles and laser-skin interaction is essential to developing a practical, working knowledge of fractional laser technology. Selective photothermolysis is the cornerstone of laser treatment and allows for safe and effective lasing of targeted chromophores in the skin [1]. The three chromophores in the skin (hemoglobin, water, melanin) may be selectively targeted because of each element's affinity to absorb particular wavelengths of light. When a particular wavelength with sufficient energy is absorbed by the intended chromophore, the target is destroyed. In order to avoid collateral photothermal destruction, the pulse width for a given laser must be shorter than the thermal relaxation time for its intended chromophore. Nonfractionated nonablative lasers primarily targeted hemoglobin, and thus, in combination with surface cooling, allowed thermal remodeling of the dermis with minimal damage to the avascular epidermis. Such an approach does not constitute true resurfacing as there is no re-epithelialization, and dermal effects were limited, in part, by a lack of epidermal regenerative signals in the wound healing process [2].

The first laser to incorporate fractional photothermolysis (Fraxel by Reliant Technologies Inc, Mountain View, CA) utilized a wavelength targeting water (1550 nm) in a non-ablative fashion. While the laser thermally denatured dermal

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collagen and epidermal tissue, it was considered nonablative because the skin's barrier function was retained with the sparing of the stratum corneum. By pixelating the laser energy, small (< 400 μm in diameter) columns of evenly spaced thermal damage were created, with depth of penetration proportional to energy per pixel. Each pixelated column of energy is referred to as a microscopic thermal zone (MTZ). By creating MTZ in only a fraction of the treatment area, the intervening, undamaged epidermis served as a reservoir of viable tissue for rapid repair of the coagulated MTZ in epidermal tissue, thus facilitating rapid and predictable epidermal healing.

Within the MTZ, coagulated material containing melanin, elastin, and other dermal contents has been histologically demonstrated to condense into a button-shaped conglomerate known as microepidermal necrotic debris (MEND) [3]. Transepidermal elimination of the MEND correlates clinically with the bronzing of skin and mild exfoliation seen in the first week following treatment. The wound healing response created by fractional photothermolysis is thought to account for the long-term dermal effects such as neocollagenesis. Although not fully elucidated, it is believed that increased expression of heat shock proteins, increased collagen III deposition, and an increased myofibroblast population play a role in this process [3].

Similarly, the evolution of ablative laser technology to the fractionated state can be seen as one of necessity. Continuous wave ablative lasers, which vaporize the entire epidermis and papillary dermis, were used for resurfacing in the 1980s and 1990s, at times with exceptional results. However, such lasers were hindered by bulk heating phenomena, and have largely fallen out of favor due to their unpredictable nature and unacceptable healing times. To better control nonspecific (bulk) heating, short and ultra-pulsed ablative lasers with high peak power were created which had the advantage of reliable ablation depth with decreased risk of scarring, but prolonged recovery times following resurfacing procedures remained unattractive [4]. Fractionating the pulsed ablative laser energy into smaller individual spot sizes (i.e. 120 μ) covering only a fraction of the treated area (usually 5–30 %) allowed for rapid re-epithelialization from the undamaged, adjacent epidermis that separates the MTZs [5]. Histologically, the MTZ of ablative fractionated laser differ from nonablative fractionated MTZs in that the former MTZ is marked by a central column of stratum corneum, epidermal, and dermal ablation lined by a thin eschar and surrounded by an annular coagulation zone (the so-called penumbra). Hantash et al. demonstrated increased heat shock protein expression and collagen modeling with these zones 3 months post treatment, and their hypothesis that greater degrees of tissue injury with ablative (vs. nonablative) fractionated laser lead

to prolonged neocollagenesis and dermal remodeling appears to be playing out per the review of literature presented below [6].

Nonablative Fractional Lasers

NAFLs are currently approved by the Food and Drug Administration (FDA) for the treatment of pigmented lesions, periorbital rhytides, skin resurfacing, melasma and soft tissue coagulation, acne and surgical scars, and actinic keratosis [7]. However, NAFLs are routinely used, successfully, for several off-label indications, such as cosmetic rejuvenation, and have become popular due to their relative comfort compared to AFL treatments. NAFL may also offer a lower incidence of adverse side effects, which includes erythema, edema, pain and post-inflammatory hyperpigmentation [8]. The following sections will focus on the three most common indications for NAFLs and AFLs: dyspigmentation, scarring, and photoaging.

Disorders of Pigmentation

In the last 2 years, three controlled trials have demonstrated no additional benefit from NAFLs when compared with standard, topical therapies in the treatment of melasma [9–11]. In 2012, Karsai et al. compared the effects of broad-spectrum sunscreen with or without four adjuvant 1550 nm treatments in a prospective controlled trial of 51 patients. Their results showed an identical improvement in both groups, leading to their conclusion that NAFLs do not show any benefit over using a broad-spectrum sunscreen by itself [9].

Similarly, a randomized controlled study in 2010 compared 1550 nm NAFL to triple topical therapy (hydroquinone 5 %, tretinoin 0.05 %, and triamcinolone acetonide 0.1 % cream). Twenty patients were given either a total of four laser treatments spaced every two weeks apart, or triple topical therapy used daily. A similar efficacy between the two regimens was noted, with a majority of patients in both groups experiencing recurrence of melasma within 6 months. Given the cost and pain associated with NAFL however, the authors concluded that triple therapy should continue to be the standard of care [10]. Later in 2010, several of the same authors performed a randomized, controlled, split-face study of 29 patients comparing triple topical therapy with 4–5 sessions of 1550 nm laser. Their results showed a significant post-inflammatory hyperpigmentation (PIH) in areas treated with the laser and, again, the authors concluded NAFL was not superior to topical therapy [11].

In addition to melasma, NAFL has shown limited efficacy in the treatment of other pigmentary disorders. A

pilot study from 2012 evaluated the improvement in erythema dyschromicum perstans (EDP) and PIH using a 1550 nm laser. Two similar test spots in eight patients with EDP and six with PIH were given either five treatments of NAFL in combination with topical bleaching regimen or the topical bleaching regimen alone. At three-month follow-up, three patients were noted to have developed laser-induced PIH, and overall laser therapy provided no added benefit [12]. In summary, one must be approach NAFL cautiously when treating dyspigmentation, as it may worsen/induce hyperpigmentation. Topical bleaching agents (such as triple preparations) and strict photoprotection should be considered first line, especially in year-round sunny environments.

Scars (Acne, Burn, and Surgical) and Striae

Patients that undergo NAFL treatment for acne scarring experience 1–3 days of intense erythema that generally resolves within one week, a maximum of 26–50 % improvement in scars, and a high tolerability [13]. The severity of acne scarring is an important factor to consider when counseling patients on the potential benefits of NAFL. In a study of eighty-seven patients, those patients with moderate acne scarring showed better improvement than those with severe scarring after six sessions of 1540 nm NAFL [14]. A review done by Ong et al. looked at 26 studies (13 AFL, 13 NAFL) focusing on acne scarring and noted overall improvement with NAFL, however it did not break down results into types of acne scar (ice pick, boxcar, rolling, and hypertrophic). Further studies examining the efficacy of NAFL in treatment of these different types of scars could help direct treatment in the future [13].

Benefit with NAFL in atrophic processes other than acne scarring has also been demonstrated. In a study of 51 patients with striae rubra or alba, de Angelis et al. demonstrated at least 50 % overall visual improvement which was sustained at 18–24 months following a series of treatments with 1540-nm NAFL [15]. Histological sections from treatment areas revealed thickening of the epidermis and dermis, neocollagenesis, and increased elastin deposition [15]. Improvement in striae with minimal adverse effects has also been demonstrated following treatment with 1550 nm NAFL [16, 17].

The benefits of NAFL are not limited to atrophic scarring. In a randomized, controlled trial of 17 adults with mature thermal burn scars, Haedersdal et al. found significant ($P=0.0007$) improvement in scar texture 12 weeks following completion of three 1540 nm NAFL treatments when compared to no treatment [18]. Similarly, Waibel et al. treated ten subjects with second- or third-degree burn scars in a single arm pilot study and found improvement in skin

texture, dyschromia, and scar elevation in 90 %, 80 %, and 80 % (respectively) of patients following five monthly treatments with 1550-nm NAFL [19].

While pulsed dye laser has long been viewed as the gold standard for correction and/or prevention of hypertrophic or otherwise unsightly post surgical scars, Tierney et al. found a more significant improvement overall with 1550-nm NAFL than PDL ($P<0.001$) in a split scar study following Mohs surgery [20]. However, in a randomized, controlled split scar trial of 18 patients who had received Mohs surgery in the previous three years, Verhaeghe et al. were unable to ascertain a statistically significant improvement between control and 1540-nm NAFL using a validated Physician Global Assessment, but the patient's global assessment favored 1540-nm NAFL at 3 month follow-up ($P=0.02$) [21]. In our opinion, NAFL, in its infancy, if has demonstrated significant potential in the treatment of post-surgical, burn, and other traumatic scarring with minimal adverse effects, however the optimal time to treat, treatment parameters, and appropriate follow-up have yet to be elucidated.

Cosmetic Rejuvenation

There is an ever-expanding market for safe, reliable, and well-tolerated technologies capable of reversing cutaneous photodamage, rhytides, and dyspigmentation. In 2007 Wanner et al. used comparative photography to demonstrate statistically significant improvements ($P<0.001$) in cutaneous photodamage that were retained for 9 months in 73 % of facial and 55 % of non-facial sites following three sessions of 1550-nm NAFL [22]. Others have since shown similar benefit in the treatment of facial rhytides, but improvements have been less well sustained at twelve weeks following treatment [23]. Regarding treatment of nonfacial sites, Peterson et al. recently published a comprehensive guide to rejuvenation of the aging chest, which supported the safety and efficacy of NAFLs in this location [24].

Given the early success of NAFL in cutaneous rejuvenation several studies have sought to expand the cosmetic applicability of such devices. For example, Saedi et al. demonstrated a 17 % objective reduction in pore size using 1440 NAFL, however their study was hampered by a short (2 week) follow-up period [25]. Leyden and colleagues recently studied an at-home handheld 1410-nm NAFL unit (PaloVia device) in 124 patients with periorbital rhytides. Treatments were daily for four weeks (active phase) and then twice daily for either four or twelve weeks (maintenance phase), with 90 % of subjects reporting wrinkle improvement by one or more grades in the Fitzpatrick Wrinkle Scar after the active phase and 79 % following the maintenance phase [26]. Such studies only sample

NAFLs potential for in office and at-home cosmetic rejuvenation.

Ablative Fractional Lasers

AFLs are currently approved by the FDA for treatment of wrinkles, rhytides, furrows, fine lines, textural irregularities, pigmented lesions, and vascular dyschromia [7]. While side effects can potentially be more severe than in NAFL, AFL is a safe and effective treatment modality when used correctly. However there is a longer downtime and more pain during the treatment for patients in AFL compared to NAFL. Mild to moderate side effects include prolonged erythema, acneiform eruptions, milia formation, herpes simplex infection, and postinflammatory hyperpigmentation, the latter of which is almost universally seen in darker skin types (Fitzpatrick III–VI). Although the cutaneous response to ultrapulsed ablative resurfacing is more predictable when fractionated as compared to older nonfractionated delivery devices, severe side effects still occur following aggressive treatment to include scarring, particularly on nonfacial locations and areas of thin skin such as the lower eyelid [27].

Disorders of Pigmentation

AFLs are less commonly used for melasma. A comparative study published in 2010 evaluated the treatment of melasma in 30 Fitzpatrick skin type II–IV females with topical cream (Kligman's formula) alone, 10600-nm AFL alone, or a combination of the two. While patient satisfaction index and overall efficacy were 100 % for all groups at 1 month follow-up, only the combination group maintained statistically significant improvement at 6 and 12 month follow-up ($p < 0.001$) [28]. A single case report has also documented successful treatment of melasma in a Fitzpatrick skin type V female using 10600-nm AFP [29], although it is our recommendation that patients with type IV–V skin only be treated by physicians with extensive AFL experience.

Scars (Acne, Burn, and Surgical) and Striae

To date, the majority of controlled trials assessing the efficacy of AFL in scarring have focused on acne scars. Ong et al. recently concluded in a thorough review that acne scar improvement utilizing AFL ranged from 26–83 %, compared to the 26–50 % improvement with NAFL discussed above [13]. The reader is directed to this review for a more in-depth analysis of AFL (and NAFL) in acne scarring.

The data supporting AFP for nonacne atrophic scars is limited. In a prospective study by Cervelli et al. comparing

30 patients who underwent 10600-nm AFL (Active and Deep Fx, Ultrapulse Encore, Lumenis Ltd., Santa Clara, CA) to 30 different patients who underwent classic diamond fraise dermabrasion in the treatment of post-traumatic and pathologic atrophic scars, statistically significant improvements ($p < 0.05$) in pigmentation, texture, and overall appearance were noted in the AFL group [30]. Likewise, Weiss et al. published similar improvement in mature (>6 months duration) atrophic postoperative and traumatic scars in 15 women following a series of treatments with 10600-nm AFB (Fraxel Repair, Solta Medical, Hayward, CA) [31].

More recently, attention has shifted to the prevention or minimization of unsightly postsurgical scars using early AFL treatment. Jung et al. treated 23 Korean females (Fitzpatrick skin type III–V) 2–3 weeks post-thyroidectomy in an uncontrolled study using 10600-nm AFP (Lutronic Corporation, Goyang, Korea) and found statistical improvement in the Vancouver scar scale at 3-month follow-up ($p < 0.001$) when compared to pretreatment. Aesthetic improvement was accompanied by minimal adverse effects and high patient satisfaction [32]. Drawing on previous experience with intraoperative wound edge treatment with pulsed CO₂ [33], Ozog et al. recently demonstrated benefit from similar intraoperative treatment with AFL [34]. While the exact parameters (energy and thus depth of penetration and density in particular) and time course (intraoperative versus suture removal vs. months later) remain undefined in scar prevention/ abatement, this concept holds significant potential and should be aggressively pursued with larger studies.

Although no controlled trials have yet been conducted, case reports and series demonstrate a role for AFLs in the treatment of hypertrophic thermal burn scars. The first report was of an AFL device was used to treat a disfiguring scar that was over 50 years old [35]. Following that case report, another was published demonstrating the effective treatment of a 30-year-old thermal burn scar on a skin type IV female patient [36]. Ozog and colleagues recently published a report of 10 burn scar patients who experienced similar benefit. Histological evaluation of treated areas suggested a reorganization of the type I and III collagen profile to that of unwounded skin may largely explain the observed benefit [37]. Furthermore, Kineston et al. have demonstrated improved range of motion in a morphea-related lower extremity contracture following 10600-nm AFL [38], and studies are currently underway at our institution to evaluate functional improvement in traumatic scar patients.

Cosmetic Rejuvenation

Rejuvenation of photoaging as well as improvement in pigmentary abnormalities by more targeted superficial ablation has been a driving force behind the advancement of

AFL. Tierney et al. recently published a review specific for comparing NAFL with AFL and determined that AFL produces greater improvements in texture abnormalities. These authors went on to conduct a prospective, single blinded study on the treatment of lower eyelid rhytides with AFL utilizing a CO₂ laser. They concluded the fractional CO₂ laser produced results were on par with the earlier, fully ablative devices for improvement of skin texture and laxity of lower eyelid skin. In addition, AFL produced significantly greater results in periocular and perioral rhytides, skin texture, and skin laxity when compared to NAFL [39]. In 2012, Tierney published a blinded, single arm trial in which >60 % improvement ($p < 0.05$) was safely accomplished for lower eyelid laxity, rhytides, and overall cosmesis 6 months following 2–3 10600-nm AFL sessions with a target ablation depth of 400 micrometers [40].

Discussion

Many expert opinions exist regarding which laser is ideal for select indications. Based on the wealth of studies noted above, it appears that NAFLs have less downtime and pain for most conditions. However, NAFLS may not be as effective per treatment compared to AFLs. According to Park et al., at 4 months post-treatment, AFL treatment shows “profound skin changes” and collagen remodeling on rats when compared to NAFL [41]. Kim et al. showed that AFL (2940 nm) on fresh (3 weeks postsurgery) thyroidectomy scars was more effective than NAFL (1550 nm) [42]. However, Alajlan and Alsuwaidan showed similar patient satisfaction and improvement as well as side effects with NAFL (1550 nm) versus AFL (10600 nm) with acne scarring [43]. Note that this was a superficial treatment and the fluence and depth of penetration of the energy must be considered when analyzing data (see question #1 below).

All things considered, one area that NAFL may have an advantage over AFL is in atrophic scars (though the author typically uses AFL at lower energy and higher density versus using NAFL). A randomized controlled trial comparing a nonablative fractional 1550-nm Er:Glass laser to an ablative CO₂ fractional laser in the treatment of striae distensae showed no statistical difference between the two treatment arms [44]. Given that both ablative and nonablative fractional thermolysis are very effective and relatively safe, one could conclude that NAFL is a better approach due to decreased downtime and pain. This highlights the importance of an appropriate risk/benefit discussion with the patient, in conjunction with using the 12 questions below, when deciding the optimal treatment and desired results for that patient.

It has become very difficult to assess what the optimal laser may be when there are so many devices with many different variables in today’s laser market. The following list should be considered when reviewing the literature, as well as when purchasing and/or using the different devices that deliver fractionated energy. To date, there is no conversion table that allows one to compare different lasers (or a similar laser produced by different manufacturers) in an “apples to apples” manner; thus, the following questions will help one assess the important aspects of fractionated laser treatment.

1. Power: Peak power and pulse duration of each microbeam and total amount of fluence possible will influence the depth (depth of energy delivered often is correlated with fluence and/or bulk heating). When treating scars, for instance, there will be no expectation for improvement/remodeling if the energy does not reach the depth of the scar.
2. Diameter: Diameter of the microbeam and the amount of coagulation, if any peripherally (Er:YAG typically has no coagulation, versus CO₂ which has some that can vary)
3. Density: density of the microbeams (note every company assess this density differently, be clear on how they define density). If you have too much overlap with your density then the laser can be just like traditional nonfractionated ablative lasers.
4. Mechanism: How the energy is delivered (stamping versus rolling, for example, and how many options for each of the devices, e.g., square, circle, hexagon)
5. Flexibility: How does the device allow for variability and the ability to alter fluence, density and frequency settings to allow more versatility intraoperative or overall? (Pain is often correlated with higher fluence and frequency, so lowering one or the other, especially in AFL, may allow for a more tolerable treatment.)
6. Endpoint: How many treatments do you need to accomplish a particular endpoint? Some lasers allow one to be more aggressive and reach an endpoint early, but with more side effects and downtime. Assessing a patient’s activities of daily living will allow the practitioner to determine if the patient can afford the amount of downtime needed in one chunk versus many smaller treatments.
7. Ease of use: How easy and algorithmic is the use of the laser? This is especially true if a physician is not performing the procedures. Is one device more capable of developing algorithmic approach for staff and/ or less susceptible to complications?
8. Pain: How painful is the procedure? Does the provider have the ability for conscious sedation? Means to minimize pain can alter total duration of treatment time

within the clinic for the staff and/or provider. For example, conscious sedation increases pre- and post-operative time for the clinic and thus cost to the provider and patient. How much topical anesthetic needs to be used? How many nerve blocks does the patient need? How do authors control pain? A provider access to various modalities will have to be taken into account when deciding on a laser.

9. Duration: Total duration of the treatment from pre-op consent, numbing, post-op follow up, and the potential amount of counseling needed after procedure (hand-holding) should be taken into consideration. More time means more resources.
10. Downtime: Total downtime, as mentioned above in #6, to achieve a desired endpoint is very important.
11. Side-effect potential: The more aggressive settings and lasers often increase risks, including pigmentation risk, scarring, and infectious complications, thus increasing medical legal considerations, duration of therapy (#9 above) as well as downtime (#10).
12. Plausibility of the technology and technique: When things are too good to be true, they often are!

Future of Fractionation

AFL certainly has the advantage in a new exciting area where one uses the ablative vertical channels to enhance drug and product delivery. In 2010, a study utilizing porcine animal models demonstrated fractional CO₂ lasers may be safely used to facilitate the transdermal delivery of topically applied medications [45•]. Following that, another study demonstrated using a fractional CO₂ laser facilitated the delivery of both patch-coated hydrophilic drugs and a protein vaccine [46•]. The authors compared the amounts of substrates recovered from fractional CO₂ laser treated skin with topically applied drugs versus tape-stripped skin or control skin with patch-applied drugs. The laser treated skin was superior to the other two modalities and also showed efficient uptake by epidermal Langerhans and dermal dendritic cells as well as the presence of the above mentioned compounds in draining lymph nodes. An in vivo study was later conducted evaluating the effect of treatment density of ablative fractional lasers as well as the molecular weight of drugs in transcutaneous delivery [47].

Another area that is developing is the use of AFL for hair and sweat gland/ duct regeneration. Beachkofsky et al. showed that in three patients there was hair regrowth in burns scars and grafted skin after AFL [48]. Neiner et al. presented a patient that had sweat development after AFL in scarred areas that previously did not have the ability to sweat [49]. These new areas of research provide a large

Table 1 Indications and efficacy of nonablative and ablative lasers

Laser	Indications	Strength of recommendation	Level of evidence
Nonablative fractional lasers			
1410 nm	Melasma [50]	B	2
	Periorbital rhytides [26]	B	2
1440 nm	Facial pores [25]	B	2
1540 nm	Acne scars [14, 52, 54]	A	2
	Burn scars [18]	B	2
	Surgical scars [21, 51]	B	2
	Striae distensae [15]	B	2
	Photodamage [53]	B	2
1550 nm	Striae distensae [17, 44•, 56]	B	2
	Periorbital rhytides [57, 59]	B	2
	Photodamage [22, 23]	B	2
	Acne scars [60]	B	2
	Burn scars [19]	B	2
	Surgical scars [20, 58]	B	2
	Hypertrophic scars [55]	B	2
Ablative fractional lasers			
2940 nm	Photodamage [67–70]	A	2
	Acne scars [71]	B	2
10600 nm	Acne scars [13, 43, 62–65]	A	2
	Photodamage [39, 66]	B	2
	Post-traumatic scars [30, 31]	B	2
	Surgical scars [31, 32, 34]	B	2
	Burn scars [35–37]	B	2
	Striae distensae [44•, 61]	B	2
	Periorbital rhytides [40]	B	2
	Melasma [28, 29]	B	2

SORT Criteria [72]

Strength-of-Recommendation Grades

A: Consistent, good-quality patient-oriented evidence*

B: Inconsistent or limited-quality patient-oriented evidence*

C: Consensus, disease-oriented evidence,* usual practice, expert opinion, or case series for studies of diagnosis, treatment, prevention, or screening

*Patient-oriented evidence measures outcomes that matter to patients: morbidity, mortality, symptom improvement, cost reduction, and quality of life

*Disease-oriented evidence measures intermediate, physiologic, or surrogate end points that may or may not reflect improvements in patient outcomes (e.g., blood pressure, blood chemistry, physiologic function, pathologic findings)

Study Quality

Level 1 – good quality patient oriented evidence

Level 2 – limited-quality patient oriented evidence

Level 3 – other evidence

array of potential uses of lasers that AFL may have the advantage over NAFL (Table 1).

Conclusion

To optimally treat patients with fractionated devices one must understand the laser–tissue interactions and account for the questions proposed within this article. In general, the authors' experiences mimic the literature for skin resurfacing and rhytides, and our tendency is to use AFL as we see a better long-term results. AFL does induce more pain, erythema, and crusting that lasts longer. Careful selection of patients and skin type can minimize postinflammatory hyperpigmentation (PIH) and caution should be maintained as more energy is used, no matter the device.

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