5 Temperature Profiles and Oxygenation Status in Human Skin and Subcutis Upon Thermography-Controlled wIRA-Hyperthermia

A. R. Thomsen, M. R. Saalmann, N. H. Nicolay, A. L. Grosu, and Peter Vaupel

Abbreviations

HT	Hyperthermia (mild HT, 39–43 °C)
i.v.	Intravenous
pO_2	Oxygen partial pressure, O_2 tension (mmHg)
ROI	Region of interest
RT	Radiotherapy, radiation treatment
stO_2	Oxyhemoglobin (HbO_2) saturation, tissue (%)
T	Temperature (°C)
wIRA	Water-filtered infrared A irradiation

5.1 Introduction

In radiation oncology, localized wIRA-hyperthermia (wIRA-HT) is an effective adjunct for sensitizing superficial tumors to radiation treatment [1]. This sensitization may result from hyperthermia (HT)-induced improvements of tissue oxygenation (i.e., increase in oxygen partial pressure, pO_2, "reversing hypoxia") due to a temporary increase in local blood flow in the temperature range between 39 and 43 °C (exposure

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time approx. 1 h). It is noteworthy to mention that in mild hyperthermia, additional mechanisms such as (a) stimulation of anti-tumor immune responses, (b) optimization of chemotherapeutic effects (HT level: 40–43 °C), (c) inhibition of DNA repair (HT level ≥41 °C), and (d) the triggering of liposomal release of drugs (HT level: 41–42 °C; [2]) may also be responsible for improving therapeutic outcomes.

"Probably no area in hyperthermia research is more important than the need to accurately assess the resultant temperature of tumors or normal tissues following heating" [2]. Although skin surface temperatures can adequately be monitored by thermography [3], minimally invasive temperature measurements are required to guarantee effective heating and adequate hyperthermia levels (39–43 °C) in deeper tissue layers [4, 5]. This study thus focuses on assessing temperature distribution in skin and subcutis of healthy volunteers upon localized wIRA treatment. As the tissue oxygen level is a major factor for cellular radiosensitivity [6], HT-induced changes in skin and subcutaneous pO_2 values and oxyhemoglobin (HbO_2) saturations in the microvasculature of the subpapillary tissue and the upper dermis layer are also assessed.

For further orientation, the histomorphology of the human skin and subcutis is schematically shown in Fig. 5.1.

5.2 Materials and Methods

5.2.1 Delivery of wIRA-Hyperthermia

Superficial hyperthermia was applied using the TWH 1500 wIRA-hyperthermia system (Hydrosun®, Müllheim, Germany) with two radiators, controlled independently by two thermographic cameras and safety pyrometers. Radiators were positioned 34 cm between radiator exit and skin surface, resulting in an approximate irradiance of 200 mW/cm^2.

For the application of hyperthermia, the lower abdominal wall (10 treatment sessions) and the lumbar region (2 treatment sessions) of healthy volunteers (1 female,

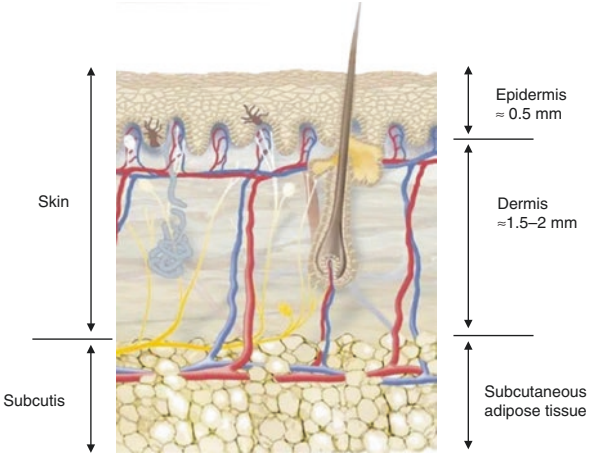

Fig. 5.1 Histomorphology of human skin and subcutis (schematic, modified from Beiersdorf-Eucerin). Mean thickness of skin layers according to [7]

and 2 males, age: 35–49 years) were exposed to wIRA irradiation for approximately 60 min. Participation in this procedure has been found to be ethically sound by the local ethics authority, and volunteers gave their informed consent.

5.2.2 Noninvasive Monitoring of Skin Surface Temperatures (Thermography)

Using this therapeutic approach, maximum skin surface temperature is continuously regulated by a control circuit for each of the two radiators, which is a key element of the TWH 1500 system: When thermography assesses a hot spot and a temperature above a defined maximum (*switch off temperature*: 43 °C), the power supply to the respective radiator is instantly switched off via a relay. As soon as the temperature of the hot spot drops (to *switch on temperature:* 42.5 °C), the radiator is turned back on. In steady-state conditions, between 1 and 4 on–off cycles take place per minute. The resulting peaks in temperature traces are visible in thermography records, but also in superficial skin layers, measured invasively as described below.

A typical example of serially assessed thermographic images during the onset (0–10 min) of wIRA-HT of the skin surface and in situ positioning on the temperature probes is shown in Fig. 5.2. Respective mean region of interest (ROI) temperatures are presented in the upper right corners.

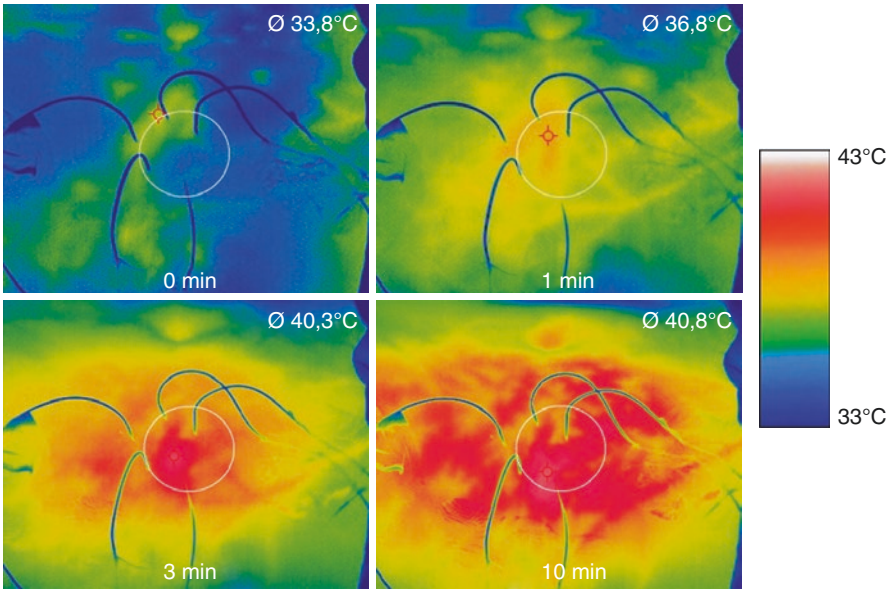

Fig. 5.2 Examples of serially assessed thermography images during the first 10 min of wIRA-HT of the skin surface (abdominal wall). Invasive temperature and pO_2 probes are placed in defined tissue depths as shown in Fig. 5.4 Color-coded temperature range: 33–43 °C

5.2.3 Minimally Invasive Measurement of Skin and Subcutis Temperatures (Thermometry)

Tissue temperatures within skin and subcutis of the abdominal wall were measured using fiber-optic sensors (OTG-M600, Opsens, Quebec, Canada). Characteristic and representative traces of skin surface, and intradermal and subcutaneous temperatures before, during, and after wIRA-HT are shown in Fig. 5.3.

5.2.4 Assessment of the Tissue Oxygenation Status

The corresponding tissue oxygen partial pressures (pO_2) were assessed with the Oxylite Pro system (Oxford Optronix, Abington, UK).

Fiber-optic temperature probes (diameter: 0.7 mm) and oxygen sensors (diameter: 0.4 mm) were transepidermally inserted via 1.1 mm i.v. catheters (Vasofix™ Safety, Braun, Melsungen, Germany) down to defined tissue depths (subepidermal ≈0.5 mm, and 1–20 mm within the dermis and subcutis). For positioning of invasive catheters and probes, see Fig. 5.4.

In selected situations, hyperspectral tissue imaging (TIVITA™, Diaspective Vision, Am Salzhaff, Germany) was used to visualize the HbO_2 saturation (stO_2) in the microcirculation of the subpapillary/upper dermis layers [8] of healthy volunteers ($n = 3$) and in superficial chest wall tumors (two patients).

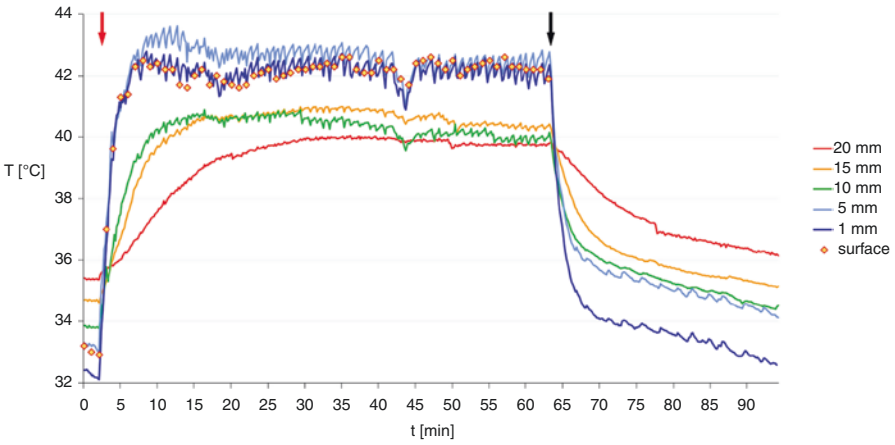

Fig. 5.3 Characteristic traces of subepidermal, intradermal, and subcutaneous temperatures (tissue depths: 1–20 mm; colored lines) and thermographically monitored skin surface temperature (open red symbols) in the region of interest (ROI) of the abdominal wall during wIRA treatment. Start (red arrow) and end (black arrow) of wIRA irradiation are indicated. Subepidermal temperatures (1 mm, dark blue line) and temperatures in the upper subcutis (5 mm, light blue line) reach higher values than the skin surface. On–off cycles due to regulation of the wIRA radiators result in multiple spikes in temperature curves. Spikes are most pronounced in superficial tissue layers, but remain visible down to a tissue depth of 15 mm

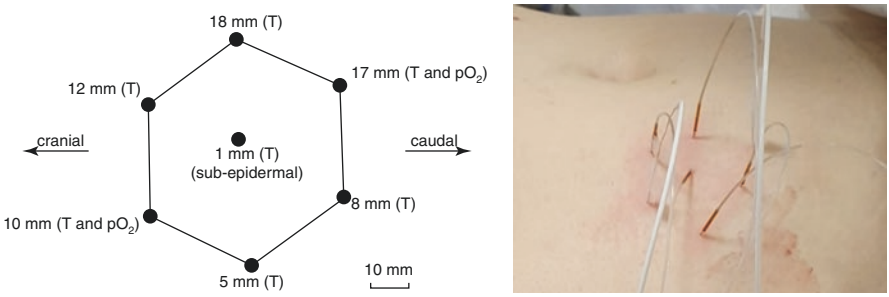

Fig. 5.4 Positioning of invasive catheters and probes in the abdominal wall. Schematic map (left) and actual in situ setup (right) in a representative experiment

Registration of preheating and postheating temperature and oxygen levels completed the data collection upon wIRA exposure.

5.3 Results and Discussion

5.3.1 Temperature Profiles

As shown in Fig. 5.5, upon wIRA irradiation, mean temperature of the skin surface increased from a baseline of 33.4 ± 1.9 °C (mean ± SD) to 41.7 ± 0.4 °C, with the most superficial invasive probe at 1 mm recording a baseline temperature of 33.1 ± 1.7 °C, increasing to 41.8 ± 0.7 °C (10 experiments). In a tissue depth of 20 ± 1 mm, i.e., in deep subcutis, the mean temperature increased from a baseline of 34.9 ± 1.1 °C to 40.1 ± 0.6 °C (11 experiments). According to these data, wIRA irradiation results in mild hyperthermia with tissue temperatures ≥39 °C, extending to tissue depths up to 25 mm, thus confirming earlier, sporadic measurements in superficial cancers [9, 10].

Upon the start of heating, increases in tissue temperatures were steepest close to the body surface, where T > 40 °C was achieved within 4 ± 2 min, whereas up to 30 min of wIRA heating were required to reach this temperature at a depth of 20 ± 1 mm. Results in intermediate tissue layers are exemplified in Fig. 5.3.

The highly significant linear correlation between subepidermal and skin surface temperatures for a representative treatment session is shown in Fig. 5.6. There is clear evidence that the maximum tissue (i.e., subepidermal) temperatures can reach 43.5 °C, with the maximum skin surface temperature being 42.5 °C. Considering data collected in all treatment sessions, a reversing of the temperature gradient is observed, as shown in Fig. 5.7. In normothermic conditions and at hyperthermia levels ≤42 °C, no substantial gradients between mean subepidermal and skin surface temperature are found (−0.4 to 0 °C, n.s.), which means that both measuring locations yield similar temperatures. With subepidermal temperatures ≥42 °C, a temperature gradient is evident, and with subepidermal temperatures ≥43 °C, a mean temperature difference of +0.8 °C toward skin surface is observed, indicating

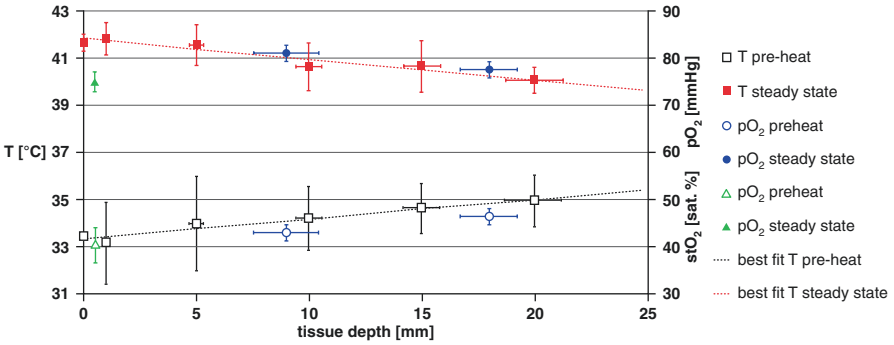

Fig. 5.5 Tissue temperatures T (squares) and pO_2 values (circles) in the skin and subcutis as functions of tissue depth before (lower part) and during steady-state wIRA irradiation (upper part). Baseline and steady-state stO_2 values (triangles) in the upper dermis upon wIRA exposure (values are means ±SD)

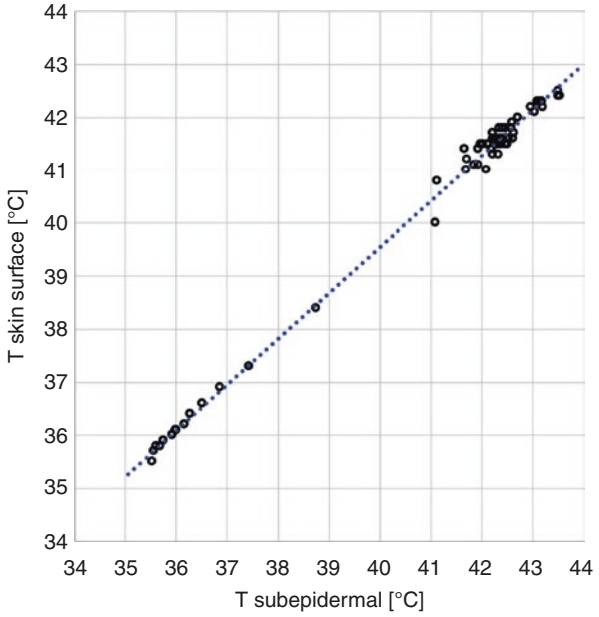

Fig. 5.6 Correlation between skin surface temperatures (monitored by thermography) and subepidermal temperatures (measured by invasive probes, thermometry) before, during heating up, and in the steady-state phase of wIRA-hyperthermia. While a fraction of subepidermal values reaches 43.5 °C during HT, all skin surface temperatures stay below 43 °C. Dotted line: best fit

that wIRA-HT yields the highest temperatures in the upper dermis and not at the skin surface (Figs. 5.5 and 5.6). This transepidermal gradient probably relates to increasing heat loss from the skin surface by thermal radiation and convection. Since hemoglobin is a major photochrome for wIRA, HT-induced hyperemia (associated with a higher hemoglobin content) in the subepidermal microvasculature might also contribute to this effect.

When wIRA exposure is terminated, mean temperatures of the uncovered skin surface dropped below 39 °C (i.e., below the lower level of mild HT, obligatory in

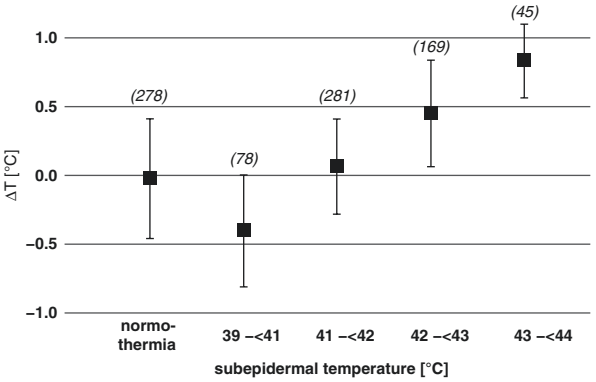

Fig. 5.7 Transepidermal temperature gradients (calculated by subtraction of skin surface temperature from subepidermal temperature) as a function of subepidermal temperatures. Mean values ± SD. Values in brackets: number of measurements

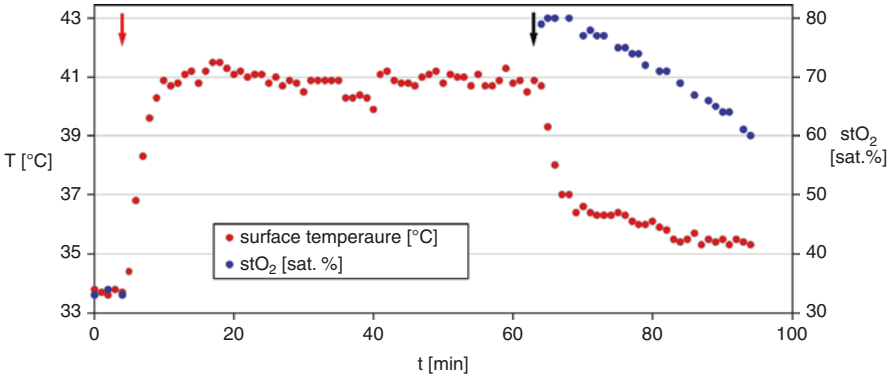

Fig. 5.8 wIRA-hyperthermia causes an increase in the mean subepidermal HbO_2 saturation (stO_2) values starting from a pretreatment level of 33 sat. % up to 80 sat. % at the end of treatment (blue dots), with a steady decline after termination of wIRA exposure. Start (red arrow) and end (black arrow) of wIRA irradiation are indicated. While the surface temperatures (red dots) returned close to baseline within approx. 30 min, stO_2 values remained at significantly elevated levels for more than 40 min. (As wIRA irradiation interferes with hyperspectral imaging, HbO_2 saturations cannot be assessed *during* wIRA exposure)

the oncologic setting) within less than 2 min (Figs. 5.3 and 5.8). In tissue depths of 1–5 mm, mean temperatures dropped to the same extent (see representative examples in Fig. 5.3), whereas at depths of 10 and 20 mm, mean tissue temperature reached 39 °C within 2.5 and 4 min, respectively. These observations demonstrate that effective hyperthermia levels are only maintained for a short period in uncovered skin. This is of relevance for clinical application of superficial HT as a radiosensitizer, for which it is presumed that a simultaneous or quasi-simultaneous application of HT and subsequent radiotherapy provides the most effective synergy [1]. In contrast to the experimental setting applied here, clinical routine aims to maintain tissue temperatures after the wIRA irradiators are switched off. When wIRA-HT is used as a radiosensitizer in the clinical setting, the patient is covered either with a prewarmed dressing gown or with a prewarmed silicone flab when

being transferred from the HT unit to the linear accelerator [1]. Therefore, the actual decline in temperature in clinical practice is expected to be significantly slower than observed in the study described herein, where the skin was left uncovered. However, additional investigations are needed to quantify the temperature decline in "heat-insulated" tissues between end of wIRA-HT and subsequent start of RT. In any case, this time interval should be kept very short (≤5 min).

5.3.2 Tissue Oxygenation

5.3.2.1 Oxyhemoglobin Saturations Assessed by Hyperspectral Imaging

Noninvasive monitoring of HbO_2 saturation (stO_2) in the subepidermal microvasculature also confirmed a distinct increase in tissue oxygenation upon wIRA exposure. This effect is visible both in the abdominal wall of healthy volunteers (Fig. 5.9a) and in the skin affected by locally invasive recurrent breast cancer (Fig. 5.9b). The mean HbO_2 saturation (stO_2) in human skin before wIRA exposure was 41%. Upon heating the skin up to 41.7 °C, the saturation almost doubled (Fig. 5.5, green triangles; Fig. 5.10, boxes and whiskers on the left). When wIRA irradiation was terminated, stO_2 values decreased only slightly and thus remained distinctly elevated, even after skin temperatures dropped to baseline, as shown in Figs. 5.8 and 5.10. From these data, it is concluded that improved tissue oxygenation considerably outlasts tissue

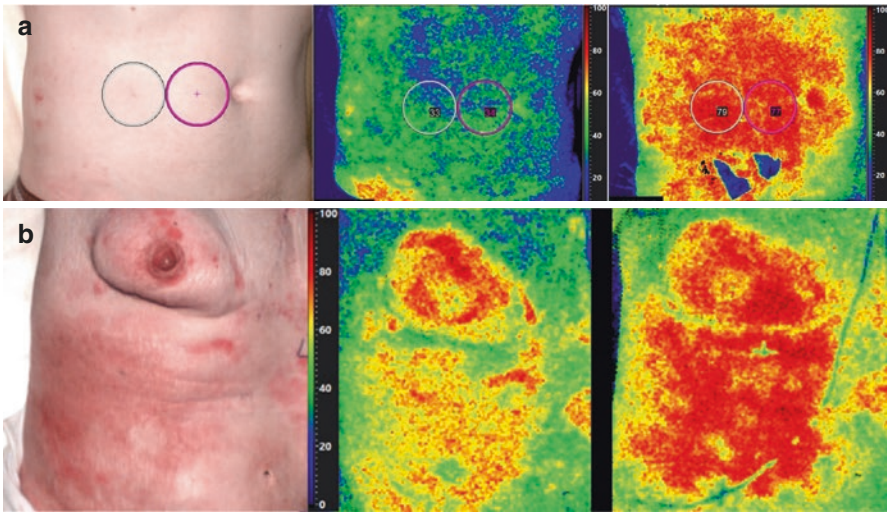

Fig. 5.9 Imaging of HbO_2 saturations in the upper dermis of the abdominal wall of a healthy volunteer (**a**), and in the outer tissue layer (≈1 mm) of a large-size, inflammatory recurrent breast cancer (**b**). Topographic aspect of the treatment area (left panels), stO_2 imaging before (central panels), and at the end of wIRA-hyperthermia (right panels). The malignant inflammatory condition evidently causes higher stO_2 baseline values

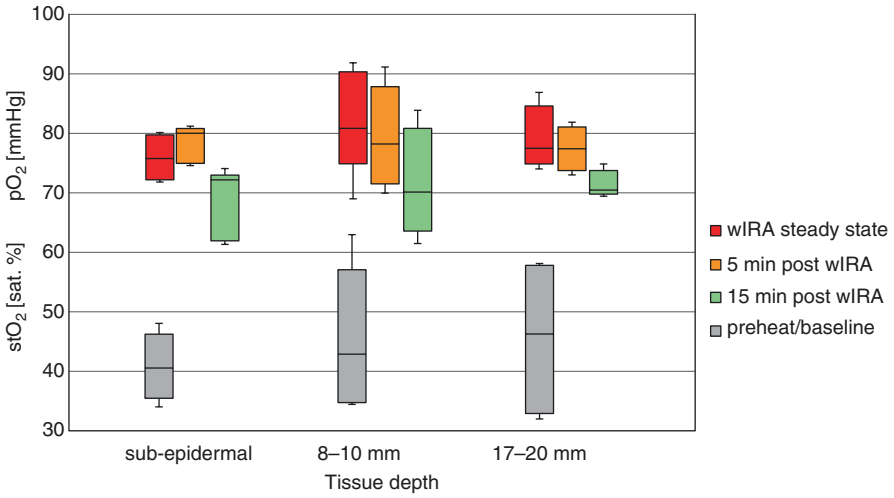

Fig. 5.10 pO_2 and stO_2 values before, during, and following wIRA-hyperthermia. Postheating pO_2 and stO_2 remained at significantly elevated levels within the time frame of subsequent radiotherapy. Subepidermal stO_2 was assessed using hyperspectral skin imaging (n = 3), pO_2 in the subcutis with invasive probes (n = 6 for 8–10 mm, n = 4 for 17–20 mm tissue depths). Boxes show medians with first and third quartiles and whiskers show range

temperature rises upon wIRA-hyperthermia; i.e., oxygenation-dependent radiosensitization is expected to be fully active/maintained during RT in our clinical setting.

Hyperspectral skin imaging was found to be a versatile and noninvasive method to assess HbO_2 saturations in upper skin layers. Since this method only covers the subpapillary microcirculatory vessels in the upper dermis [11], invasive pO_2 measurements are required for oxygenation measurements in the lower dermis down to the subcutis.

5.3.2.2 Assessment of Tissue pO_2 Values

In all tissue depths addressed (subepidermal, 8–10 mm, and 17–20 mm), wIRA-HT caused a marked, highly significant increase in the oxygenation. Mean tissue oxygen tensions in the subcutis rose from 43 to 81 mmHg at tissue depths of 8–10 mm, and from 46 to 77 mmHg at tissue depths of 17–20 mm (Figs. 5.5 and 5.10). Oxygenation reached a maximum within 25–30 min of wIRA-HT and remained at this significantly higher level in the further course of treatment. Upon cessation of wIRA irradiation, oxygenation only slowly decreased and remained at significantly elevated levels within the typical time frame of subsequent radiotherapy protocols (Figs. 5.10 and 5.11).

A similar pattern was observed by Hartel et al. [12] when using wIRA-hyperthermia to improve healing of surgical wounds. These authors have assessed postoperative pO_2 values in a tissue depth of 20 mm. On day 2, the baseline pO_2 before wIRA irradiation was 32 mmHg vs. 42 mmHg after treatment. On day 10, the respective data were 34 mmHg vs. 46 mmHg, both improvements greatly outlasting the actual time of the wIRA exposure.

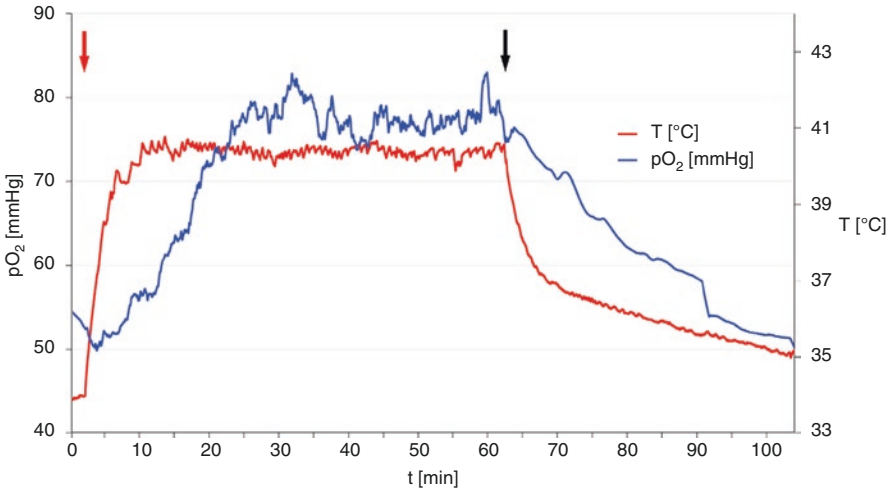

Fig. 5.11 Characteristic tissue temperatures T and pO_2 traces in the subcutis of the abdominal wall during wIRA treatment and post-treatment (tissue depth: 8 mm). Start (red arrow) and end (black arrow) of wIRA irradiation are indicated. Note: tissue pO_2 rises and declines much slower than tissue temperature

As mentioned above, tissue oxygenation status before, during, and after wIRA-hyperthermia was assessed by two different approaches in our experiments:

1. By an indirect, noninvasive approach, using hyperspectral analysis of oxygen saturation (stO_2) of hemoglobin present in subepidermal microvasculatures (Figs. 5.8 and 5.10). Although measurement in deeper tissue layers is technically not possible, this method offers the advantage of noninvasive imaging of larger skin areas (Fig. 5.9).
2. By direct, minimally invasive microsensor measurements of tissue oxygen pressures ($p0_2$, Figs. 5.10 and 5.11). In principle, this method may be applied at any tissue depth (Fig. 5.4).

Compared to preheating values, wIRA-HT causes a significant improvement of the tissue O_2 status. Both hyperspectral imaging of stO_2 and direct measurement of tissue pO_2 show that this effect outlasts the period needed for subsequent RT (Figs. 5.10 and 5.11).

In Table 5.1, both baseline and steady-state pO_2 values upon superficial wIRA-HT are listed together with known literature data.

5.4 Summary and Outlook

wIRA-HT is a reliable treatment modality for efficiently heating skin and subcutaneous tissue up to a depth of approx. 25 mm. In the set temperature range (mild hyperthermia, 39–43 °C), tissue oxygenation is substantially improved in all tissue

Table 5.1 Mean oxygen partial pressures (pO_2) in different layers of human skin and subcutis under thermoneutral conditions (NT) and steady-state superficial wIRA-hyperthermia (HT). Noteworthy to mention: "Transcutaneous" pO_2 values are assessed from the heated (≈44 °C) skin surface and have been used for monitoring of "arterialized" blood oxygen tensions

Tissue layer	Mean pO_2 (mmHg)	References
Epidermis	8	Wang et al. [13], Carreau et al. [14]
Subepidermal layer	35 ≈34 (NT @ 33 °C)[a] ≈50 (HT @ 40 °C)[a]	Wang et al. [13] This study
Dermis	50 (45–54)[b] 37 (30–45)[b] 42	Evans and Naylor [15] Baumgärtl et al. [16] Keeley and Mann [17]
Subcutis	56 50–55 43 (NT@ 34 °C)[b] 81 (HT@40.5 °C)	Keeley and Mann [17] Vaupel et al. [18] This study

[a] Estimated from HbO_2 saturation measurements considering the respective shifts of the HbO_2-binding curves at lower or higher temperatures (standard HbO_2 curve refers to 37 °C).
[b] Steady increase with increasing tissue depth.

depths examined (≈0.5–20 mm). Improvement of oxygenation considerably outlasts the wIRA heating period. In the case of superficial tumors reaching into deeper tissue layers, combination of wIRA-HT with microwave HT may broaden the application range [19].

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