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Review Article

Principles and working mechanisms of water-filtered infrared-A (wIRA) in relation to wound healing

Grundlagen und Wirkprinzipien von wassergefiltertem Infrarot A (wIRA) in Bezug zur Wundheilung

Abstract

The experience of the pleasant heat of the sun in moderate climatic zones arises from the filtering of the heat radiation of the sun by water vapor in the atmosphere of the earth. The filter effect of water decreases those parts of infrared radiation (most parts of infrared-B and -C and the absorption bands of water within infrared-A), which would cause – by reacting with water molecules in the skin – only an undesired thermal load to the surface of the skin. Technically water-filtered infrared-A (wIRA) is produced in special radiators, whose full spectrum of radiation of a halogen bulb is passed through a cuvette, containing water, which absorbs or decreases the described undesired wavelengths of the infrared radiation. Within infrared the remaining wIRA (within 780-1400 nm) mainly consists of radiation with good penetration properties into tissue and therefore allows – compared to unfiltered heat radiation – a multiple energy transfer into tissue without irritating the skin, similar to the sun's heat radiation in moderate climatic zones. Typical wIRA radiators emit no ultraviolet (UV) radiation and nearly no infrared-B and -C radiation and the amount of infrared-A radiation in relation to the amount of visible light (380-780 nm) is emphasized.

Water-filtered infrared-A as a special form of heat radiation with a high tissue penetration and with a low thermal load to the skin surface acts both by thermal (related to heat energy transfer) and thermic (temperature depending, with a relevant change of temperature) as well as by non-thermal (without a relevant transfer of heat energy) and non-thermic (not depending on temperature, without a relevant change of temperature) effects. wIRA produces a therapeutically usable field of heat in the tissue and increases tissue temperature, tissue oxygen partial pressure, and tissue perfusion. These three factors are vital for a sufficient tissue supply with energy and oxygen. As wound healing and infection defense (e.g. granulocyte function including their antibacterial oxygen radical formation) depend decisively on a sufficient supply with energy and oxygen, one explanation for the good clinical effect of wIRA on wounds and wound infections can be the improvement of both the energy supply per time (increase of metabolic rate) and the oxygen supply. In addition wIRA has non-thermal and non-thermic effects, which are based on putting direct stimuli on cells and cellular structures.

wIRA can considerably alleviate the pain (with remarkably less need for analgesics) and diminish an elevated wound exudation and inflammation and can show positive immunomodulatory effects. wIRA can advance wound healing or improve an impaired wound healing both in acute and in chronic wounds including infected wounds. Even the normal wound healing process can be improved.

wIRA is contact-free, easily applied, without discomfort to the patient, with absent consumption of material and with a good effect in the depth. The irradiation of the typically uncovered wound is carried out with a wIRA radiator.

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Keywords: water-filtered infrared-A (wIRA), infrared-A radiation, wound healing, thermal and non-thermal effects, thermic and non-thermic effects, energy supply, oxygen supply, tissue oxygen partial pressure, tissue temperature, tissue blood flow, reduction of pain, wound exudation, inflammation, immunomodulatory effects, acute wounds, chronic venous stasis ulcers of the lower legs, problem wounds, wound infections, infection defense, contact-free method, absent expenditure of material, quality of life, prospective, randomized, controlled, double-blind studies

Zusammenfassung

Die Erfahrung der angenehmen Wärme der Sonne in gemäßigten Breiten entsteht durch die Filterung der Wärmestrahlung der Sonne durch Wasserdampf in der Erdatmosphäre. Durch die Wasserfilterung werden die Strahlungsanteile gemindert (sogenannte Wasserbanden innerhalb des Infrarot A sowie die meisten Teile des Infrarot B und C), die sonst durch Wechselwirkung mit Wassermolekülen in der Haut eine unerwünschte thermische Belastung der obersten Hautschicht hervorrufen würden. Technisch wird wassergefiltertes Infrarot A (wIRA) in speziellen Strahlern erzeugt, in denen die gesamte Strahlung eines Halogen-Strahlers durch eine Wasser enthaltende Küvette hindurchtritt, so dass die genannten unerwünschten Strahlungsanteile innerhalb des Infrarot gemindert oder herausgefiltert werden. Innerhalb des Infrarot stellt das verbleibende wIRA (im Bereich 780-1400 nm) vorwiegend Strahlung mit gutem Eindringvermögen in das Gewebe dar und erlaubt gegenüber ungefilterter Infrarotstrahlung einen mehrfachen Energieeintrag in das Gewebe bei geringerer thermischer Belastung der Hautoberfläche, vergleichbar der Sonnenwärmestrahlung in gemäßigten Breiten. Typische wIRA-Strahler emittieren keine Ultraviolett-Strahlung (UV) und nahezu keine Infrarot-B- und Infrarot-C-Strahlung, und der Anteil der Infrarot-A-Strahlung ist im Verhältnis zum Anteil des sichtbaren Lichts (380-780 nm) betont.

Wassergefiltertes Infrarot A als spezielle Form der Wärmestrahlung mit hohem Eindringvermögen in das Gewebe bei geringer thermischer Oberflächenbelastung wirkt sowohl über thermische (auf Wärmeenergietransfer bezogene) und temperaturabhängige (mit Temperaturänderung auftretende) als auch über nicht-thermische (ohne relevanten Wärmeenergietransfer) und temperaturunabhängige (ohne relevante Temperaturänderung auftretende) Effekte. wIRA erzeugt ein therapeutisch nutzbares Wärmefeld im Gewebe und steigert Temperatur und Sauerstoffpartialdruck im Gewebe sowie die Gewebedurchblutung, drei entscheidende Faktoren für eine ausreichende Versorgung des Gewebes mit Energie und Sauerstoff. Da Wundheilung und Infektionsabwehr (z.B. Granulozytenfunktion einschließlich ihrer antibakteriellen Sauerstoffradikalbildung) entscheidend von einer ausreichenden Versorgung mit Energie und Sauerstoff abhängen, stellt die Verbesserung sowohl der Energiebereitstellung pro Zeit (Steigerung der Stoffwechselleistung) als auch der Sauerstoffversorgung eine Erklärung für die klinisch gute Wirkung von wIRA auf Wunden und Wundinfektionen dar. Zusätzlich hat wIRA nicht-thermische und ohne relevante Temperaturänderung auftretende Effekte, die darauf beruhen, direkte Reize auf Zellen und zelluläre Strukturen zu setzen.

wIRA vermag Schmerzen deutlich zu mindern (mit bemerkenswert niedrigerem Analgetikabedarf) und eine erhöhte Wundsekretion und Entzündung herabzusetzen sowie positive immunmodulierende Effekte zu zeigen. wIRA kann sowohl bei akuten als auch bei chronischen Wunden einschließlich infizierter Wunden die Wundheilung beschleuni-

gen oder bei stagnierender Wundheilung verbessern. Selbst der normale Wundheilungsprozess kann verbessert werden.
wIRA ist ein kontaktfreies, verbrauchsmaterialfreies, leicht anzuwendendes, als angenehm empfundenes Verfahren mit guter Tiefenwirkung. Die Bestrahlung der typischerweise unbedeckten Wunde erfolgt mit einem wIRA-Strahler.

Schlüsselwörter: wassergefiltertes Infrarot A (wIRA), Infrarot-A-Strahlung, Wundheilung, thermische und nicht-thermische Effekte, temperaturabhängige und temperaturunabhängige Effekte, Energiebereitstellung, Sauerstoffversorgung, Sauerstoffpartialdruck im Gewebe, Gewebetemperatur, Gewebedurchblutung, Schmerzminderung, Wundsekretion, Entzündung, immunmodulierende Effekte, akute Wunden, chronische venöse Unterschenkel-Ulzera, Problemwunden, Wundinfektionen, Infektionsabwehr, kontaktfreies, verbrauchsmaterialfreies Verfahren, Lebensqualität, prospektive, randomisierte, kontrollierte, doppeltblinde Studien

What is water-filtered infrared-A (wIRA)? Why wIRA?

The experience of the pleasant heat of the sun in moderate climatic zones arises from the filtering of the heat radiation of the sun by water vapor in the atmosphere of the earth [1], [2], [3], see Figure 1. Mankind has developed in the evolution under the influence of this water-filtered heat radiation of the sun [4]. In contrast to this in the desert the sun is stinging and burning, as the water vapor is missing there in the atmosphere of the earth.
The filter effect of water decreases those parts of infrared radiation (most parts of infrared-B and -C and the absorption bands of water within infrared-A), which would cause – by reacting with water molecules in the skin – only a thermal load to the surface of the skin [1], [2], [3], see Figure 1.
Technically water-filtered infrared-A (wIRA) is produced in special radiators, whose whole incoherent broad-band radiation of a 3000 Kelvin halogen bulb is passed through a cuvette, containing water, which absorbs or decreases the described undesired wavelengths within infrared [1], [2], [4], see Figure 2: an example of the resulting spectrum with visible light (VIS) and water-filtered infrared-A (wIRA) is shown in Figure 3.
Within infrared the remaining wIRA (within 780-1400 nm) mainly consists of radiation with good penetration properties into tissue and therefore allows – compared to unfiltered heat radiation of conventional infrared bulbs with large amounts of infrared-B (defined as 1400-3000 nm) and -C (defined as 3000-1,000,000 nm) – a multiple energy transfer into tissue without irritating the skin (high energy transfer with limited temperature increase), similar to sun heat radiation in moderate climatic zones [1], [2].
Based on the water-filtering typical wIRA radiators emit almost no infrared-B and -C radiation and have a decreased irradiance of the absorption bands of water within infrared-A. In contrast to the sun typical wIRA radiators emit no ultraviolet (UV) radiation and the amount of infrared-A radiation in relation to the amount of visible light (380-780 nm) is emphasized (depending on the filtering of the visible light, approximately 75% of the radiation is water-filtered infrared-A), see Figure 4.
The water-filtering leads to high penetration properties with a low thermal load to the surface of the skin, see Figure 5. This is the basis that wIRA is able to essentially improve even energy-related specific factors of tissue metabolism, especially in regeneration or impaired conditions like wounds. Compared to other infrared radiation sources, there is typically no sense of discomfort or burning during irradiation with wIRA when applying an appropriate irradiance.
Within the spectra of infrared-A and water-filtered infrared-A radiation effects especially of the energy-rich wavelengths near to visible light – approximately 780-1000 nm (800-900 nm [5], [6], [7], 800 nm [8], 820 nm [9], [10], [11], 830 nm [12]) - have been described both *in vitro* and *in vivo*, and these wavelengths seem to represent the clinically most important part within infrared-A and wIRA [13], see as well section about non-thermal and non-thermic effects below.
For special purposes, like photodynamic therapy (PDT), the filtering of the visible light can be adapted to special recommendations, see section perspectives in [14].

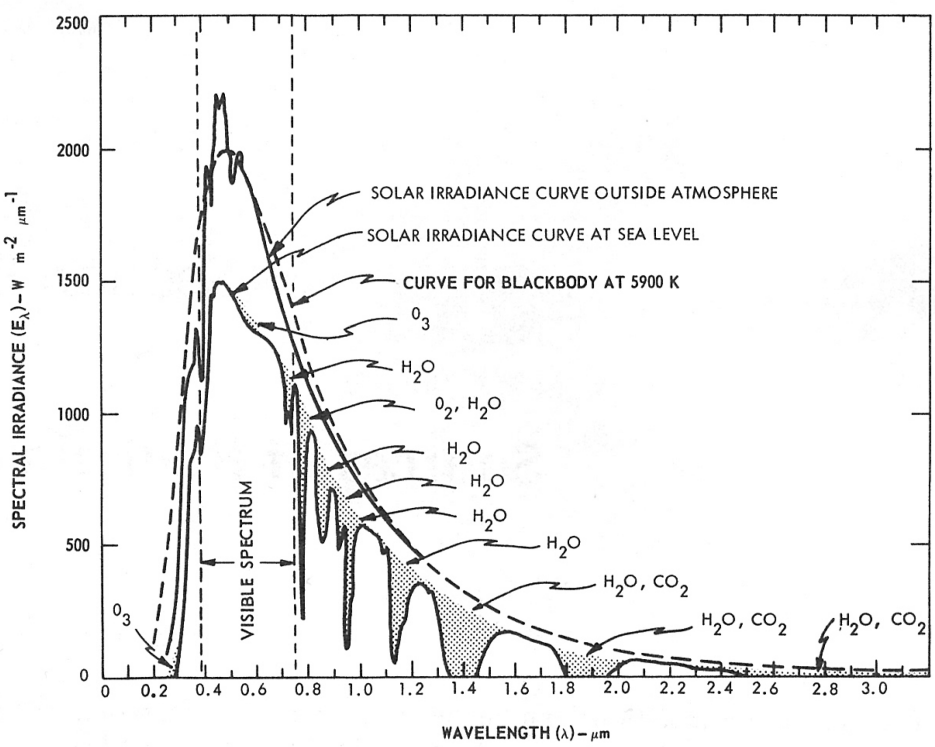

Figure 1: Spectral solar irradiance outside the atmosphere and at sea level,
in both cases with the sun at the zenith and for a mean Earth-sun separation. Shaded areas indicate absorption at sea level due to the atmospheric constituents shown (from [97], adapted from [98]).
For comparison of Figures 1, 3 and 4: 1000 W m^{-2} μm^{-1} = 100 mW cm^{-2} μm^{-1} = 1 mW cm^{-2} (10 nm)$^{-1}$

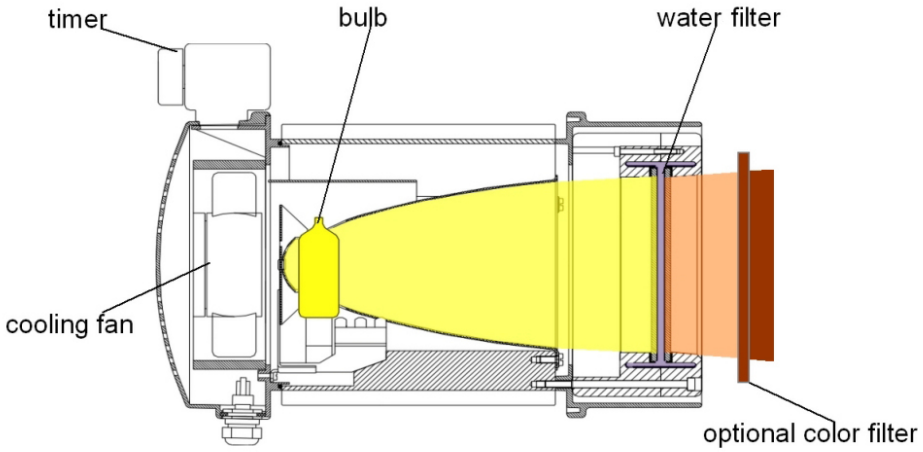

Figure 2: Cross-section of a water-filtered infrared-A radiator (Hydrosun, Müllheim, Germany)
The whole incoherent broad-band radiation of a 3000 Kelvin halogen bulb is passed through a cuvette, containing water, which absorbs or decreases the undesired wavelengths within infrared (most parts of infrared-B and -C and the absorption bands of water within infrared-A). The water is hermetically sealed within the cuvette. A fan provides air cooling of the cuvette to prevent the water from boiling.

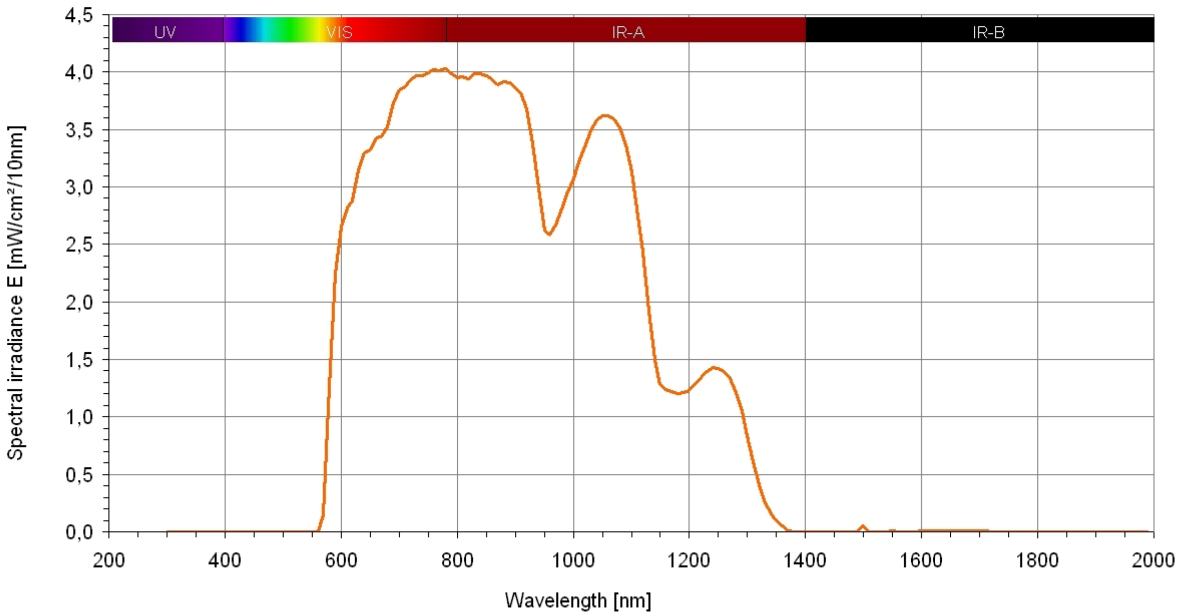

Figure 3: Spectral irradiance of a water-filtered infrared-A radiator

(Hydrosun® radiator 501 with 10 mm water cuvette and orange filter OG590) at approximately 210 mW/cm² (= 2.1 x 10^3 W/m²) total irradiance (from [1]); (visible light (VIS): 380-780 nm; infrared-A (IR-A): 780-1400 nm; infrared-B (IR-B): 1400-3000 nm)

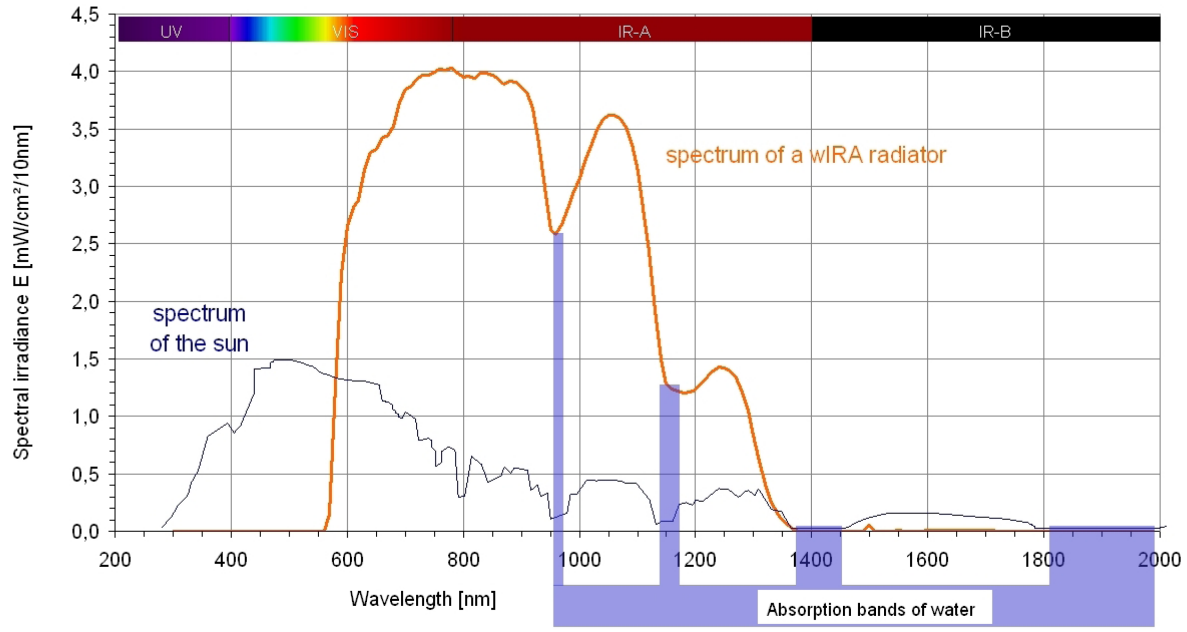

Figure 4: Comparison of the spectra of the sun at sea level and of a water-filtered infrared-A radiator

Spectral solar irradiance at sea level (with the sun at the zenith and for a mean Earth-sun separation) as in Fig. 1 (adapted from [97]) and spectral irradiance of a water-filtered infrared-A radiator (Hydrosun® radiator 501 with 10 mm water cuvette and orange filter OG590) at approximately 210 mW/cm² (= 2.1 x 10^3 W/m²) total irradiance as in Fig. 3 (from [1]).

The spectrum of the sun at sea level includes ultraviolet radiation (UV, <400 nm), visible light (VIS, 380-780 nm), and infrared radiation (IR, >780 nm). The spectrum of the water-filtered infrared-A radiator includes only visible light (VIS) and infrared radiation (IR); the visible part depends on the used color filter; the wIRA radiator does not emit ultraviolet radiation (UV).

Both spectra show the decreased irradiance of the absorption bands of water.

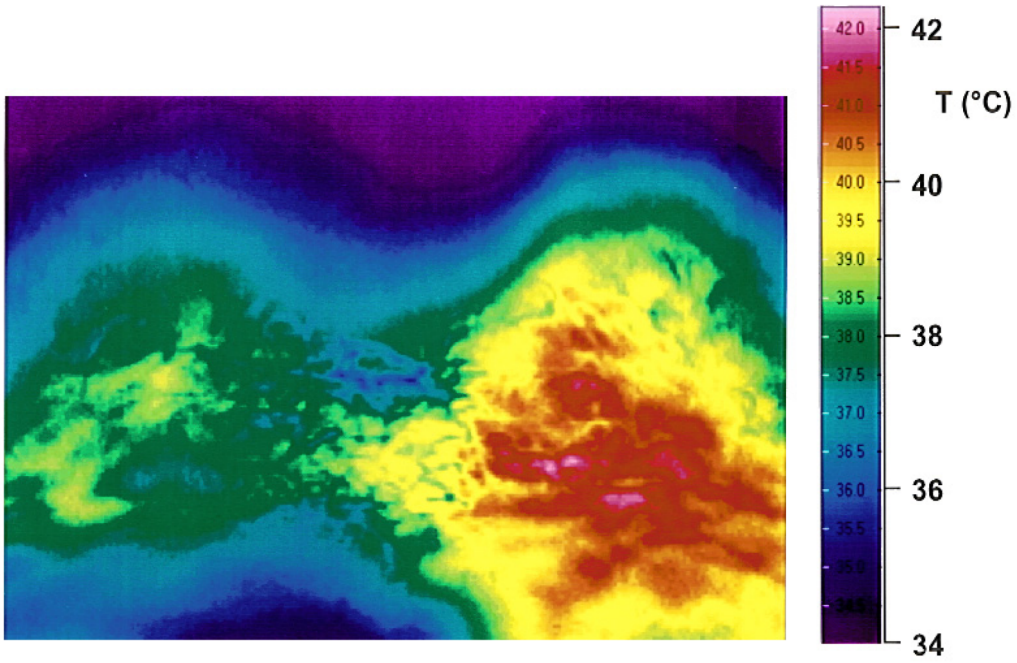

Figure 5: Comparison of irradiation with water-filtered infrared-A and with conventional infrared
Thermographical comparison of skin surface temperatures in the lumbar region 12 minutes after beginning of irradiation with water-filtered infrared-A (left) and conventional infrared (right) with the same irradiance: the skin surface temperature is higher in case of irradiation with conventional infrared (presented in the thermography), while temperature in 1 cm depth of tissue is higher when irradiating with water-filtered infrared-A (from [45]). So water-filtered infrared-A presents a high tissue penetration combined with a low thermal load to the skin surface.

Working mechanisms of wIRA

wIRA acts both by thermal and thermic effects as well as by non-thermal and non-thermic effects [1], [2].
"Thermal" effects of wIRA are related to a (heat) energy transfer (transfer of heat radiation energy, transfer of infrared radiation energy) e.g. into tissue.
The production of a therapeutically usable field of heat in tissue and the energy-related aspects derived from this belong to the thermal (and thermic, see below) effects of wIRA.

Thermal and thermic effects of wIRA and production of a therapeutically usable field of heat

As an effect related to the transfer of heat radiation energy ("thermal" effect) wIRA produces a therapeutically usable field of heat in tissue [1], [2] by

- reaching capillaries near the surface of the skin by the infrared-A radiation (primary warming)
- heat distribution by the blood (cooling of tissue areas near the surface of the skin, spreading of the heat into the depth)
- increasing capillary bloodflow near the surface of the skin with expansion of the blood flow areas accessible to the radiation and by this augmenting the second mechanism
- conduction of heat into the depth
- secondary energy release by stimulation of metabolism (increase of metabolism) caused by the increase of temperature (in accordance with the reaction velocity temperature rule a 3°C higher temperature means approximately 30% more speed of reaction and by this more energy provision and release in the tissue)
- relatively high primary depth effectiveness of wIRA.

Thermal effects of wIRA – transfer of heat energy, e.g. bringing an amount of heat (heat energy) into tissue – can lead to a temperature increase in the tissue and by this to temperature depending ("thermic") effects (like the desired sufficient energy production in the tissue, see below). Therefore thermal effects can represent the basis of such thermic effects.
Based on its special properties, wIRA allows a high energy transfer into tissue (with relevant thermal effects) combined with a limited temperature increase in the tissue (limited thermic effects, ideal dosing properties). This is especially of importance concerning safety aspects, see separate section about safety aspects below.
An additional example of a temperature depending effect (thermic effect) of wIRA might be the activating of transient receptor potential channels of the vanilloid (TRP-V) family depending on the increased temperature.

Non-thermal and non-thermic effects of wIRA

Non-thermal and non-thermic effects of wIRA (without a relevant transfer of heat energy and without a relevant change of temperature) are based on putting a stimulus on cells and cellular structures as a specific (direct) radiation effect. Reactions of the cells at infrared radiation – even partly at very small irradiances – are e.g. target oriented growth of surface extensions (plasmodia) [5], influence on the cytochrome c oxidase [9], [15], [16], target oriented growth of neurons [8], stimulation of wound repair [17], [18] as well as cell protective effects of infrared-A [19], [20], [21], [22] (including signalling pathway [20], [21]) and water-filtered infrared-A (wIRA) [23], [24], [25]. For wIRA with appropriate therapeutic irradiances and doses it could not only be demonstrated, that it is harmless for human skin (no induction of matrix metalloproteinase 1) [13], [24], but that it has cell protective effects against the damages caused by UV radiation [23], [24], [25]. (Safety aspects of the clinical use of wIRA are discussed as well in a separate section below.) In addition, wavelengths within wIRA have been shown to influence adhesive interactions between cells and extracellular matrices [9], playing a regulative role in wound repair processes, and may have a positive effect on cosmetic results [26]. It is also supposed that wIRA has immunomodulatory effects [1], [2].
Concerning both thermal and thermic as well as non-thermal and non-thermic effects of wIRA the mediation by pathways like nitric oxide in vasodilatation or by cytokines or neurotropines should also be taken into account [27].

Energy-related aspects of wound healing and oxygen

Wound healing and infection defense (e.g. function of granulocytes including their antibacterial oxygen radical formation) represent processes with an extremely high energy demand [1], [26], [27]. Hence they depend on a sufficient supply with energy and oxygen quite decisively. On the long run energy must be provided mostly aerobically (with oxygen). Oxygen plays a double role in wound healing: as an agent in the energy production and as a substrate for the oxygen radical formation of the granulocytes (respiratory burst) [1].
Wound repair and energy production therefore depend on the integrity of the following three vital factors [1], [26], [27]:

- *tissue temperature*
- *tissue oxygen partial pressure*
- *tissue perfusion.*

Even one single factor lying clearly in the pathological area can deter energy production and wound healing or makes them both impossible [1], [26], [27]:

- Below 28° C no wound healing is possible (too slow metabolism in accordance with the reaction velocity temperature rule) [1], [28] and the center of chronic wounds is often relatively hypothermic [1], [26], [27] – while e.g. both preoperative [1], [29] and postoperative [1], [26], [30] heat supply to the operation field can improve healing of acute wounds.
- Without a sufficient oxygen partial pressure no aerobic energy production (and no granulocyte function) is possible (the center of chronic wounds frequently has an oxygen partial pressure near zero [1], [26], [27], [31], [32], [33], [34], [35], [36], [37], [38], [39], [40], [41]), which increases markedly the risk of wound infections [26].
- A sufficient tissue blood flow including capillary blood flow is required for the transport of high-energy substrates to the tissue and for the removal of metabolic waste products [1].

The complex interaction of growth factors, cytokines, proteases and others in the context of wound healing with differences between acute and chronic wounds as well as influences of the age and the importance of the extracellular matrix – with e.g. an outweighing of inflammation mediators and proteases (matrix metalloproteinases) in chronic wounds – are today already quite well-known in detail [42], [43].
wIRA augments the cellular energy provision per time considerably by increasing all three factors, where the effects of wIRA on these three factors have been proven by different study groups by means of various methods [1], [26]:

- Tissue temperature, proved in humans by means of a direct measuring of the tissue temperature with stitch probes [44], [45], [46] as well as with implanted probes (in 2 cm of tissue depth in operation wounds) [26] and thermographically [27], [47], [48] as well as in addition in animal experiments with stitch probes up to 7 cm of tissue depth [49];
  e.g. wIRA can increase the temperature in 2 cm of tissue depth by approximately 2.7 °C [26], the field of heat can reach into a depth of approximately 5(-7) cm [49].
- Oxygen partial pressure in the tissue, proved in humans by means of a direct oxygen partial pressure measurement in the tissue with implanted probes in operation wounds [26] as well as by means of measuring of the oxygen saturation of the hemoglobin with an external white light-measuring probe [50];
  e.g. wIRA can increase the oxygen partial pressure in 2 cm of tissue depth by approximately 30% [26].
- Tissue blood flow/capillary blood flow, proved in humans by means of blood flow measurement with laser Doppler perfusion imaging (= scanning laser Doppler imaging) [47], [48], [51] and by means of blood flow measurement at two depths with an external laser Doppler-measuring probe [50] as well as in animal experiments by means of color microsphere technique up to 7 cm of tissue depth [49];

e.g. wIRA can increase superficial blood flow to approximately 8 times the amount [47], the field of increased blood flow can reach into a depth of approximately 5(-7) cm [49].

In contrast to this, hyperbaric oxygenation (HBO) [34], [35], [36] primarily increases only one factor, the oxygen partial pressure in the tissue.

The clinically beneficial effect of wIRA on problem wounds and wound infections – including the effects to decrease pain, inflammation, and hypersecretion and to have immunomodulatory effects – can be explained by the improvement in both the energy provision per time (increase of the metabolic rate) and the oxygen supply (e.g. for the function of granulocytes) as well as by non-thermal and non-thermic cellular effects [1], [13].

Due to its penetration properties, wIRA allows a multiple energy transfer into subcutaneous tissue (2-3 cm) without irritating or overheating the skin like unfiltered heat radiation [1], [2], [26]. As many postoperative wound healing impairments and infections originate primarily in the subcutaneous layer, wIRA has advantages for local warming in acute wound healing compared to other sources such as heating bandage systems or hot packs, whose heat is absorbed in the epidermal layers and may cause burning of the skin [26], [52].

Taking the holistic point of view of quantum physics [53] into account, water-filtered infrared-A can be described as flow of photons (quanta) both with non-thermal and non-thermic as well as with thermal and thermic effects [13]. From the point of view of modern physics with its probabilistic approach [53], [54], regarding the interaction of elements within a system (with an irreversibility of time and a sequence of events and small influences leading to divergent ways and results (butterfly phenomenon)), many systems in the world, especially biological systems, are unstable thermodynamic systems, capable to build up and represent complex structures and being far away from a stable (unstructured) point (chaos) [13]. Energy delivery to the system can maintain such an unstable thermodynamic system [13], [54]. In this sense an adequate infrared irradiation with appropriate irradiances can help maintain such a desired unstable thermodynamic system: on the macroscopic level predominantly with thermal (transfer of energy) and thermic effects (clinically with increased tissue temperature, perfusion and tissue oxygen partial pressure as energy-related important variables [26]) and on the microscopic/molecular level both with non-thermal and non-thermic as well as with thermal and thermic effects on cells and cell structures [13].

Principles of clinical applications of wIRA

wIRA can always be taken into consideration when a depth effective heat application is desired/indicated clinically (with good tolerance to high power density and with a high energy flow into the tissue). wIRA can always be taken into account when pathogenetically at least one factor which can be influenced positively by the thermal and thermic as well as by non-thermal and non-thermic effects of wIRA is impaired or suboptimal [1].

Advantages of wIRA

- *Decrease of pain, inflammation, and hypersecretion and positive immunomodulatory effects* [1]. All four effects are clinically important. Especially the pain reduction (or the pruritus reduction in morphea [55], [56]), seen in a variety of indications, e.g. in verrucae [2], herpes, wounds [1], [26], [27], [57], [58], [59], scleroderma [60], and observed in different study groups, with its positive consequences for the patients (less pain, remarkably less need for analgesics, less side-effects of analgesics) should be emphasized as an important clinical effect of wIRA.
- contact-free, easily used procedure
- "clean" procedure (compared to e.g. fango)
- without expenditure of material
- usable for a single body region (single radiator)
- gentle concerning blood circulation (compared with full bath)
- no need for a fixing at the body (compared with a "warm pack")
- usable at all sorts of positionings
- offers freedom of movement
- possible combination of "heat and motion" [61]
- ideal dosing properties (dosing primarily by variation of the distance from the radiator)
- continuously rising temperature without heat shock and overheating of the superficial skin layers
- subjectively pleasant (even on wounds), therefore unproblematic use also with children
- good effects in the depth
- long lasting heat depot
- relatively low technical expenditure
- low time expenditure for staff
- easy feasibility
- limited time expenditure for the patient

Altogether, wIRA is:

- fundamentally better than "red light" (unfiltered infrared), because a considerably higher irradiance is possible with more warming in the depth and less heating of the surface and
- also a better alternative to "wet warm packs" and other heating methods.

Beside the possibility that wIRA radiators are used in hospitals or in offices of physicians or surgeons, wIRA radiators can be used – under the supervision of the responsible physician – directly at home or similarly in a nursing home: especially when for a longer period of time a wound shall be irradiated once or twice daily and the patient itself or his family or an ambulatory nursing care service takes care to use the radiator appropriately, a wIRA radiator can be provided on loan [1].

Fundamental recommendations for the clinical use of wIRA

The following fundamental recommendations can be given for clinical use of wIRA:

- Typically wIRA acts only on bare skin, i.e. wIRA does not penetrate clothes or most kinds of bandages or wound dressings.
- If possible, irradiation should be vertical to the skin; irradiation distance should be at least as indicated by the distance rod of the radiator (depends on the type of radiator, e.g. 25 cm) [1].
- Irradiation time should be at least 20 minutes (better 30 minutes) [1].
- If the patient gets too warm, at full term the irradiation distance should be extended (and by this the irradiance decreased); if possible, the irradiation should not be stopped [1].
- In routine clinical practice often markedly larger irradiation distances than the minimum distance are used. Then the typical total irradiances (wIRA and visible light) are approximately 80-160 mW/cm² (depending on size of the irradiated area, on tissue temperature and amount of subcutaneous soft tissues, e.g. lower used irradiances at the tibial border compared to the anterior part of the thigh), corresponding to wIRA irradiances of only 60-120 mW/cm² [13].
- Special caution, i.e. a larger irradiation distance, should be taken in patients with an impaired sensation (e.g. diabetic polyneuropathy) or a deteriorated ability to express themselves, and when irradiating cold tissue or tissue badly supplied with blood or an area with low subcutaneous tissue (e.g. tibial border) [1].

wIRA for the improvement of wound healing in dermatology and surgery

Acute wounds and especially chronic wounds, intractable wounds or infected problem wounds should be irradiated with wIRA ideally once or twice per day for (20-)30 minutes each (longer irradiation times per day are possible and often helpful), at least three times per week for (20-)30 minutes [1]. wIRA does not replace other sensible/necessary therapeutic procedures (such as the important compression garment therapy of chronic venous stasis ulcers of the lower legs [62], [63], [64]) but complements them. Correspondingly the therapy with wIRA has to be embedded in an overall therapeutic concept. wIRA can be used independently from therapy preferences concerning wound management (e.g. moist wound management). Typically for wIRA irradiation the wound has to be uncovered, see Figure 6, as most bandages or wound dressings (with the exception of e.g. some tested transparent foils) are not adequately permeable for wIRA (as demonstrated by spectral transmission measurements) [1].

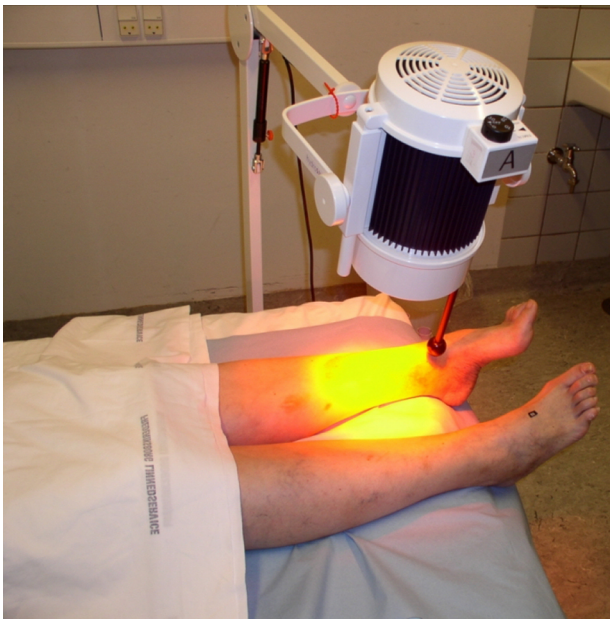

Figure 6: Example for an irradiation of a wound with a water-filtered infrared-A radiator
(published with kind approval of Prof. James Mercer, Tromsø/Norway) [27]

According to modern concepts [65] for the assessment of wound healing also other end-points and variables of interest aside from a complete wound closure have to be used like reduction of pain, improvement of quality of life, improvement of the cosmetic result, reduction of scars, clinically relevant shortening of the time of wound healing and improved quality of healing [1]. Nowadays great importance is placed on the reduction or avoidance of pain in order to improve the wound healing and to avoid the formation of a pain memory with chronification of the pain [66], [67] associated with the application of management strategies of common acute and chronic wounds.

Safety aspects of the clinical use of wIRA

wIRA in clinical use at appropriate irradiances has been described since more than 15 years as helpful and safe [1], [2], [23], [24], [26], [27], [34], [44], [45], [46], [47], [48], [49], [55], [57], [58], [59], [61], [68], [69], [70], [71], [72], [73], [74], [75], [76], [77], [78], [79], [80], [81].

In accordance with previous investigations [19], [20], [21] water-filtered infrared-A (wIRA) at appropriate irradiances is unlike ultraviolet-A especially not implicated in photoaging of the skin, mediated by the collagenase matrix metalloproteinase 1 (MMP-1) [13], [23], [24]. wIRA can even be implicated in a protective manner [13], [19], [20], [22], [23], [24].

Investigations of human skin fibroblasts after single exposures between 15 minutes and 8 hours to wIRA or 15-45 minutes to ultraviolet-A (UV-A) radiation at two physiologic temperatures as well as after repeated exposures with wIRA are presented in [13]: Single exposure of cultured human dermal fibroblasts to UV-A radiation yielded a very high increase in MMP-1 mRNA expres-

sion (11-fold expression for conventional Reverse Transcriptase Polymerase Chain Reaction (RT-PCR) and 76-fold expression for quantitative real-time RT-PCR) and a dose-dependent decrease in cell survival. In contrast, even at an investigated disproportionally high irradiance wIRA did not produce cell death and did not induce an increase in MMP-1 mRNA expression. Additionally, repeated exposure to wIRA did not induce MMP-1 mRNA expression.

The results of the recent publication [13], in which particularly a great effort to avoid any temperature alteration of the cells was undertaken, are consistent with publications of several study groups [13], [19], [20], [21], [22], [23], [24], [82] and contradict publications primarily of one study group [83], [84], [85], [86], which described undesired effects of infrared-A and wIRA radiation in cell cultures.

Reasons for the different results are presented in detail in [13]: so [13] used normal skin fibroblasts and not foreskin fibroblasts of the newborn or young child which are well known to behave differently and are not representative of human skin. Effects on cells depend not only on the irradiation dose but also on the irradiance. In some other publications it was not taken into account that cell cultures, which represent a monolayer of cells and which have in contrast to human skin no horny layer and no heat distribution by blood circulation, cannot be irradiated with the same irradiance as a living skin (the remarkable difference between irradiating a material without circulation and a living patient is described and documented, for example, in two infrared thermography video sequences in [27]): corresponding to this partly the three- to tenfold (e.g. 333 mW/cm² [83]) of a physiologic irradiance was used in cell cultures [83], [84], [85], [86]. In [13] with careful and effortful temperature fixing of the cells, which prevented an overheating of the cells, no undesired thermic effects were seen even at the investigated disproportionally high irradiance. Such a temperature fixing is important to avoid misinterpretations, as MMP-1 mRNA, whose increase is interpreted partly as an indication for skin aging, shows an increased expression already by temperature increase about a threshold – a pure thermic effect independent from the cause of the temperature increase and thus also independent from specific properties of infrared-A or wIRA radiation. Interestingly a current publication with emphasis to avoid any overheating [82] from the same institute as the publications [83], [84], [85], [86] showed no damaging effect of water-filtered infrared-A radiation (0, 100, 250, 500, 1000 J/cm²) to a glyceraldehyde-3-phosphate dehydrogenase (GAPDH) solution as a model enzyme for environmentally induced protein damage, while irradiation with UV-A (0, 100, 250, 500, 1000 J/cm²), UV-B (0, 250, 500, 1000, 2000 mJ/cm²), and gamma-irradiation (0, 50, 100, 250, 500 Gy) caused a dose-dependent increase in protein modification (fragmentation and aggregation) and loss of enzyme activity with complete loss of enzyme activity at the highest doses. The striking difference between appropriate and inappropriate irradiances can be illustrated by the maximum skin temperature: Mercer [47] showed that a clinically typical irradiation with wIRA increased skin surface temperature (starting from 32.5 °C) by nearly 6 °C to a mean of 38.2 °C (maximum value was 39.1 °C). In accordance with that skin surface temperature (starting with approximately 32 °C) reaches approximately only 38 °C even under Mediterranean conditions in the summer at noon after 30 minutes stay in the sun [13]. These approximately 38(-39) °C are decisively lower than the induced "43 °C for 90 minutes" with inappropriately high irradiance [87]: above 39.5-40 °C heat-shock proteins can be induced [13] (the heat-shock-induced matrix metalloproteinase-1 expression in human epidermal keratinocytes is mediated by the transient receptor potential vanilloid-1 kation channel [88]), and this is a thermal effect and especially a thermic effect (temperature limits are exceeded), independent from the cause of exceeding temperature limits, and not a direct radiation effect. Some more examples of inappropriate irradiances *in vivo* and *in vitro* are presented in [13].

Appropriate therapeutic irradiances of wIRA – typically within the range 60-120 mW/cm² – are clearly lower than the above described investigated disproportionally high irradiance (333 mW/cm² [83]), particularly if the difference between living skin and cell culture is taken into account. The infrared-A irradiance by the sun at the surface of the earth on sea-level during the summer at noontime in moderate climatic zones is once more considerably lower (maximum approximately 20 mW/cm²) – and even under extreme atmospheric conditions at the equator only approximately 34 mW/cm². Therefore related to infrared-A irradiances and doses no indications for a necessary or sensible protection of the skin against infrared-A or wIRA radiation of an appropriate therapeutic use or of the sun can be seen [13] in contrast to the undisputedly sensible and necessary protection against an excessive UV irradiation.

As explained in the section about thermal and thermic effects of wIRA, wIRA with its special properties allows a high energy transfer into tissue (with relevant desired thermal effects, like increase of tissue temperature, tissue oxygen partial pressure, and tissue perfusion) combined with a limited temperature increase in the tissue (with limited thermic effects, omitting undesired effects) and with ideal dosing properties.

Clinical indications for wIRA

A review concerning clinical indications for wIRA *in acute wounds* including prospective, randomized, controlled, double-blind studies is presented in [89].

A review concerning clinical indications for wIRA *in chronic wounds* including prospective, randomized, controlled, double-blind studies is presented in [14].

Clinical indications for wIRA outside wound healing are [1]:

In dermatology: wIRA alone (which means without simultaneously topically administered substance and without the subject of photodynamic therapy PDT) can be used for therapeutic purposes in recalcitrant common hand and foot warts (one therapy cycle with continous keratolysis with salicylic acid plaster, bloodless curettage, one wIRA irradiation of 30 minutes per week for 6-9 weeks [2], [55]), in herpes labialis, herpes zoster (fast decrease of pain in the acute phase as observed in casuistics), condylomata acuminata, scleroderma [60], [72], morphea [55], [56], acne papulopustulosa [90], [91], and possibly in alopezia areata.
wIRA can be used to improve the penetration of topically applied substances [69], [70], [71] (like cortisone or local anaesthetics) as an alternative to an occlusive dressing. This can be considered (indications under investigation) in neurodermitis, psoriasis, herpes zoster (with acyclovir topically), acne papulopustulosa (with topical acne therapeutic [91]), alopezia areata (with topical cortisone).
wIRA can be used within a photodynamic therapy PDT (and a photodynamic diagnosis PDD = fluorescence diagnosis FD) – if clinically an indication for a PDT or a PDD with PDT is given – together with one or several absorption bands in the visible range in actinic keratosis [73], [74] and in (superficial) basal cell carcinomas (BBC) [74], [92]. Perspectives for a use of PDT (with wIRA) in wound healing are presented in [14].
In physiotherapy, sports medicine, and orthopedics: the clinical application of wIRA can be in preventive, therapeutic, regenerative, or rehabilitative intention. Muscular hardenings, myogeloses [66], lumbago, diseases of the rheumatic disorders circle [76], M. Bechterew [77], arthroses, arthritises, contusions; fibromyalgia (preferably wIRA in combination with motion, i.e. wIRA with a small amount of ergometer work) [93], regeneration after sports [78] (wIRA alone or wIRA in combination with motion), postoperative rehabilitation [89], [94], improvement of lipolysis (wIRA in combination with motion) [61].
In neonatology: keeping or rising of the body temperature, generating a "heat depot" ahead of a necessary transport of a neonate [79].
In oncology: (local or systemic) hyperthermia in combination with radiotherapy (e.g. in metastatic breast cancer [95]), hyperthermia in combination with chemotherapy [96].

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