Novel Approach to Facial Rejuvenation by Treating Skin and Muscle Tissue for Facial Lifting: Preliminary Data from Multicenter Clinical Trial

Brian M. Kinney, M.D.[1], Charles M. Boyd, M.D., MBA[2]

1. Clinical Associate Professor of Plastic Surgery, USC Keck School of Medicine, Los Angeles, CA, USA
2. Boyd Beauty, Birmingham, MI, USA

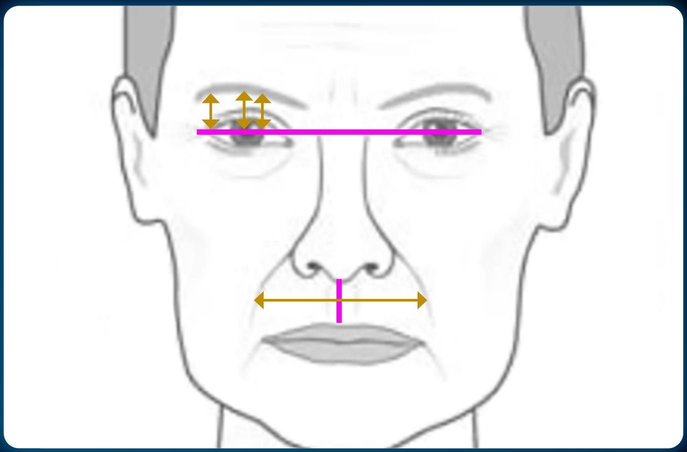
Accepted at American Academy of Facial Plastic and Reconstructive Surgery 2022 Annual Meeting, Washington, DC

+23.1% Lifting Effect

95.2% Patient Satisfaction

Methodology

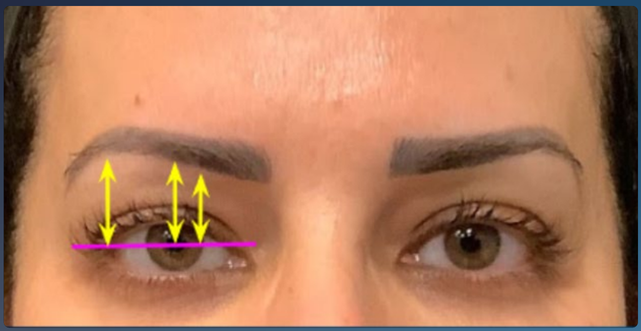
- 24 patients recruited at two sites
- Four 20-minute full face treatments
- Lifting effect assessed as:
  - Brow lift: Distance of eyebrow from the pupils' line at several points
  - Cheek lift: Distance between left and right nasolabial fold
- Patient satisfaction & Treatment comfort



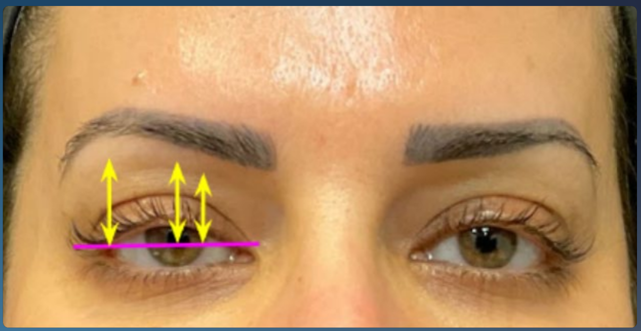
Measurement locations of the lifting effect

Example of eyebrow lift results

44 year old patient
Eyebrow lift +2 mm on average



Baseline



Follow up

Histological Analysis of Human Skin Indicates Quantitative Increase of Collagen and Elastin Fibers after Synchronized Radiofrequency with Facial Muscle Stimulation

Karan Lal, DO, MS[1] and David Goldberg, M.D., J.D.[1]

1. Skin Laser and Surgery Specialists, a Division of Schweiger Dermatology, Hackensack, NJ, USA

Presented at American Society for Dermatologic Surgery (ASDS) Annual Meeting 2022, Denver, CO.

+27%
Increase in Collagen

+129%
Increase in Elastin

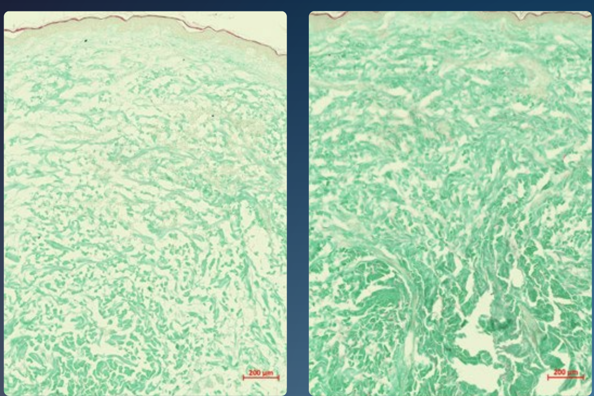
Methodology

- 7 patients allocated to Active (N=6) and Control (N=1) groups
- Active group: Four 20-minute RF+HIFES full face treatments (Control group - no treatments)
- Punch biopsies of skin tissue collected at baseline, 1-month and 3-month follow-ups
- Evaluation of digital photographs, satisfaction, comfort and safety

Preliminary Results

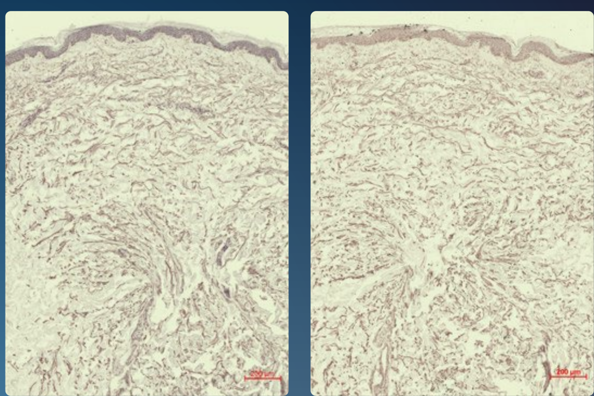
- Increased levels of elastin and collagen at 1-month and 3-month follow-ups
- Visible improved facial appearance
- Patients report high rates of satisfaction with the treatment
- No adverse events

Collagen - Trichrome Stain



Baseline — 3 months

Elastin - Orcein Stain



Baseline — 3 months

Novel technology for Facial Muscle Stimulation Combined with Synchronized Radiofrequency Induces structural changes in Muscles tissue: Porcine Histology Study

Brian Kinney, MD[1]; Jan Bernardy, DVM[2]; Rea Jarosova MSc[2]

1. Division of Plastic Surgery, The University of Southern California Keck School of Medicine, Beverly Hills, CA, USA
2. Veterinary Research Institute, Brno, Czech Republic

Presented at 41st Annual Conference of the American Society for Laser Medicine and Surgery. 2022; San Diego, CA

+19.2% Increase in Muscle Density

+21.2% Increased nr. of Myonuclei

+19.8% Increased nr. of Muscle Fibers

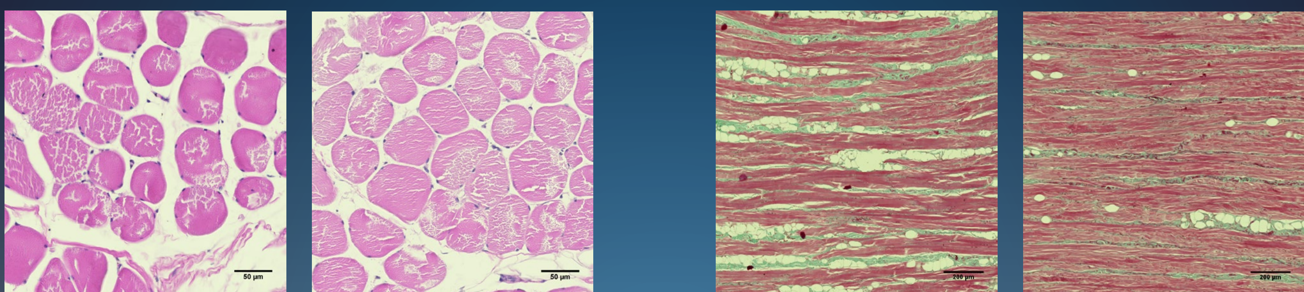
Methodology

- 8 Large white pigs (60-80 kg) divided into 2 groups
- Active group (6 sows): Four 20-minute treatments of forehead
- Control group (2 sows): No treatment
- Punch biopsies of muscle tissue collected at baseline, 1 and 2 months after last treatment

Results

- All results in active group were significant
- Control group showed insignificant changes
- Muscle temperature during treatment up to 39.5°C

Example of muscle tissue samples



Baseline | 2 Months After | Baseline | 2 Months After

A Combined Effect of Novel HIFES Technology with Synchronized Radiofrequency for Qualitative Improvement of Facial Muscles

Yael Halaas, M.D., FACS[1]

1. Yael Halaas, MD, New York, NY, USA

Accepted at American Academy of Facial Plastic and Reconstructive Surgery 2022 Annual Meeting, Washington, DC

+30%

Increase in Muscle Tone

Methodology

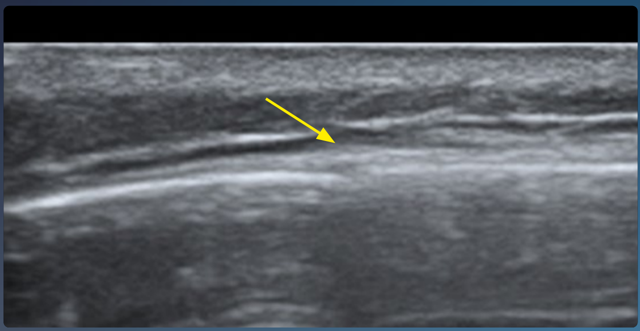
- 10 enrolled patients
- Four 20-minute simultaneous treatments on the forehead and the cheeks
- Ultrasound scans of m. frontalis and m. zygomaticus major taken at baseline, immediately after last treatment, 1 month after last treatment, and 3 months after last treatment
    - Echogenicity measurements
- Subject satisfaction
- Therapy comfort assessment

Results

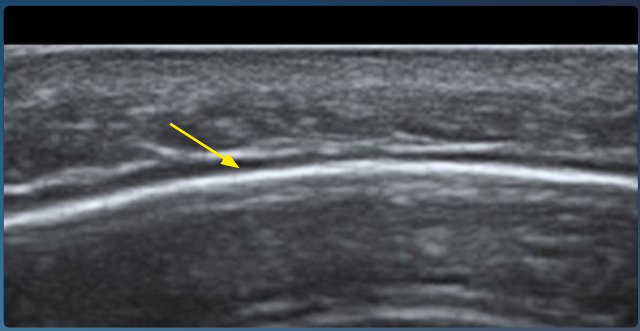
- Interim findings suggest:
    - Enhanced muscle structure and quality
    - Enhancement of facial visual appearance
    - High patient satisfaction

Ultrasound scans of the frontalis muscle

Darker representation of the muscle at the after scan indicates densification of the muscle and increased muscle tone.



Baseline



After the last treatment

Effects of noninvasive synchronized radiofrequency and novel HIFES: Histological analysis of Porcine dermal Collagen and Elastin

David Kent[1], MD; Jan Bernardy, DVM[2]; Rea Jarosova MSc[2]

1. Skin Care Physicians of Georgia, Macon, GA, USA
2. Veterinary Research Institute, Brno, Czech Republic

Accepted for American Society for Dermatologic Surgery (ASDS) Annual Meeting 2022, Denver, CO.

+26% Increase in Collagen

+110% Increase in Elastin

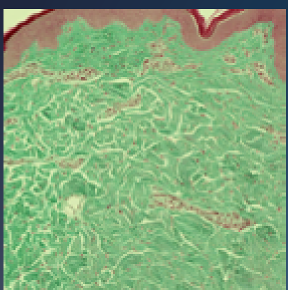
Methodology

- 8 Large White female pigs, 60-80 kg
- Active (N=6): Four 20-minute treatments on belly
- Control (N=2): Untreated
- Three biopsy explants obtained at baseline, 1 and 2 months post-reatment

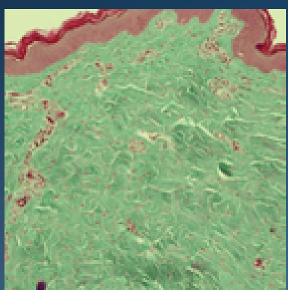
Results

- Active group showed highly significant changes
- Elastin and collagen did not change in control group
- Skin temperature was maintained at 40 – 42°C throughout the treatment.
- No adverse events observed

Collagen - Trichrome Stain

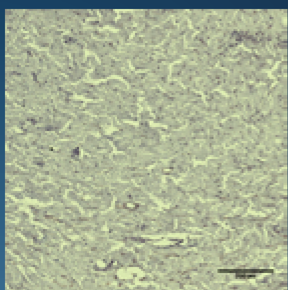


Baseline

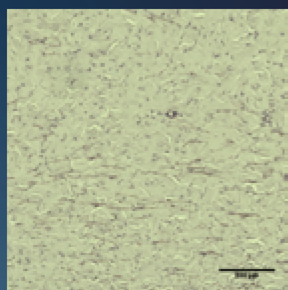


2 Months After

Elastin - Orcein Stain



Baseline



2 Months After

Novel Approach to Facial Rejuvenation by Treating Skin and Muscle Tissue for Wrinkles Reduction: Preliminary Data from Multicenter Clinical Trial

Yael Halaas, M.D.[1], Richard Gentile M.D.[2]

1. Plastic and cosmetic surgeon at Facial Plastic and Reconstructive Surgery, New York, NY, USA,
2. Gentile Facial Plastic and Aesthetic Laser Center, Youngstown, OH, United States

Accepted for American Academy of Facial Plastic and Reconstructive Surgery 2022 Annual Meeting, Washington, DC

95.0% Patient Satisfaction

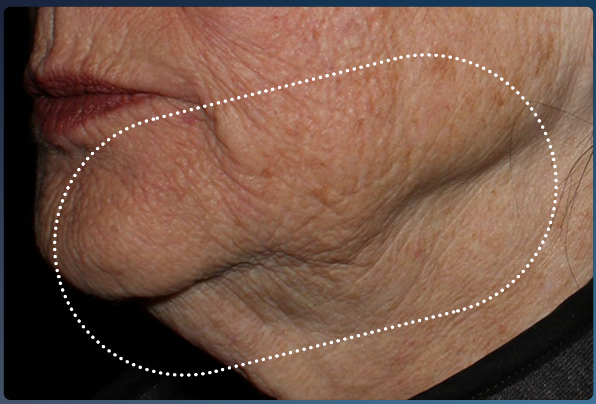
+25.3% Skin Evenness Improvement

-36.8% Wrinkle Reduction

Methodology

- 24 subjects (23 females, 1 male)
- Four 20-minute full face treatments
- Evaluation of
  - Wrinkle severity via automated 3D photo assessment
  - Patient satisfaction
  - Treatment comfort

Sixty-two year old patient



Baseline

3M FU

Simultaneous Emission of Synchronized Radiofrequency and HIFES for Non-invasive Facial Rejuvenation:

The Mechanism of Action

Sebastian Cotofana M.D., Ph.D., Ph.D.[1], Yael Halaas M.D., FACS[2] Brian Kinney M.D., FACS[3], David Goldberg M.D., J.D.[4], Joel Cohen M.D.[5]

[1] *Department of Clinical Anatomy, Mayo Clinic College of Medicine and Science, Rochester, MN, USA*
[2] *Yael Halaas, MD, New York, NY, USA*
[3] *Division of Plastic Surgery, The University of Southern California Keck School of Medicine, Beverly Hills, CA, USA School of Medicine, Los Angeles, CA*
[4] *Skin Laser and Surgery Specialists, Schweiger Dermatology, Hackensack, NJ*
[5] *AboutSkin Dermatology and AboutSkin Research, Greenwood Village and Lone Tree, CO, USA*

Abstract

EMFACE is a unique device specifically developed for non-invasive face lifting and wrinkle reduction by targeting all facial layers; skin, connective tissue framework, and facial muscles. It utilizes both Synchronized RF and HIFES technologies simultaneously. Heating the facial tissue to effective temperatures and HIFES stimulation of only specific facial muscles results in a combined effect that causes textural changes to the skin, smoothing, wrinkle reduction, facial repositioning, and an overall lifting effect. The simultaneous and targeted manner of both technologies yields unique benefits by inducing a synergistic effect in the facial soft tissues that cannot be achieved by using these technologies consecutively or as a standalone procedure.

Keywords: HIFES, Radiofrequency, Simultaneous, Application, Supramaximal, Contraction, Muscle, Fat, Reduction, Hypertrophy, Face, Lift

Introduction

Facial aging is a continuous and unstoppable process resulting from age-related changes in all structures present in the face: skin, fat, muscle, fascia, and bone.[1,2] Age-related changes of all facial soft tissues start at different decades and progress at different speeds, which vary between individuals of different gender and ethnicity. All changes together result in reduced support for the bone-overlying soft tissues, which then follow the effect of gravity. Repositioning and restructuring the affected tissues and layers is the aim of aesthetic procedures via surgical and non-surgical procedures.[1,2]

Amongst non-invasive aesthetic procedures, radiofrequency (RF) is considered the gold standard for facial skin treatment.[3] The effect of RF on the skin tissue is based on dermal heating, which leads to structural changes within the skin and the overall improvement in skin quality.[4] However, these skin heating procedures focus solely on improving skin quality and textural improvement, but not the overall facial appearance.

The overall facial appearance is not only influenced by skin quality but also by the facial volume and density of the underlying structures, including the fascial system, facial ligaments, and facial muscles. Therefore, the extent of facial laxity is a composite effect of all implicated structures of which the facial muscles and their interconnection with the skin play a fundamental role.[5]

The most frequently performed non-surgical treatment to date is the administration of soft tissue fillers, which help to restore facial volume.[6] However, soft tissue fillers only attempt to cover the aging symptoms and do not affect facial muscles, which play a crucial role in natural skin mobility.[7] Currently, the only way to alter facial muscles is through a surgical lift procedure, where the skin and fat tissues are separated from the muscle, and the muscles are then repositioned.[8]

Recently, HIFES technology has been introduced to the market to target the facial muscles and their connective tissue frameworks for lifting and tightening of the facial contours. This novel technology induces electrical fields to contract facial muscles selectively. These delicate facial muscles are crucial for supporting the facial soft tissues and play a structural role in a more youthful appearance.

EMFACE is the first device on the market utilizing the simultaneous application of both the synchronized RF and HIFES technologies for non-invasive facial lifting and wrinkle reduction. While the HIFES technology targets the muscle and overlying fascial tissue, the synchronized RF heating induces structural changes to the dermal and subdermal architecture. This approach ultimately results in an improved appearance through changes in all facial tissue layers.

The Role of Facial Muscles and Fascial Framework in Aesthetic Appearance

It is widely accepted that facial skin changes over time, with facial wrinkles being only the tip of the iceberg. Loss of structural support due to volume depletion and changes to the facial muscles and their connective tissue framework results in an increased soft tissue laxity which is additionally influenced by the effects of gravity. Facial muscles have been found to age through the process of sarcopenia, which manifests as a loss of muscle mass and volume, similar to skeletal muscles.[9,10] Since the facial muscles are interconnected via the fascial system and the overlying skin, weakening of these muscles may result in a visible descent of the tissue sagging as we age. The weaker the facial muscles are and the lower is the resting muscle tone, the higher muscle effort is needed to avoid sagging and to hold the overlying tissues in place. When being too weak, they become unable to hold the tissue, resulting in e.g. eyebrow drop or cheek sagging. When the resting muscle tone is increased, the muscles have the strength large enough to hold the overlying tissue in place without dropping and without the need to stay contracted.

Specifically, the muscles in the cheeks are interconnected by the midfacial superficial musculoaponeurotic system (SMAS).[11] Weakening of the cheek muscles, especially the zygomaticus muscles, allows for the hypothesis that as we age, the resulting facial muscle weakness can promote midfacial soft tissue descent, resulting in the increased severity of the nasolabial fold, formation of jowls, and loss of jawline contour.[12] Targeting these muscles and its surrounding connective tissue architecture might allow for midfacial soft tissue repositioning.

Also, the same muscle weakening could be expected for the frontalis muscles due to aging or long-term use of neurotoxins. The frontalis muscles are largely responsible for eyebrow movements[13]. Their connection with the skin is ensured via the supra-frontalis fascia (located superficial to the frontalis muscle) and the sub-frontalis fascia (located deep below the frontalis muscle). Aging of the forehead structures may result in eyebrow ptosis[14] and heaviness, which along with skin aging, may lead to laxity and wrinkle formation in the region.

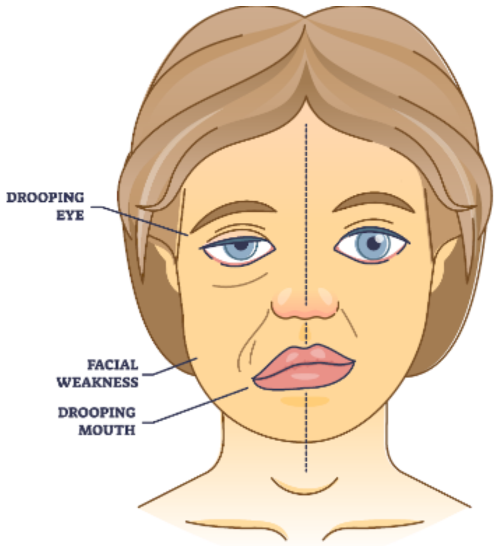


Figure 1: Visualization of the effect caused by weakened facial muscles on the left in comparison to healthy muscles on the right.

In contrast to skeletal muscles, the facial muscles are embedded in a connective tissue framework that interconnects all tissues from bone to skin. Interestingly, in addition, they are connected directly to the brain via the cranial nerves and are responsive to emotional input and the limbic system. Emotional states affect facial contours via resting tone of the muscles and the SMAS. Therefore, the facial muscles need to be seen within their connective tissue environment and addressed accordingly. Assuming that facial muscles affect skin movement alone without the support of a connective tissue environment creates an incomplete picture of facial muscle anatomy.

The combination of age-related facial changes results in an alteration of the facial shape which cannot be improved by targeting the skin alone. Therefore, more **profound treatment algorithms need to be applied to address age-related facial changes.**[15,16] This may include addressing **deeper fascial and muscle layers together**, as they have the ability to promote facial repositioning; treating the skin alone will not have such comparable effects.

How EMFACE Targets Facial Muscle and Fascial Tissues?

The Mechanism of HIFES Stimulation

Increased laxity of the overlying skin and the connective tissue framework increases the disconnect between muscular contraction and skin movement; this is more prevalent as we age. Therefore, inducing positive changes to the connective tissue and facial muscle unit will restore the connection between the layers, rejuvenating all layers, including the skin.

The EMFACE utilizes HIFES technology, specifically designed to selectively induce supramaximal contractions of small delicate muscles in the face. The technology generates strong electrical fields that affect the underlying neuronal and muscle tissue. These electrical fields depolarize the membrane of the motor neurons that innervate the muscle. When the motor neurons are depolarized, a signal is created that travels along the neuron, all the way to the neuromuscular junction - the place where the motor neuron is connected to the muscle. These signals overcome the barrier of the neuromuscular junction and progress to the muscle, which is thus forced to contract. This process bypasses the voluntary intention of the brain, inducing a forced contraction through electrical stimulation.

During each treatment, energy is applied to the facial soft tissues, and muscular contractions are induced. The HIFES technology induces up to 250 energy impulses per second (= 250 Hz), which does not allow any time for the facial muscles to relax in between the individual signals. As the muscle is unable to relax, with additional stimuli it is forced to contract even further which continuously builds up the contraction power with every additional signal. The appropriate selection of these two factors (electrical field strength and frequency) results in the so-called “supramaximal contraction”.

Although it is poorly understood how and to what extent the facial muscles adapt to external stimuli, research studies conducted in skeletal muscles have revealed that heat shock proteins (HSP) and satellite cells (SC) may be activated by intense muscle exercise as a response to the applied stimuli.[17,18] HSP are the signaling molecules playing a crucial role in muscle remodeling through the promotion of muscle protein synthesis.[19,20] SCs are muscle-derived stem cells responsible for myofiber development and renewal.[21] In a resting state, the SCs remain quiescent, ready to be activated, and provide differentiation to create new myonuclei to existing muscle fibers or generate new muscle fibers. Together, HSP and SC activation can support muscle micro-protein structure alterations. In a healthy muscle this may lead to densification of the muscle tissue and to overall improvement of the muscle quality. In atrophied muscle, the muscle structure alteration may lead to hypertrophic response reversing the atrophy. However, it is not only the muscle reacting to the signaling molecules. It has also been documented that the fascial layer remodels itself in response to heat and mechanical stimuli.[22]

Future studies will need to identify similarities between skeletal and facial muscles or provide conclusive evidence that facial muscles behave similarly or differently when targeted by external stimuli.

The Role of Synchronized RF Heating on Facial Muscles and Fascial Framework

Simultaneously with the HIFES stimulation, the EMFACE delivers Synchronized Radiofrequency that heats the facial tissue. Such stimuli affect the connective tissue framework and the facial muscle unit with consecutive adaptive changes to the overlying facial soft tissues.

According to previous studies on skeletal muscles[19,20,23–25], HSPs can also be activated by heat within the range of 40℃. Together with the muscular contractions, the heat thus may further increase the levels of released HSP[26,27], this effect has been shown in abdominal muscle [28,29], gluteal muscle [30,31], or in the muscles of the upper extremity.[29,30] A recent study by Kinney et al.[32] measured the facial muscle temperature during the treatment with the EMFACE device and showed that the temperatures in the targeted muscle tissues reached up to 40℃, indicating that a similar effect could also be seen in the facial muscles during the EMFACE treatment.

The primary effect of Synchronized RF heating on the subdermal tissues can be seen in the fascial framework. The fascial framework primarily consists of collagen and elastin, which are known to be heat responsive. Therefore, heating to adequate temperatures may induce remodeling of collagen and elastin within the fascial framework, leading to increased elasticity and tightness of the fascial web.[22]

Clinical Effect of EMFACE on Facial Muscles and Fascial Tissues

Forehead application

The EMFACE applicators are designed to target specific muscles of the face. The forehead applicator has been designed to specifically target the frontalis muscle and its surrounding connective tissue environment, composed of the supra-frontalis fascia (located superficial to frontalis muscle) and of the sub-frontalis fascia (deep to frontalis muscle), enveloping the only eyebrow elevator like a sleeping bag. The applied stimulus during the treatment with the EMFACE device affects the connective tissue framework and the facial muscle unit simultaneously, which have a soft tissue thickness in the range of 3 – 7 mm[33] for the forehead. The applied energy induces changes to the entire unit, which results in its structural alteration. A tighter fascia (sleeping bag) allows for the relaxation of the enveloped muscle, which in turn most likely reduces its baseline contractile tonus. The latter effect is clinically visible in the form of reduced horizontal forehead lines. Since the frontalis muscle is an eyebrow elevator, strengthening formerly atrophied frontalis muscle may aid with eyebrow ptosis and lead to brow elevation.

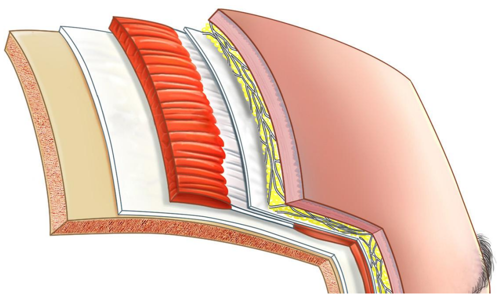


Figure 2: The frontalis muscles is enveloped by the supra-frontalis and sub-frontalis fascias. The condition of both the muscle and the fascias affects the overall appearance of forehead.

Affecting the connective tissue framework and the facial muscle unit of the forehead indirectly influences the glabellar muscles. All upper facial muscles (consisting of frontalis, procerus, corrugator supercilii, and orbicularis oculi) connect with the skin at the level of the upper margin of the eyebrow both in the midline and laterally. Affecting the frontalis m. will indirectly influence the eyebrow depressors and cause, most likely, a **change in their position** (relative to the underlying bone) by being pulled upward. Muscular contractions of the glabellar muscles are not observed during the treatment. The effect is thus indirect, only due to the supporting fascial framework, which stabilizes and guides muscular actions.

Cheek application

The cheek applicators are designed to stimulate the zygomaticus major and minor muscles and the risorius muscle.

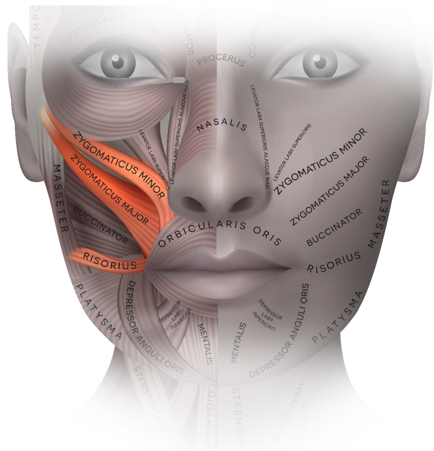


Figure 3: The cheek muscles stimulated by EMFACE cheek applicators: Zygomaticus major & minor muscles and risorius muscle.

The zygomaticus minor muscle is attached to the skin at the nasolabial fold. The zygomaticus major muscle is connected to the underlying maxilla by a connective tissue sheet termed the transverse facial septum.[34] This septum forms the inferior boundary of the midfacial fat compartment and forms a biomechanical unit with the overlying muscle. Stimulating this unit allows for conformational change of the septum, elevating the entire cheek, increasing the midfacial volume[2], and improving the nasolabial fold.[35]

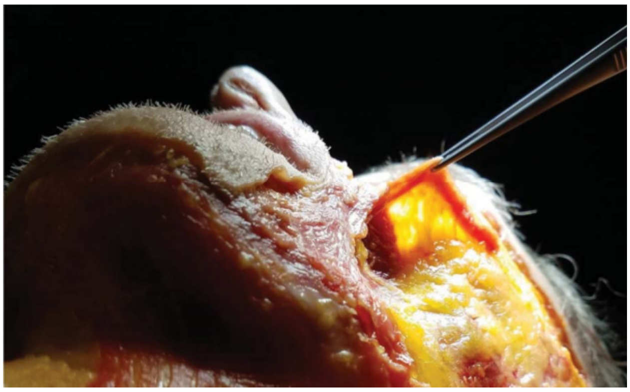


Figure 4: Cadaveric dissection of the left side of the face showing the transverse facial septum connecting the zygomaticus major muscle to the maxilla. Image taken from Cotofana et al.[34]

Repositioning the midfacial soft tissues, especially the superficial fat compartments, influences the balance between total facial elevators and depressors. The platysma is the strongest facial depressor, due to its extent and fascial connection to the SMAS, the superficial temporal fascia, and the orbicularis oculi muscle. Decreasing the caudally oriented vector of the midface will shift the balance toward the zygomatic facial elevators, allowing for repositioning not only midfacial but lower facial soft tissues. The resulting clinical effect is a reduction in jowls and an increase in jawline contouring. In addition, the masseter muscle, deeper muscles of facial expression like the buccinator or levator anguli oris do not display muscular contractions during the treatment.

It is important to note, facial muscles are not expected to increase in their thickness as compared to the structural changes observed in skeletal muscle following strength training. However, these delicate muscles do keep their genetically predisposed thickness: frontalis muscle approx. 3 mm[36], zygomaticus major approx. 3.6 mm[37], and approx. 0.5 mm for the zygomaticus minor[38] and risorius muscles.[39] Future studies will need to identify similarities or differences between these muscle groups.

The effect of EMFACE on muscle structure has been investigated in a study by Kinney et al.[32], who found a 19.2% increase in muscle density and a 21.2% increase in the number of myonuclei after four EMFACE treatments. Structural changes post-EMFACE treatments were also suggested in a study by Halaas et al.[40], who used ultrasound echogenicity to evaluate muscle quality, also called muscle tone. In this study, the muscle quality increased by 30%.

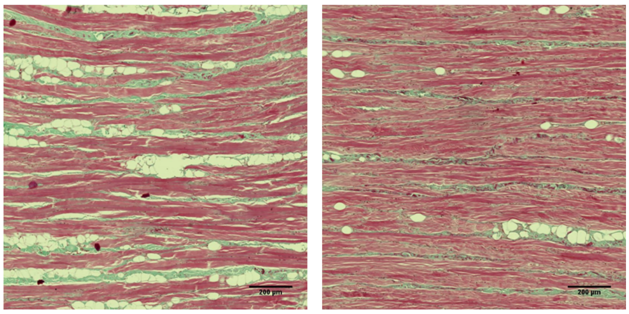


Figure 5: Histologic images of muscle tissues before (left panel) and 2 months after (right panel) the treatment with the EMFACE device[32].

Additionally, clinical studies on the EMFACE device further support the proposed mechanism of action. A clinical study by Kinney and Boyd et al.[41] investigating EMFACE found a brow lifting effect of 23.1% coupled with 91.2% patient satisfaction. In addition, a study by Halaas and Gentile et al.[42] reported a 36.8% wrinkle reduction. These studies additionally revealed that clinical changes peak at approximately 2 to 3 months post-treatment, which is in line with the time frame needed for structural changes to be implemented into the connective tissue framework and the facial muscle unit.

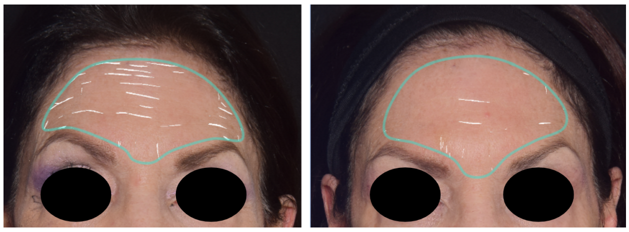


Figure 6: Example of patient results in wrinkle reduction as evaluated by automated software. Baseline on the left and 1 month after on the right. Taken from Halaas et al.[42]

The effect of EMFACE on facial skin tissue

Regarding skin, fine lines and wrinkles accompanied by loss of skin volume are usually the first indicators of skin aging, a normal physiological process influenced by genetic and hormonal changes. However, external factors also influence aging, e.g., exposure to UV radiation, skin[43,44], smoking[45], diet, air pollution[46], or chemicals and toxins.[47,48] During the skin aging process, the dermal blood vessel structure is disrupted, and in turn, the dermis is not supplied with nutrition and oxygen, thus slowing cellular regeneration.

The major building blocks of the skin are collagen and elastin fibers, responsible for skin elasticity and firmness. These components are also affected by aging. During the aging process, collagen and elastin synthesis decreases, collagen bundles lose their extensible configuration and become fragmented[48], and the elastin fiber network is degraded, leading to the loss of structural integrity of microfibrils.[49] As the extracellular matrix is degraded, skin thickness is also reduced.[50,51]

As a result of aging, collagen and elastin deficiencies are the main cause of wrinkle formation. Amount of skin collagen and elastin is deacreasing every year due to aging process. It is estimated that adult skin loses 1%[52] of overal collagen content annualy.

Effect of RF heating

RF heating is known to address aging factors within the skin effectively. EMFACE utilizes a novel Synchronized RF electrode that allows the simultaneous application of an RF field together with HIFES, which is impossible with any other RF technology. During the 20-minute treatment, the skin tissue is heated to 40-42°C. This therapeutic temperature range is reached within the first 2 minutes of the treatment, as documented by the thermal probe measurements and by thermal camera by Kent et al.[53]

Radiofrequency current flow achieves the heating through the dermal and subcutaneous tissues. As the RF current flows through the tissue, a portion of the RF energy is absorbed by the tissue, transforming the energy into heat and the desired thermal effect. The level of RF energy absorption in the tissue depends on the RF frequency[54] and tissue impedance[55], among other factors. Since the skin, muscle, and fat tissues have different impedances[56], it is possible to selectively target the energy and achieve the thermal effect only in the desired tissue(s).

When the therapeutic temperature is reached in the skin tissue for the desired time period, the hydrogen bonds tying the collagen fibers together begin to unwind, and collagen denaturation occurs. However, these temperatures do not lead to permanent damage.[57] As the tissue dissipates the mentioned thermal effect, the bonds begin to renature, and the skin's architecture is changed to a more youthful level.[57] After repeating this process during multiple treatments, the structure of older collagen and elastin fibers is changed. It begins to take on the structure similar to newly formed collagen and elastin fibers.

This thermal effect is also accompanied by a heat-induced wound healing response and increased fibroblast activity. Fibroblasts are the dermal cells responsible for producing new collagen and elastin fibers. As we age, their activity decreases to a level equivalent to an overall "net loss" of fibers. This means that the amount of newly formed fibers does not exceed the number of fibers being degraded, which accelerates the appearance of skin aging. Nevertheless, studies have shown that heat stress increases fibroblast activity, leading to an increased synthesis of collagen and elastin - neocollagenesis & neoelastogenesis.[58]

RF heating supports the skin to regain its volume, elasticity, and a more youthful appearance by restoring the collagen and elastin fiber structure and enhancing the synthesis of new collagen fibers.

Clinical studies on EMFACE, which focused on structural changes, demonstrated a prominent skin remodeling effect. The outcomes of a study performed on a porcine model by Kent et al.[53] correlated with the human histology study by Goldberg et al[59]., as both found that collagen increased by 27% and 26%, respectively. In addition, elastin was found to have doubled in the study by Kent et al.[53], while in the Goldberg study[59], the elastin levels increased by 129%.

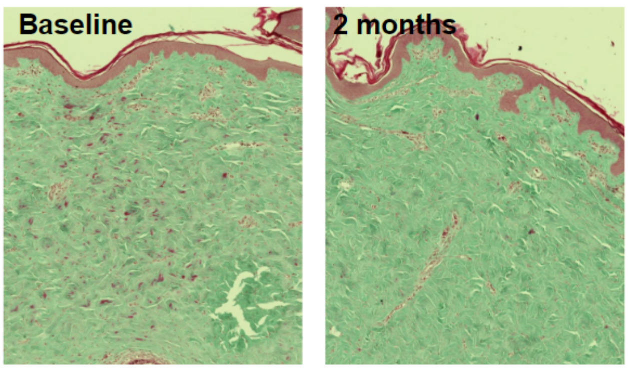


Figure 7: Densification of the collagen fiber network at 2 months post EMFACE treatment (right) in comparison to baseline (left) documented in Kent et al.

The effect on skin has also been documented in additional studies. For example, a study by Halaas and Gentile et al.[42] reported 36.8% wrinkle reduction and

25.3% skin evenness improvement. Wrinkle improvement was also reported in a study by Cohen et al.[60] Similar to the muscle studies, the skin results also peaked at 2 to 3 months post-treatment.

The Effect of EMFACE on Fat Tissue

During the treatment with EMFACE, the temperature in the fat tissue does not exceed the 43°C[61] needed for induction of an apoptotic process. Any direct effects in the fat tissue thus have not been observed.

Summary

EMFACE is a unique device specifically developed for non-invasive face lifting and wrinkle reduction by targeting all facial layers; skin, connective tissue framework, and facial muscles. It utilizes both Synchronized RF and HIFES technologies simultaneously. Heating the facial tissue to effective temperatures and HIFES stimulation of only specific facial muscles results in a combined effect that causes textural changes to the skin, smoothing, wrinkle reduction, facial repositioning, and an overall lifting effect. The simultaneous and targeted manner of both technologies yields unique benefits by inducing a synergistic effect in the facial soft tissues that cannot be achieved by using these technologies consecutively or as a standalone procedure.

References

1. Coleman S, Grover R. The anatomy of the aging face: Volume loss and changes in 3-dimensional topography. *Aesthet Surg J*. 2006;26(1):S4-S9. doi:10.1016/j.asj.2005.09.012
2. Kavanagh S, Newell J, Hennessy M, Sadick N. Use of a neuromuscular electrical stimulation device for facial muscle toning: a randomized, controlled trial. *J Cosmet Dermatol*. 2012;11(4):261-266. doi:10.1111/jocd.12007
3. Gold MH. The increasing use of nonablative radiofrequency in the rejuvenation of the skin. *Expert Rev Dermatol*. 2011;6(2):139-143. doi:10.1586/edm.11.11
4. de Araújo AR, Soares VPC, da Silva FS, Moreira T da S. Radiofrequency for the treatment of skin laxity: mith or truth. *An Bras Dermatol*. 2015;90(5):707-721. doi:10.1590/abd1806-4841.20153605
5. Swift A, Liew S, Weinkle S, Garcia JK, Silberberg MB. The Facial Aging Process From the “Inside Out.” *Aesthet Surg J*. 2021;41(10):1107-1119. doi:10.1093/asj/sjaa339
6. De Vos MC, Van den Brande H, Boone B, Van Borsel J. Facial Exercises for Facial Rejuvenation: A Control Group Study. *Folia Phoniatr Logop*. 2013;65(3):117-122. doi:10.1159/000354083
7. Kim K, Jeon S, Kim JK, Hwang JS. Effects of Kyunghee Facial Resistance Program (KFRP) on mechanical and elastic properties of skin. *J Dermatol Treat*. 2016;27(2):191-196. doi:10.3109/09546634.2015.1056078
8. Van Borsel J, De Vos MC, Bastiaansen K, Welvaert J, Lambert J. The Effectiveness of Facial Exercises for Facial Rejuvenation. *Aesthet Surg J*. 2014;34(1):22-27. doi:10.1177/1090820X13514583
9. Nikolis A, Frank K, Guryanov R, et al. Differences in Temporal Volume between Males and Females and the Influence of Age and BMI: A Cross-Sectional CT-Imaging Study. *Facial Plast Surg*. 2021;37(05):632-638. doi:10.1055/s-0041-1725201
10. Cotofana S, Lowry N, Devineni A, et al. Can smiling influence the blood flow in the facial vein?—An experimental study. *J Cosmet Dermatol*. 2020;19(2):321-327. doi:10.1111/jocd.13247
11. Whitney ZB, Jain M, Zito PM. Anatomy, Skin, Superficial Musculoaponeurotic System (SMAS) Fascia. In: *StatPearls*. StatPearls Publishing; 2022. Accessed August 31, 2022. http://www.ncbi.nlm.nih.gov/books/NBK519014/
12. Joshi K, Hohman MH, Seiger E. SMAS Plication Facelift. In: *StatPearls*. StatPearls Publishing; 2022. Accessed August 31, 2022. http://www.ncbi.nlm.nih.gov/books/NBK531458/
13. Pessino K, Patel J, Patel BC. Anatomy, Head and Neck, Frontalis Muscle. In: *StatPearls*. StatPearls Publishing; 2022. Accessed September 9, 2022. http://www.ncbi.nlm.nih.gov/books/NBK557752/
14. De Jong R, Hohman MH. Brow Ptosis. In: *StatPearls*. StatPearls Publishing; 2022. Accessed August 31, 2022. http://www.ncbi.nlm.nih.gov/books/NBK560762/
15. Sulamanidze MA, Paikidze TG, Sulamanidze GM, Neigel JM. Facial Lifting with “APTOS” Threads: Featherlift. *Otolaryngol Clin North Am*. 2005;38(5):1109-1117. doi:10.1016/j.otc.2005.05.005
16. Rohrich RJ, Pessa JE. The Fat Compartments of the Face: Anatomy and Clinical Implications for Cosmetic Surgery: *Plast Reconstr Surg*. 2007;119(7):2219-2227. doi:10.1097/01.prs.0000265403.66886.54
17. Moss FP, Leblond CP. Satellite cells as the source of nuclei in muscles of growing rats. *Anat Rec*. 1971;170(4):421-435. doi:10.1002/ar.1091700405
18. Schultz E, McCormick KM. Skeletal muscle satellite cells. In: *Reviews of Physiology, Biochemistry and Pharmacology, Volume 94*. Vol 94. Reviews of Physiology, Biochemistry and Pharmacology. Springer Berlin Heidelberg; 1994:213-257. doi:10.1007/BFb0030904
19. Kakigi R, Naito H, Ogura Y, et al. Heat stress enhances mTOR signaling after resistance exercise in

human skeletal muscle. *J Physiol Sci*. 2011;61(2):131-140. doi:10.1007/s12576-010-0130-y
20. Yoshihara T, Naito H, Kakigi R, et al. Heat stress activates the Akt/mTOR signalling pathway in rat skeletal muscle. *Acta Physiol*. 2013;207(2):416-426. doi:10.1111/apha.12040
21. Mauro A. SATELLITE CELL OF SKELETAL MUSCLE FIBERS. *J Biophys Biochem Cytol*. 1961;9(2):493-495. doi:10.1083/jcb.9.2.493
22. Myers TW. Fascial Fitness: Training in the neuromyofascial web. *IDEA Fit J April*. Published online 2011:38-45.
23. Kobayashi T, Goto K, Kojima A, et al. Possible role of calcineurin in heating-related increase of rat muscle mass. *Biochem Biophys Res Commun*. 2005;331(4):1301-1309. doi:10.1016/j.bbrc.2005.04.096
24. Uehara K, Goto K, Kobayashi T, et al. Heat-Stress Enhances Proliferative Potential in Rat Soleus Muscle. *Jpn J Physiol*. 2004;54(3):263-271. doi:10.2170/jjphysiol.54.263
25. Goto K, Okuyama R, Sugiyama H, et al. Effects of heat stress and mechanical stretch on protein expression in cultured skeletal muscle cells. *Pflugers Arch*. 2003;447(2):247-253. doi:10.1007/s00424-003-1177-x
26. Halevy O, Krispin A, Leshem Y, McMurtry JP, Yahav S. Early-age heat exposure affects skeletal muscle satellite cell proliferation and differentiation in chicks. *Am J Physiol-Regul Integr Comp Physiol*. 2001;281(1):R302-R309. doi:10.1152/ajpregu.2001.281.1.R302
27. Halaas Y, Duncan D, Bernardy J, Ondrackova P, Dinev I. Activation of Skeletal Muscle Satellite Cells by a Device Simultaneously Applying High-Intensity Focused Electromagnetic Technology and Novel RF Technology: Fluorescent Microscopy Facilitated Detection of NCAM/CD56. *Aesthet Surg J*. 2021;41(7):NP939-NP947. doi:10.1093/asj/sjab002
28. Jacob CI, Rank B. Abdominal Remodeling in Postpartum Women by Using a High-intensity Focused Electromagnetic (HIFEM) Procedure: An Investigational Magnetic Resonance Imaging (MRI) Pilot Study. *J Clin Aesthetic Dermatol*. 2020;13(9 Suppl 1):S16-S20.
29. Samuels JB, Katz B, Weiss RA. Radiofrequency Heating and High-Intensity Focused Electromagnetic Treatment Delivered Simultaneously: The First Sham-Controlled Randomized Trial. *Plast Reconstr Surg*. 2022;149(5):893e-900e. doi:10.1097/PRS.0000000000009030
30. Jacob C, Kinney B, Busso M, et al. High Intensity Focused Electro-Magnetic Technology (HIFEM) for Non-Invasive Buttock Lifting and Toning of Gluteal Muscles: A Multi-Center Efficacy and Safety Study. *J Drugs Dermatol JDD*. 2018;17(11):1229-1232.
31. Palm M. Magnetic Resonance Imaging Evaluation of Changes in Gluteal Muscles After Treatments With the High-Intensity Focused Electromagnetic Procedure. *Dermatol Surg*. 2020;Publish Ahead of Print. doi:10.1097/DSS.0000000000002764
32. Kinney B, Bernardy J, Jarosova R. Novel Facial Muscle Stimulation technology with Synchronized Radiofrequency Promotes structural changes in Muscles tissue: Porcine Histology Study. In: *Accepted for Presentation at: American Academy of Facial Plastic and Reconstructive Surgery (AAFPRS) 2022 Annual Meeting. October 20-23*. ; 2022.
33. Bravo BSF, de Melo Carvalho R, Penedo L, et al. Applied anatomy of the layers and soft tissues of the forehead during minimally-invasive aesthetic procedures. *J Cosmet Dermatol*. Published online May 30, 2022. doi:10.1111/jocd.15131
34. Cotofana S, Gotkin RH, Frank K, Lachman N, Schenck TL. Anatomy Behind the Facial Overfilled Syndrome: The Transverse Facial Septum. *Dermatol Surg*. 2020;46(8):e16-e22. doi:10.1097/DSS.0000000000002236
35. Hernandez CA, Davidovic K, Avelar LET, et al. Facial Soft Tissue Repositioning With Neuromodulators: Lessons Learned From Facial Biomechanics. *Aesthet Surg J*. Published online April 13, 2022:sjac090. doi:10.1093/asj/sjac090
36. Abe T, Spitz RW, Wong V, et al. Assessments of Facial Muscle Thickness by Ultrasound in Younger Adults: Absolute and Relative Reliability. *Cosmetics*. 2019;6(4):65. doi:10.3390/cosmetics6040065
37. Şatıroğlu F, Arun T, Işık F. Comparative data on facial morphology and muscle thickness using ultrasonography. *Eur J Orthod*. 2005;27(6):562-567. doi:10.1093/ejo/cji052
38. Hwang K, Kim DH, Kim DJ, Kim YS. Anatomy and Tensile Strength of the Zygomatic Ligament: *J Craniofac Surg*. 2011;22(5):1831-1833. doi:10.1097/SCS.0b013e31822e802a
39. Alfen NV, Gilhuis HJ, Keijzers JP, Pillen S, Van Dijk JP. Quantitative facial muscle ultrasound: Feasibility and reproducibility: Facial Muscle Ultrasound. *Muscle Nerve*. 2013;48(3):375-380. doi:10.1002/mus.23769
40. Halaas Y MD. Muscle Quality Improvement Underlines the Non-invasive Facial Remodeling Induced by a Simultaneous Combination of a Novel Facial Muscle Stimulation Technology with Synchronized Radiofrequency: American Academy of Facial Plastic and Reconstructive Surgery. Published online October 19, 2022.
41. Kinney B, Boyd C. Safety and Efficacy of Combined HIFES Tissue Stimulation and Monopolar RF for Facial Remodeling. In: *Accepted for Presentation at: American Academy of Facial Plastic and Reconstructive Surgery 2022*. ; 2022.
42. Halaas Y, Gentile R. The Interim Results of Novel Approach for Facial Rejuvenation. In: *Accepted for Presentation at: American Academy of Facial Plastic*

and Reconstructive Surgery (AAFPRS) 2022 Annual Meeting. October 20-23, 2022.

43. Ansary TM, Hossain MdR, Kamiya K, Komine M, Ohtsuki M. Inflammatory Molecules Associated with Ultraviolet Radiation-Mediated Skin Aging. *Int J Mol Sci*. 2021;22(8):3974. doi:10.3390/ijms22083974
44. Fuks KB, Hüls A, Sugiri D, et al. Tropospheric ozone and skin aging: Results from two German cohort studies. *Environ Int*. 2019;124:139-144. doi:10.1016/j.envint.2018.12.047
45. Amer M, Farag F, Amer A, ElKot R, Mahmoud R. Dermapen in the treatment of wrinkles in cigarette smokers and skin aging effectively. *J Cosmet Dermatol*. 2018;17(6):1200-1204. doi:10.1111/jocd.12748
46. Schikowski T, Hüls A. Air Pollution and Skin Aging. *Curr Environ Health Rep*. 2020;7(1):58-64. doi:10.1007/s40572-020-00262-9
47. Wong QYA, Chew FT. Defining skin aging and its risk factors: a systematic review and meta-analysis. *Sci Rep*. 2021;11(1):22075. doi:10.1038/s41598-021-01573-z
48. Tobin DJ. Introduction to skin aging. *J Tissue Viability*. 2017;26(1):37-46. doi:10.1016/j.jtv.2016.03.002
49. Langton AK, Sherratt MJ, Griffiths CEM, Watson REB. Review Article: A new wrinkle on old skin: the role of elastic fibres in skin ageing: Elastic fibres and skin ageing. *Int J Cosmet Sci*. 2010;32(5):330-339. doi:10.1111/j.1468-2494.2010.00574.x
50. Papakonstantinou E, Roth M, Karakiulakis G. Hyaluronic acid: A key molecule in skin aging. *Dermatoendocrinol*. 2012;4(3):253-258. doi:10.4161/derm.21923
51. Adatto MA, Adatto-Neilson RM. Facial treatment with acoustic wave therapy for improvement of facial skin texture, pores and wrinkles. *J Cosmet Dermatol*. 2020;19(4):845-849. doi:10.1111/jocd.13327
52. Ganceviciene R, Liakou AI, Theodoridis A, Makrantonaki E, Zouboulis CC. Skin anti-aging strategies. *Dermatoendocrinol*. 2012;4(3):308-319. doi:10.4161/derm.22804
53. Kent D, Fritz K, Salavastru C. Effect of Synchronized Radiofrequency and Novel Soft Tissue Stimulation: Histological Analysis of Connective Tissue Structural Proteins in Skin. In: *Accepted for Presentation at: American Society for Dermatologic Surgery (ASDS) Annual Meeting 2022*. ; 2022.
54. Kreindel M, Mulholland S. *The Basic Science of Radiofrequency-Based Devices*. IntechOpen; 2021. doi:10.5772/intechopen.96652
55. Lack EB, Rachel JD, D’Andrea L, Corres J. Relationship of energy settings and impedance in different anatomic areas using a radiofrequency device. *Dermatol Surg Off Publ Am Soc Dermatol Surg Al*. 2005;31(12):1668-1670. doi:10.2310/6350.2005.31306
56. Bouazizi A, Zaïbi G, Samet M, Kachouri A. Parametric study on the dielectric properties of biological tissues. In: ; 2015:54-57. doi:10.1109/STA.2015.7505138
57. Weiner SF. A Review of Radio Frequency for Skin Tightening by Dr . Steven Weiner (Finally ! A Radiofrequency System That Makes Sense : The Infini From Lutronic). In: ; 2013.
58. Elsaie ML. CUTANEOUS REMODELING AND PHOTOREJUVENATION USING RADIOFREQUENCY DEVICES. *Indian J Dermatol*. 2009;54(3):201-205. doi:10.4103/0019-5154.55625
59. Goldberg DJ, Lal K. Histological Analysis of Human Skin after Radiofrequency Synchronized with Facial Muscle Stimulation for Wrinkle and Laxity Treatment. In: *Accepted at American Society for Dermatologic Surgery (ASDS) Annual Meeting 2022*. CO.
60. Cohen JMD, Robb CWMD. Treating skin, muscle and connective tissue of face with novel device combining RF heating and HIFES stimulation for facial rejuvenation.
61. Franco W, Kothare A, Ronan SJ, Grekin RC, McCalmont TH. Hyperthermic injury to adipocyte cells by selective heating of subcutaneous fat with a novel radiofrequency device: Feasibility studies. *Lasers Surg Med*. 2010;42(5):361-370. doi:10.1002/lsm.20925

EMFACE®

Simultaneous Emission of Synchronized Radiofrequency and HIFES™ for Non-invasive Facial Rejuvenation

A unique combination of RF and HIFES

Facial aging is a complex process resulting not only from skin aging but also from changes in the volume and density of the underlying structures, including the fascial system, facial ligaments, and facial muscles.[1] EMFACE is the first device in the non-invasive facial aesthetic segment that utilizes the simultaneous application of Synchronized RF and HIFES technology to treat multiple facial layers simultaneously.

EMFACE effect on facial skin

The loss of the amount of elastin and collagen and quality impairment of the remaining fibers contribute to the worsening of skin quality and skin aging.[2] EMFACE uses unique Synchronized RF along with the real-time impedance-based system to quickly heat the skin tissue to 40-42°C[3], the temperature needed to stimulate an increase in fibroblast activity, leading to an increased synthesis of new collagen and elastin fibers.[4] In addition, the old collagen and elastin fibers decompose and denature and are rebuilt again.[4]

Clinical studies on EMFACE focusing on structural changes demonstrated a prominent skin remodeling effect. These studies found that collagen increase ranged between 26 - 27% and elastin increase ranged between 110-129% two to three months following the procedure.[3,5] Additional study[6] investigating changes in skin texture and facial appearance reported a 36.8% wrinkle reduction and 25.3% skin evenness improvement three months post procedure.

Although Synchronized RF heating ensures skin texture improvement, treating only textural concerns is not enough. As we age, facial tissue becomes saggy due to changes in the facial musculature and laxity in the connective tissue. Therefore, it is necessary to target the underlying structures to achieve a more youthful appearance.

EMFACE effect on facial muscles

To achieve a complete and more targeted approach to treating all facial layers, the EMFACE utilizes HIFES technology, specifically designed to target the small delicate facial muscles. Facial muscles undergo atrophy and loss of muscular tone due to aging, similarly to the skeletal muscle, and also due to the long-term use of neurotoxins.[7,8]

HIFES technology selectively induces supramaximal contractions in the facial elevator muscles. The intense contractions are strong stimuli that trigger a tissue response leading to promotion of muscle protein synthesis[9,10] and to myofiber renewal[11]. Such processes lead to structural remodeling of the targeted muscles, which has been seen in EMFACE study[12] showing 19.2% increase in muscle density and 21.2% increase in number of myonuclei, which provide the muscle with nutrition. These results were coupled with reduced fibrotic and fat infiltration within the muscle tissue at two months post-procedure.

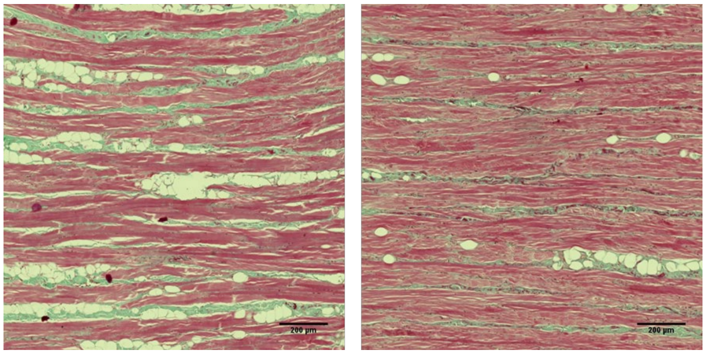


Figure 1: Histologic images of muscle tissues before (left panel) and 2 months after (right panel) the treatment with the EMFACE device.

The structural changes do manifest as increased resting muscular tone, which is necessary for maintaining the lifted facial appearance. The weaker the facial muscles are, the higher muscle effort is needed to avoid sagging and to hold the overlying tissues in place.[13] When being too weak, they become unable to hold the tissue, resulting in e.g. eyebrow drop or cheek sagging. When the resting muscle tone is increased, the muscles have the strength large enough to hold the overlying tissue in place without dropping and without the need to stay contracted.[13] EMFACE was found to increase the muscle tone by 30%[14] which was then shown to lead to an overall lifting effect by 23.1%.[6]

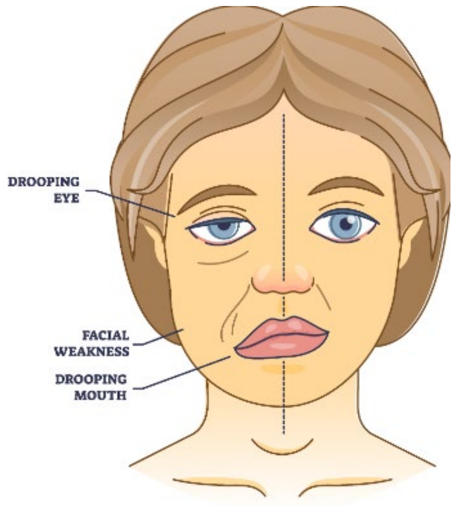


Figure 2: Visualization of the effect caused by weakened facial muscles on the left in comparison to healthy muscles on the right.

The synergy of RF and HIFES

The expression of HSP or SC is higher when the muscle is exposed to the simultaneous delivery of heating of around 40°C and supramaximal contractions compared to individual or consecutive energy applications.[15,16] This simultaneous delivery induces a strong signal, which is followed by a stronger response in the skin, muscle and fascial tissue, leading to more pronounced structural remodeling. [9,10,17–19]

Aside from the muscle and skin tissues, the EMFACE also affects the subdermal connective tissue. The facial fascial framework is largely composed of elastin, collagen, and connective tissue, and their degradation is part of the aging process. Synchronized RF heating with EMFACE may support the fascial framework via collagen and elastin remodeling, similar to what has been documented in previous skin tissue studies. In addition, the fascial support structures have also been found responsive to mechanical stimuli, which in case of EMFACE is delivered with HIFES stimulation.[20] The combination of both the heating and mechanical stress on the fascial support structures may lead to fascial remodeling, leading to increased fascial tightness and elasticity.[20]

Clinical effects

Due to the unique design and energy delivery, EMFACE applicators do not induce the stimulation of the depressors since the stimulation of the depressors could potentially lead to a worsening of rhytides. The forehead application targets the frontalis muscle (brow elevator) and corresponding fascias while avoiding the depressors in the glabella. Restoring the tonus of the frontalis muscle and tightening the fascias in combination with the skin remodeling leads to reduced horizontal forehead lines, brow elevation, and skin texture improvement.

The cheek application primarily targets the more superficial muscles of the cheeks (zygomaticus major/minor & risorius), which are all interconnected elevating units. In contrast, other deeper muscles, such as masseter m. are unaffected. Stimulation of these superficial muscles leads to an elevation of the entire cheek, increasing the midfacial volume and improving the nasolabial fold. Increasing the pull of these elevators further leads to a repositioning not only of the midface but of the lower facial soft tissues. The resulting clinical effect is a reduction in jowls and an increase in jawline contouring. The combined effect of HIFES with Synchronized RF manifests as an overall textural improvement of the skin.

Concluding comments

EMFACE uses Synchronized RF and HIFES energies simultaneously to target all facial layers; skin, fascia, connective tissue framework, and facial muscles to achieve full-face aesthetic remodeling. Affecting all these layers in a noninvasive manner leads to a textural improvement of the skin, wrinkle reduction, and an overall lifting effect visible in the cheeks and the forehead. Aside from multiple clinical studies using various evaluation methods, the results of the procedure are supported by a high patient satisfaction rate of 91.2%[21].

1. Swift, A., Liew, S., Weinkle, S., Garcia, J. K. & Silberberg, M. B. The Facial Aging Process From the "Inside Out". *Aesthet. Surg.* J. 41, 1107–1119 (2021).
2. Tobin, D. J. Introduction to skin aging. J. *Tissue Viability* 26, 37–46 (2017).
3. Kent, D., Bernardy, J. & Jarosova, R. Effect of Synchronized Radiofrequency and Novel Soft Tissue Stimulation: Histological Analysis of Connective Tissue Structural Proteins in Skin. in *Accepted for presentation at: American Society for Dermatologic Surgery (ASDS) Annual Meeting 2022. October 6-10, 2022 (CO).*
4. Elsaie, M. L. CUTANEOUS REMODELING AND PHOTOREJUVENATION USING RADIOFREQUENCY DEVICES. *Indian J. Dermatol. 54, 201–205 (2009).*
5. Goldberg, D. J. & Lal, K. Histological Analysis of Human Skin after Radiofrequency Synchronized with Facial Muscle Stimulation for Wrinkle and Laxity Treatment. in *Accepted at American Society for Dermatologic Surgery (ASDS) Annual Meeting 2022 (CO).*
6. Halaas, Y. & Gentile, R. The Interim Results of Novel Approach for Facial Rejuvenation. in *Accepted for presentation at: American Academy of Facial Plastic and Reconstructive Surgery (AAFPRS) 2022 Annual Meeting. October 20-23, 2022.*
7. Nikolis, A. et al. Differences in Temporal Volume between Males and Females and the Influence of Age and BMI: A Cross-Sectional CT-Imaging Study. *Facial Plast. Surg. 37, 632–638 (2021).*
8. Cotofana, S. et al. Can smiling influence the blood flow in the facial vein?—An experimental study. *J. Cosmet. Dermatol. 19, 321–327 (2020).*
9. Kakigi, R. et al. Heat stress enhances mTOR signaling after resistance exercise in human skeletal muscle. *J. Physiol. Sci. 61, 131–140 (2011).*
10. Yoshihara, T. et al. Heat stress activates the Akt/mTOR signalling pathway in rat skeletal muscle. *Acta Physiol. 207, 416–426 (2013).*
11. Mauro, A. SATELLITE CELL OF SKELETAL MUSCLE FIBERS. *J. Biophys. Biochem. Cytol. 9, 493–495 (1961).*
12. Kinney, B., Bernardy, J. & Jarosova, R. Novel Facial Muscle Stimulation technology with Synchronized Radiofrequency Promotes structural changes in Muscles tissue: Porcine Histology Study. in *Accepted for presentation at: American Academy of Facial Plastic and Reconstructive Surgery (AAFPRS) 2022 Annual Meeting. October 20-23 (2022).*
13. Kavanagh, S., Newell, J., Hennessy, M. & Sadick, N. Use of a neuromuscular electrical stimulation device for facial muscle toning: a randomized, controlled trial. *J. Cosmet. Dermatol. 11, 261–266 (2012).*
14. Halaas, Y., M. D. Muscle Quality Improvement Underlines the Non-invasive Facial Remodeling Induced by a Simultaneous Combination of a Novel Facial Muscle Stimulation Technology with Synchronized Radiofrequency: American Academy of Facial Plastic and Reconstructive Surgery. (2022).
15. Halevy, O., Krispin, A., Leshem, Y., McMurtry, J. P. & Yahav, S. Early-age heat exposure affects skeletal muscle satellite cell proliferation and differentiation in chicks. *Am. J. Physiol.-Regul. Integr. Comp. Physiol. 281, R302–R309 (2001).*
16. Halaas, Y., Duncan, D., Bernardy, J., Ondrackova, P. & Dinev, I. Activation of Skeletal Muscle Satellite Cells by a Device Simultaneously Applying High-Intensity Focused Electromagnetic Technology and Novel RF Technology: Fluorescent Microscopy Facilitated Detection of NCAM/CD56. *Aesthet. Surg. J. 41, NP939–NP947 (2021).*
17. Kobayashi, T. et al. Possible role of calcineurin in heating-related increase of rat muscle mass. Biochem. *Biophys. Res. Commun. 331, 1301–1309 (2005).*
18. Uehara, K. et al. Heat-Stress Enhances Proliferative Potential in Rat Soleus Muscle. *Jpn. J. Physiol. 54, 263–271 (2004).*
19. Goto, K. et al. Effects of heat stress and mechanical stretch on protein expression in cultured skeletal muscle cells. *Pflugers Arch. 447, 247–253 (2003).*
20. Myers, T. W. Fascial Fitness: Training in the neuromyofascial web. *IDEA Fit. J. April 38–45 (2011).*
21. Kinney, B. & Boyd, C. Swafety and Efficacy of Combined HIFES Tissue Stimulation and Monopolar RF for Facial Remodeling. in *Accepted for presentation at: American Academy of Facial Plastic and Reconstructive Surgery 2022 (2022).*

Emface_CLIN_Mechanism-of-action-paper_EN100; 785-74EMFMOAPEN100

The mechanism of EMFACE stimulation of muscle after the application of botulinum based neurotoxin

1st Suneel Chilukuri M.D.
Refresh Dermatology, Houston, TX, USA

2nd Yael Halaas M.D., FACS
Yael Halaas, MD, New York, NY, USA

3rd Chris W. Robb M.D., Ph.D
Skin & Allergy Center, Spring Hill, TN, USA

4th Sebastian Cotofana M.D., Ph.D., Ph.D.
Department of Clinical Anatomy, Mayo Clinic College of Medicine and Science, Rochester, MN, USA

***Abstract* — EMFACE is a new device that induces supramaximal muscle contractions of delicate facial muscles while heating the skin and underlying tissues. However, many EMFACE patients are users of botulinum based neurotoxins that are used to immobilize facial muscles in order to prevent repetitive skin folding. As such, facial muscles of these patients should not be contrated during EMFACE treatments. However, clinical studies have shown that it is possible to induce contractions of these muscles by external stimulation such as during EMAFCE. However, the mechanism of how it is possible is not entirely known.**

Keywords—Botulinum toxin, BOTOX, HIFES, EMFACE, Stimulation, Facial, Muscle

I. Introduction

Neuromodulators in aesthetic medicine, such as Botox, Dysport, Xeomin or Jeuveau have become the most frequently sought nonsurgical aesthetic procedure[1]. Type A botulinum-based neurotoxins have a myriad of clinical indications[2]. They are most frequently utilized to treat dynamic facial rhytides[3] involving the glabella, frontalis and periocular regions. Botulinum neurotoxins block neurotransmitter release in the synaptic neuromuscular junction to block voluntary muscle contraction. With blocked contractions, wrinkle formation is prevented as the overlying skin is not being repetitively folded during daily activities and thus aids in maintaining a more youthful skin appearance.[4,5] By decreasing the contraction strength of some facial depressor muscles, there is temporary increased tone of elevating facial muscles. There are also secondary effects such as reduction in erythema which may allow greater light reflection.

Recently, a novel device EMFACE was introduced to stimulate botulinum neurotoxin-blocked muscles to prevent muscle atrophy. EMFACE is able to stimulate the blocked facial muscle even though it is not possible voluntarily. In fact, the use of external stimulation on neurotoxin-blocked muscles has already been documented in multiple studies [6,7], however, the mechanism of how it is possible is not exactly known.

Although it is not entirely clear, all these suggest that external stimulation has the ability to bypass the effect of botulinum neurotoxins. The goal of this paper is to summarize existing knowledge on the topic and provide a viable hypothesis that could explain why such an effect is demonstrated during an EMFACE treatment.

II. The physiology of muscle contraction

To better understand the effect of botulinum neurotoxin, it is necessary to first explain the standard function of the neuromuscular junction and muscle contraction. The neuromuscular junction is responsible for the chemical transmission of an electrical impulse from the nerve to the muscle, to produce a muscle contraction. When a nerve impulse in the form of action potential reaches a nerve ending, voltage-gated calcium (Ca2+) channels are activated, which causes an influx of Ca2+ ions into the presynaptic neuron from the extracellular space. In the presynaptic neuron, the calcium cations interact with synaptic vesicles and enable their association with the presynaptic membrane. After the fusion of synaptic vesicles with presynaptic membrane, the content of the vesicles – neurotransmitter acetylcholine (Ach) is released into the synaptic cleft - quantal release.[8]

Under normal conditions, the released Ach transmits the electrical signal to the muscle fiber by depolarizing the muscle fiber membrane. Depolarized muscle membrane activates sarcoplasmic reticulum where Ca+ ions are stored and releases them.[8] The presence of the Ca+ ions in the muscle fiber results in a sliding process between actin and myosin filaments which slide alongside each other resulting in muscle contraction. The muscle contraction lasts as long as the Ca+ ions are present in the muscle fiber, however, Ca+ ions are quickly (fraction of second) returned into the sarcoplasmic reticulum unless there is another action potential that again increases the level of Ca+ ions or keeps it at the same level.[8] The collective shortening of the sarcomeres is the molecular mechanism behind a muscular contraction.[9]

III. The effect of botulinum neurotoxin

Botulinum based neurotoxin is affecting the process of muscular contraction at the level of neuromuscular junction. When applied, it works as a protease and prevents the fusion of the vesicles with the presynaptic membrane[10]. Without this fusion, the Ach cannot be released into the neuromuscular junction and trigger the muscle contraction as described above. It is a chemical denervation that causes partial paralysis of the innervated muscle. However, such paralysis is not causing any damage to the nerve or the neuromuscular junction and is not permanent[11].

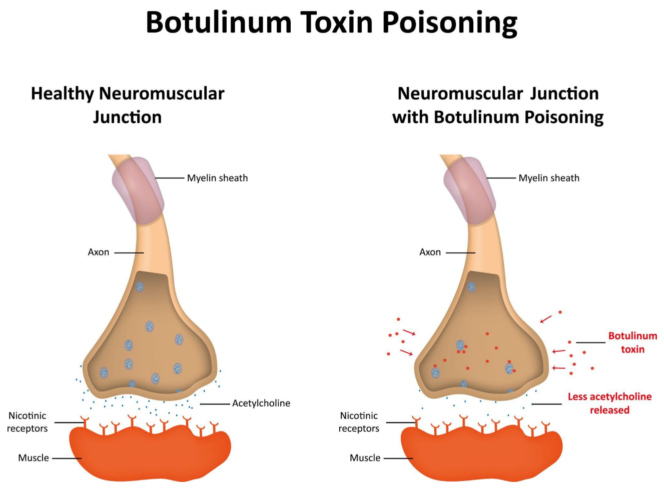


Figure 1: Botulinum toxin blocks the release of acetylcholine to neuromuscular junction, which does not allow the signal transmission into the muscle and thus blocks the muscle contraction.

IV. External stimulation of botulinum-paralysed muscle

There are two approaches to induce muscle contraction externally. First, muscles can be stimulated by applying an external electrical field to the muscle innervating neuron, where it induces an action potential, which is then carried to the neuromuscular junction.[12] Muscle can also be stimulated directly, as the muscle itself is an electrically excitable tissue.[13] If the muscle is stimulated through the neuron and, the whole muscle or all muscles innervated by this neuron are stimulated and contracted. With direct stimulation of the muscle tissue, only those muscle fibers in the electrical field are affected and a high stimulation intensity is needed to induce such contraction.[14] To contract the entire muscle by direct stimulation of the muscular tissue, a critical number of muscle fibers must be recruited.[13]

Multiple studies have shown it is possible to stimulate even the botulinum-paralysed muscles [7,15]. However, it is not entirely clear how such stimulation overcomes the barrier made by the botulinum neurotoxin. Upon the application of botulinum toxin, the membrane of the presynaptic neuron should be practically impermeable to Ach molecule due to its size as the the fusion of vesicles and presynaptic membrane ("quantal release") is blocked. Yet, the clinical trials are showing that externally it is possible to overcome this barrier and although the mechanism of how this happens is not entirely clear, several hypotheses were proposed to explain such mechanism:

Non-quantal Ach release

One of the possible explanations could be the non-quantal Ach release. It has been shown that aside from the above-described quantal release of Ach, also a non-quantal release occurs at the neuromuscular junction[16].

Non-quantal Ach release was proposed to be caused by the high-affinity choline transporter, which under normal physiological conditions returns the inactivated Ach (choline) from the synaptic cleft back to the nerve ending. Experimental findings indicate that this transporter may also transport the Ach to the neuromuscular junction. Its activity appears to be dependent on the concentration of calcium in the cytoplasm, which correlates with the firing rate of the neuron (number of induced action potentials)[16–18]. Considering that maximum firing rate of a neuron during voluntary muscle contractions reaches up to 25 Hz[19], while with external stimulation it is possible to induce firing rates in the order of hundreds of Hz, it could be assumed, that with an increased firing rate frequency, also the cytoplasmic calcium concentration increases, thus also increasing the level non-quantal Ach release.

Based on such findings, it could be hypothesized that such a non-quantal release of small amounts of Ach into the synapse still occurs, even in botulinum toxin denervated muscle. However, during voluntary contractions, the amount of the Ach is not sufficient to cause depolarization and the muscles thus remain relaxed. By applying an external high-frequency electrical field that surpasses the frequency of brain signals, the activity of the high-affinity choline transporter could be elevated, leading to exaggerated non-quantal release of Ach in amounts sufficient enough to cause muscle depolarization and contraction.

Additionally, a long-term insufficient concentration of Ach in the synapse, due to the application of botulinum toxin can lead to an increased expression of n-acetylcholine receptor (nAChR) on the postsynaptic membrane and therefore also to increase in the sensitivity of the muscle to Ach [20,21]. A lower amount of Ach would thus be needed to induce such depolarization.

Direct stimulation of the muscle fiber membrane

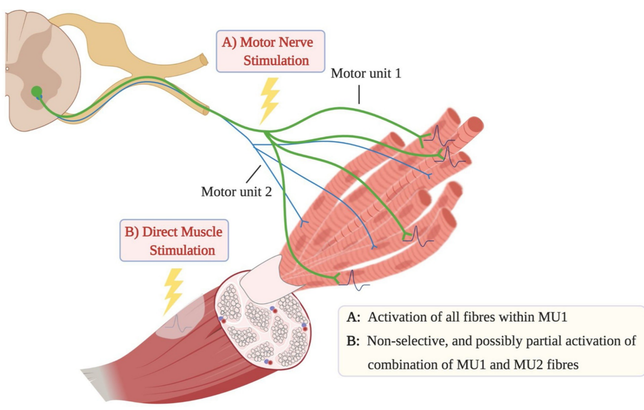


Figure 2: The principle of direct muscle stimulation vs. motor nerve stimulation. With nerve stimulation, the nerve is stimulated and signal propagates towards the muscle, while with direct stimulation the muscle fiber is stimulated directly. Image adopted from Guo et al.[22]

Another possible explanation for the externally induced contraction of botulinum-denervated muscles could be via the direct stimulation of the postsynaptic membrane. The external electrical field could possibly induce action potential directly on the muscle fiber membrane and thus trigger the influx of Ca+ ions into the muscle fiber to contract the muscle.

Nevertheless, multiple studies contradict such hypothesis. Studies investigating the use of external stimulation of muscles fully denervated by physical transection showed that very high intensity (pulses in ms) is needed to depolarize the muscle fiber membrane and induce contractions of these muscles directly, while EMFACE uses lower energy pulses in μs.[23,24] Furthermore, with direct muscle fiber membrane stimulation it is difficult to stimulate the entire muscle, rather it has been shown to stimulate only a portion of the muscle, while with EMFACE the entire muscles are contracted.

However, all these conclusions regarding the direct muscle stimulation are based on studies performed on skeletal muscles only. Facial muscles are of significantly different proportion and are much more superficial located in low depths of 3-8 mm[25]. All this may influence the response. As the facial muscles are more delicate, lower intensity may suffice to irritate the muscle membrane. Since the thickness of some facial muscles may be as small as 0.5mm[26], it may be possible that such stimulation is able to recruit enough muscle fibers to induce contraction of the entire muscle. In addition, this could actually explain the non-stimulation of the masseter muscle during the EMFACE treatment. In the vast majority of patients the masseter is not stimulated and it could be explained by the fact that the neuronal branch innervating the muscle is not in the application field, but also by the fact that masseter muscle is one of the largest facial muscles with thickness of up to 3.5mm[27] and during the treatment not enough muscle fibers are recruited to induce full masseter activation.

V. Summary & Conclusion

It is clear that it's possible to externally stimulate botulinum-denervated muscles, yet, the underlying mechanism is not. Current paper proposes a possible explanation of this phenomenon based on the existing knowledge of the processes on the neuromuscular junction and muscle contraction. However, multiple different factors may play a role in the mechanism. More experimental studies are needed to fully understand why it is possible to externally stimulate the botulinum-paralysed muscles.

In regard to EMFACE specifically, a study by Chilukuri et al.[28] showed that during the EMFACE treatment the botulinum-denervated muscles are being contracted and what is most important, the EMFACE treatment does not interfere with the effect of botulinum toxin itself. No negative effects of the EMFACE stimulation on the efficacy of the botulinum toxin were found.

References

1. Homepage. *The Aesthetic Society* https://www.theaestheticsociety.org/homepage.
2. Cohen, B. E., Bashey, S. & Wysong, A. Literature Review of Cosmetic Procedures in Men: Approaches and Techniques are Gender Specific. *Am. J. Clin. Dermatol.* **18**, 87–96 (2017).
3. Nestor, M. S., Kleinfelder, R. E. & Pickett, A. The Use of Botulinum Neurotoxin Type A in Aesthetics: Key Clinical Postulates. *Dermatol. Surg.* **43**, S344–S362 (2017).
4. Nigam, P. & Nigam, A. Botulinum toxin. *Indian J. Dermatol.* **55**, 8 (2010).
5. Small, R. Botulinum Toxin Injection for Facial Wrinkles. *Am. Fam. Physician* **90**, 168–175 (2014).
6. Fortuna, R., Horisberger, M., Vaz, M. A., Van der Marel, R. & Herzog, W. The effects of electrical stimulation exercise on muscles injected with botulinum toxin type-A (botox). *J. Biomech.* **46**, 36–42 (2013).
7. Santus, G., Faletti, S., Bordanzi, I., Pirali, F. & De Grandis, D. Effect of short-term electrical stimulation before and after botulinum toxin injection. *J. Rehabil. Med.* **43**, 420–423 (2011).
8. Gash, M. C., Kandle, P. F., Murray, I. & Varacallo, M. Physiology, Muscle Contraction. in *StatPearls* (StatPearls Publishing, 2022).
9. Sweeney, H. L. & Hammers, D. W. Muscle Contraction. *Cold Spring Harb. Perspect. Biol.* **10**, a023200 (2018).
10. Segelke, B., Knapp, M., Kadkhodayan, S., Balhorn, R. & Rupp, B. Crystal structure of Clostridium botulinum neurotoxin protease in a product-bound state: Evidence for noncanonical zinc protease activity. *Proc. Natl. Acad. Sci.* **101**, 6888–6893 (2004).
11. Satriyasa, B. K. Botulinum toxin (Botox) A for reducing the appearance of facial wrinkles: a literature review of clinical use and pharmacological aspect. *Clin. Cosmet. Investig. Dermatol.* **12**, 223–228 (2019).
12. Fu, M. J. & Knutson, J. S. Neuromuscular Electrical Stimulation and Stroke Recovery. in *Stroke Rehabilitation* 199–213 (Elsevier, 2019). doi:10.1016/B978-0-323-55381-0.00014-7.
13. Salmons, S. *et al.* Functional Electrical Stimulation of Denervated Muscles: Basic Issues. *Artif. Organs* **29**, 199–202 (2005).
14. Enoka, R. M., Amiridis, I. G. & Duchateau, J. Electrical Stimulation of Muscle: Electrophysiology and Rehabilitation. *Physiology* **35**, 40–56 (2020).
15. Adams, V. Electromyostimulation to fight atrophy and to build muscle: facts and numbers: Editorial. *J. Cachexia Sarcopenia Muscle* **9**, 631–634 (2018).
16. Vyskočil, F., Malomouzh, A. & Nikolsky, E. Non-quantal acetylcholine release at the neuromuscular junction. *Physiol. Res.* 763–784 (2009) doi:10.33549/physiolres.931865.
17. Stanley, E. F. & Drachman, D. B. Botulinum toxin blocks quantal but not non-quantal release of ACh at the neuromuscular junction. *Brain Res.* **261**, 172–175 (1983).
18. Bazalakova, M. H. & Blakely, R. D. The High-Affinity Choline Transporter: A Critical Protein for Sustaining Cholinergic Signaling as Revealed in Studies of Genetically Altered Mice. in *Neurotransmitter Transporters* (eds. Sitte, H. H. & Freissmuth, M.) vol. 175 525–544 (Springer-Verlag, 2006).
19. Purves, D. *et al.* The Regulation of Muscle Force. *Neurosci. 2nd Ed.* (2001).
20. Frick, C. G. *et al.* Long-term Effects of Botulinum Toxin on Neuromuscular Function. *Anesthesiology* **106**, 1139–1146 (2007).
21. Frick, C., Blobner, M. & Martyn, J. Up-regulation of nicotinic acetylcholine receptors cannot compensate for the decreased release of acetylcholine following infection with botulinum toxin: 9AP3-7. *Eur. J. Anaesthesiol. EJA* **25**, 132 (2008).
22. Guo, Y., E Phillips, B., Atherton, P. J. & Piasecki, M. Molecular and neural adaptations to neuromuscular electrical stimulation; Implications for ageing muscle. *Mech. Ageing Dev.* **193**, 111402 (2021).
23. Kern, H. *et al.* Home-based functional electrical stimulation rescues permanently denervated muscles in paraplegic patients with complete lower motor neuron lesion. *Neurorehabil. Neural Repair* **24**, 709–721 (2010).

24. Cameron, M. H. *Physical agents in rehabilitation : from research to practice*. (Elsevier/Saunders, [2013] ©2013, 2013).
25. Pankratz, J. *et al.* Depth Transitions of the Frontal Branch of the Facial Nerve: Implications in SMAS rhytidectomy. *JPRAS Open* **26**, 101–108 (2020).
26. Alfen, N. V., Gilhuis, H. J., Keijzers, J. P., Pillen, S. & Van Dijk, J. P. Quantitative facial muscle ultrasound: Feasibility and reproducibility: Facial Muscle Ultrasound. *Muscle Nerve* **48**, 375–380 (2013).
27. Şatıroğlu, F., Arun, T. & Işık, F. Comparative data on facial morphology and muscle thickness using ultrasonography. *Eur. J. Orthod.* **27**, 562–567 (2005).
28. Chilukuri, S. M. D. Non-invasive facial sculpting with novel technology using HIFES muscle stimulation and RF heating in patient after neuromodulator treatment.