

Thermal energy levels

Heating of the skin triggers different processes at different temperatures, resulting in a variety of outcomes. MIKE MURPHY AND PER-ARNE TORSTENSSON discuss the effects of heat shock proteins and collagen denaturation when treating the skin at variable temperatures

It is a fundamental law of physics that electric current always seeks the path of least resistance. So when radiofrequency (RF) probes are placed on the skin surface, the current will 'seek' a path which offers the lowest possible resistance, regardless of the distance between electrodes.

The stratum corneum is mostly composed of dead, flat skin cells, lipids, air pockets and very little moisture. It therefore has a very high electrical impedance (or resistance to an AC current), potentially up to 100,000 ohms. Wet skin, either due to external water or perspiration, will have a much lower impedance.

In skin, the path of least resistance is most likely a direct route from the emitter electrode through the stratum corneum to the epidermis—which has a much lower impedance compared to the stratum corneum—along the top of the epidermis, then back through the stratum corneum to the collecting electrode.

As electric current flows through these tissues, heat is generated due to the resistance to the current flow. The amount of heat generated is directly proportional to the tissue impedance, the power applied and the time for which it is applied.

Radiofrequency

The heating that takes place using typical non-invasive RF systems in the low megahertz region (0.5 – 5MHz) with skin contact electrodes is known as Joule heating. The temperature rise results from purely resistive heating resulting from electrons colliding with ions within the tissues.

Dielectric heating is also possible, as a result of friction losses from the rotation of dipole molecules induced by magnetic and or

electrical field oscillations. Dielectric heating is typically an order of magnitude smaller than Joule heating in the above frequency range.

Dipole heating is proportional to the field frequency and also proportional to the tissue permittivity. At frequencies greater than 10MHz, dielectric heating is no longer negligible in human tissues.

The absorbed electrical energy is converted into thermal energy in resistive tissues according to the following equation:

$$E_{avg} = I_{rms}^2 Z t$$

E_{avg} is the heat energy (J) averaged over a number of cycles, I_{rms} is the root mean squared current (amps), Z is the tissue impedance (ohms) and t is the current application time in seconds. Clearly high impedance tissues will generate higher temperatures per unit current.

The electrical impedance of the dermis is typically around 290 ohms while that of fatty tissue is almost 7.5 times that, at around 2180 ohms. Hence any current flowing through the fat layer will generate more heat than the dermal tissue above and so RF energy may also be used to induce lipolysis.

RF current typically generates relatively low temperatures in the skin compared to high energy lasers and IPL systems. Since the heat is generated through electrical impedance, the colour of the tissue is irrelevant. If the heat is sustained for a sufficiently long period, collagen fibres can contract and thicken during the procedure.

Further tightening is enabled from the inflammatory wound healing response which triggers new collagen synthesis. The fibrous septa, which separate the fat lobules in the subcutaneous layer, are also preferentially heated due to

the higher impedance of that layer. This results in a contraction of the fatty layer tissue which is evident as an immediate tightening reaction to the treatment.

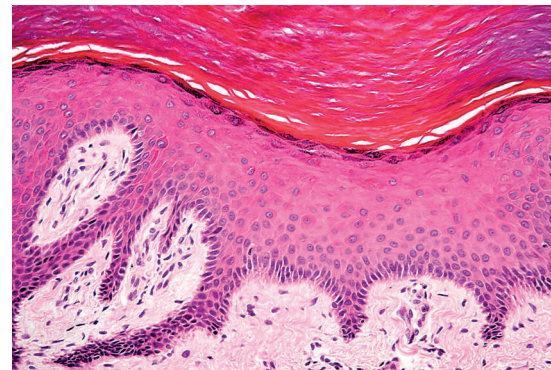
A prolonged wound-healing response lasting for more than three months may also occur, leading to dermal remodelling and the formation of new collagen fibre bundles. The ultimate result is an improvement in skin laxity and texture and an increase in dermal bulk. Wiley et al found around a 90% satisfaction rate with their patients at the three- and six-month follow-ups after RF treatments.

Clinical and histological studies have shown an increase in type I and type III collagen in addition to newly synthesised collagen.

Levels of collagen were observed to have further increased over a three month period which resulted in statistically significant improvements in skin tightening, skin texture and rhytides. Reports suggest that a low-energy, multi-pass, multi-treatment protocol results in consistently good results with minimal discomfort to the patients.

Another study using a fractional bi-polar RF unit showed both neocollagenesis and ne elastogenesis in addition to an increase in dermal cellularity and deposition of hyaluronic acid. This study also found a 28-fold increase in the level of the heat shock protein, HSP47.

The path of least resistance for RF current is through the stratum corneum to the epidermis, generating heat as it passes through



Heat shock proteins

Regardless of the method of heat generation in the dermis—by RF, lasers or IPLs—the heating process affects dermal collagen in at least two ways.

For dermal temperatures between 43–50°C, the heat generated within the dermis triggers a response from the heat shock proteins (HSP) resulting in molecular changes in the damaged collagen. HSPs reside within cells in the dermis and help to prevent irreversible cell damage under stressful conditions. They are responsible for the synthesis, transport and folding of proteins as part of a damage-control response to excess heat.

These changes include structural rearrangement of the collagen proteins through folding and unfolding activities resulting in contraction and thickening of the collagen. It has been shown that such thermally-damaged collagen can be completely replaced with new collagen through an active remodelling process mostly due to the collagen chaperone HSP47.

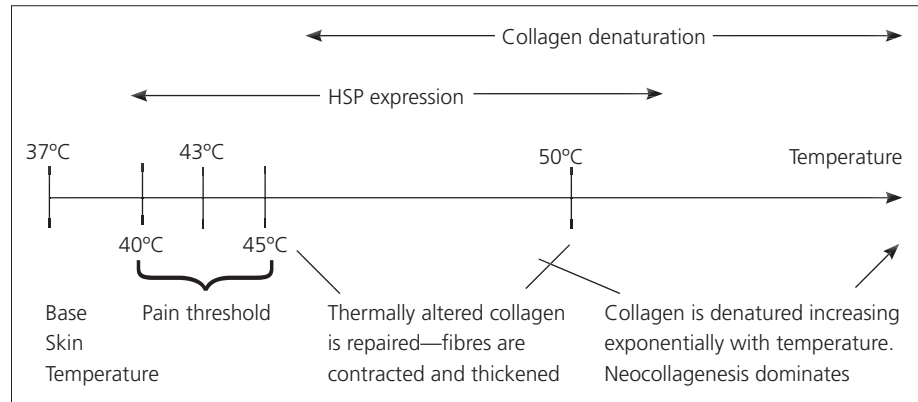
Many anecdotal reports discuss the ‘painless’ sensation during RF treatments. This indicates that the temperatures achieved in the dermis are probably below 40°C—the threshold temperature at which the pain nociceptors are activated.

Thermal pain is typically triggered between 40° and 45°C, so the clinical results from such low temperatures must be due to the HSP repair processes. However, HSP expression increases significantly at around 43°C, suggesting that a modest level of pain might lead to a better clinical outcome.

The low-energy, multi-pass and multi-treatment regime now appears to make more clinical sense since the accumulated thermal stimulation will result in further HSP expression. In particular, elevated levels of HSP47 result in the promotion of collagen synthesis, while recent research appears to indicate the role of HSP70 in determining those cells which are deemed irreversibly damaged.

Thermal denaturation

Below around 50°C, HSP expression dominates over collagen de-



naturation. However, above this temperature the denaturation process is too rapid for HSP repairs to be maintained and collagen breaks down more rapidly.

This is evident in treatments where higher energies are typically applied and where energy is applied directly into the dermal tissues via micro-needles.

For those cases where temperatures exceed 50°C, we can apply the Arrhenius Rate Equation. In such situations the temperature applied, coupled with the time for which it is applied, is critical in determining the amount of collagen denaturation, Ω :

$$\Omega = A\delta t \exp(-E_a/RT)$$

where **A** is the frequency of decomposition of the molecules (or damage rate factor, s^{-1}), **E_a** is the activation energy per mole between the native and the denatured states of tissue (J/mole), **T** is the tissue temperature (in degrees Kelvin, K), **R** is the molar gas constant (8.314 J/mole K) and **δt** is the time for which the temperature T is maintained.

It is important to note that the amount of tissue damage, Ω , is linearly dependent on time but exponentially dependent on temperature (which is directly proportional to the absorbed energy).

Studies indicate that more readily observable results are achieved at higher temperatures. Berube et al found that the increase in collagen volume was almost three times greater at 75°C compared with 65°C. This is entirely in keeping with the above theory, since a small increase in temperature results in an exponential increase in tissue

denaturation and consequently more neocollagenesis over time.

Therefore, the level of collagen damage is very sensitive to the local temperature. However, even with relatively low temperatures (<40°C) applied for sufficient periods of time, it is evident that an immediate contraction of collagen fibrils occurs, leading to significant improvements in the skin’s textural appearance.

Activation zones

It is clear that the heating of skin induces a number of reactions, including HSP expression and tissue denaturation. These processes are triggered at different temperatures and result in various outcomes at various rates.

In addition to the wound-healing response and vasodilation, at least four heat-related processes are evident: immediate collagen fibril

Graph demonstrating different temperatures triggering reactions at different rates.

Below: Results immediately following a ten minute RF session on the right hand side of the face—around the eye and forehead.



PHOTO CREDITS: Lynda V Price/XXY Photography



Left: Before and after one application of RF energy to a 68 year old female's neck

Below left: Results showing immediate improvement in the neck of an 89-year old female following one RF treatment.



ing tissues. No pain was felt during the procedure indicating relatively low temperatures (<40°C). There were no visible signs of erythema or oedema, yet instantaneous skin tightening was evident around and above the right eye.

A 68 year old female patient received one session of non-fractional treatment to her neck. A continuous power of 22W at 2MHz was applied in a continuous sweeping motion over a 30 minute session. The immediate tightening of the dermal collagen was evident with a noticeable reduction in the appearance of the wrinkles.

While this is a relatively short-term improvement, the fibroblasts in the reticular dermis will also have been stimulated. This will result in neocollagenesis in the following weeks and months. Fibroblasts typically take around six weeks before reaching the peak of collagen synthesis but can continue this process for up to nine months post-treatment.

The neck of an 89 year old female patient was treated with a continuous 19W and 2MHz for 20 minutes. There was immediate improvement in the recessed area at the base of the neck, in addition to a significant improvement in the appearance of the deep wrinkles. Further treatments will improve the appearance over subsequent months.

RF energy may be applied to the skin resulting in instantaneous collagen shrinkage, collagen denaturation, neocollagenesis and dermal remodelling. At low energies the results are mainly due to HSP expression, while higher energies cause more thermal damage and tissue denaturation. However, good clinical results are obtainable

using both processes with different levels of pain and outcomes.

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References

- Hollmig ST, Hantash BM. "Radiofrequency in Cosmetic Dermatology: Recent and Future Developments." *Cosmet Dermatol.* 2011;24:565-574
- El-Domyati M, El-Ammawi TS, Medhat W, Moawad O, Brennan D, Mahoney MG, Uitto J. "Radiofrequency facial rejuvenation: Evidence-based effect." *Journal of the American Academy of Dermatology*, Volume 64, Issue 3, March 2011, Pages 524-535.
- Wiley A, Kilmer S, Newman J, et.al. "Elastometry and clinical results after bipolar radiofrequency treatment of skin." *Dermatol Surg.* 2010, 36:877-884.
- Jacobson LG, Alexiades-Armenakas M, Bernstein L, Geronemus RG. "Treatment of nasolabial folds and jowls with a noninvasive radiofrequency device." *Arch Dermatol* 2003; 139, 1371-2.
- Sukal SA, Geronemus RG. "Thermage: the nonablative radiofrequency for rejuvenation." *Clin Dermatol* 2008; 26:602-7.
- Hantash BM, Ubeid AA, Chang H, et al. "Bipolar radiofrequency treatment induces neocollagenesis and neocollagenesis." *Lasers Surg Med*, 2009;41, 1-9.
- Morimoto RI. "Cells in Stress: Transcriptional Activation of Heat Shock Genes." *Science, New Series*, Vol. 259, No. 5100, Mar. 5, 1993, Pages 1409-1410
- Mayer MP, Bukau B. "HSP70 chaperones: Cellular functions and molecular mechanism." *Cell Mol Life Sci*, 62(6):670-684.
- Sajjadi AY, Mitra K, Grace M. "Expression of heat shock proteins 70 and 47 in tissues following short-pulse laser irradiation: assessment of thermal damage and healing." *Med Eng Phys.* 2013 Oct;35(10):1406-14. doi: 10.1016/j.medengphys.2013.03.011. Epub 2013 Apr 12.
- Dubin AE, Patapoutian A. "Nociceptors: the sensors of the pain pathway." *J Clin Invest*, Nov 1, 2010. 120(11), 3760-3772.
- Widmer C et al. "Molecular basis for the action of the collagen-specific chaperone Hsp47/SERPINH1 and its structure-specific client recognition." July 2012. www.pnas.org/cgi/doi/10.1073/pnas.1208072109.
- Murphy MJ, Torstensson P. "Thermal Relaxation Times." *Body Language Journal*, Vol 16, Issue 2, Number 62, Mar/Apr 2014.
- Murphy MJ, Torstensson P. "Thermal relaxation times: an outdated concept in photothermal treatments." *Lasers in Medical Science*, October 2013.
- Berube D, Renton B, Hantash BM. "A predictive model of minimally invasive bipolar fractional radiofrequency skin treatment." *Lasers in Surgery and Medicine*, Volume 41, Issue 7, p473-478, September 2009.

contraction; HSP expression; collagen denaturation; and fibroblast stimulation

The rate of collagen denaturation depends exponentially on the temperature—for low temperatures, the rate is slow and the HSP expression dominates. As the temperature increases, the rate of denaturation becomes too fast for the HSP processes to repair the damage and the collagen breakdown process dominates.

Clinical results

Treatment was carried out using Omniface RF—a non-ablative, bipolar system and a multi-tip, fractional bi-polar system in one unit.

The author, Dr Murphy, received treatment on the non-ablative, non-fractional setting at 2MHz in a continuous mode at a power of 14W over a period of less than ten minutes (see image on opposite page). A sweeping motion was employed on the skin surface to deliver current and heat the underly-