The present invention relates to an improved non-invasive hyperthermia device and method. The improved device and method reduces the overheating of tissue areas of low dielectric constant by regulation of the subcutaneous blood-flow, when used to heat heterogeneous sites containing tissue areas of high dielectric constant and tissue areas of low dielectric constant.
Prevention of overheating of low dielectric constant tissue

Specification

The present invention relates to an improved non-invasive hyperthermia device and method. The improved device and method reduces the overheating of tissue areas of low dielectric constant by regulation of the subcutaneous blood flow, when used to heat heterogeneous sites containing tissue areas of high dielectric constant and tissue areas of low dielectric constant.

Background of the invention

Hyperthermia devices can be used to force energy absorption in tissue to cause damage to unwanted structures and/or increase the temperature of the targeted area above the normal body temperature. This increased heat can be used to effectively treat cancer, rheumatic conditions, rhinitis, articular diseases or for cosmetic purposes.

In the case of tumour treatment, tumour cells are more sensitive to heat than the surrounding normal tissue cells. Therefore the aim is to pump energy to the tumour tissue, which irreversibly damages the tumour cells but which can be tolerated by normal tissue.

Three different electromagnetic heating techniques are commonly used in hyperthermia devices, namely, magnetic field coupled energy transfer, electrical field coupled energy transfer and radiative energy transfer. For heating biological tissue the electrical field effect is the most efficient and simplest of these three different electromagnetic heating techniques.

However, all the non-invasive deep heating methods have a well known disadvantage: the energy travelling to the targeted area has to pass through the surface and other intermediate tissues, losing energy and dangerously heating these areas. The contra selection of the surface tissues is supported by the usually lower specific heat (quicker rise of the temperature by a given energy) and the lower blood perfusion (lower circulatory cooling). These disadvantages are even more exposed in the case of the electrical field heating technique. The surface tissues are usually relatively good electric isolators and have a low dielectric constant. Due to these facts, the drop of the applied voltage can be extremely high in these tissues, which together with the higher energy absorption
could cause the voltage dependent discharge-like polymerization on the surface area. Also in the case of tissue having a heterogeneous dielectric character, the tissue part which has a low complex dielectric constant will be heated up more quickly than the tissue part having a high complex dielectric constant. For example, bone tissue and adipose tissue have a low dielectric constant in comparison to muscle tissue. This can lead to the undesired side effect of discomfort, and in extreme cases can also cause burns of the low dielectric constant tissue. The problem of the massive surface energy absorption, which could absorb the useful energy and therefore increase the risk of burn, is a real challenge. The possibility of burning of surface/adipose tissue by capacitive coupling is well-known, due to the selective electric field-energy absorption by the dielectric properties of the adipose tissue. Calculations show that the ratio of the adipose tissue ($P_a$) and muscle tissue ($P_m$) absorbed power is selectively different, and the ratio ($P_a/P_m$) is large, as a consequence of the relatively small conductivity ratio ($\sigma_a/\sigma_m$) and dominantly large permittivity ratio ($|\varepsilon_m^*\rho|/|\varepsilon_a^*\rho|$) a relatively large absorption occurs in the adipose tissue.

This is of particular importance when using an external (non-invasive) electrical field coupled energy transfer hyperthermia device to heat internal (deep-seated) tissue. In this case the device electrode is placed on the skin of the patient, above the internal tissue site to be heated. The electrical energy must travel through the skin and subcutaneous tissue layer before reaching the desired target internal tissue site. Due to the lower amount of water present, both skin and adipose tissue have a lower dielectric constant than the internal tissue. Therefore, the skin and the subcutaneous layer containing adipose tissue will absorb heat more quickly than the targeted internal site causing patient discomfort and in the worst case also causing burns to the skin and subcutaneous tissue layer.

Herein, we report the development of a method of reducing the possibility of this disadvantageous side effect of hyperthermia and of a device useful within the said method.

Lowering the temperature of skin and subcutaneous tissue decreases the dielectric constant of the cooled tissue thus increasing the difference in dielectric properties (permittivity (real part) and conductivity (imaginary part) of the complex dielectric constant) between the skin and subcutaneous tissue and the internal target tissue. Furthermore, lowering the temperature of the skin and subcutaneous area also leads to poor blood circulation at the cooled site and
therefore decreased ability to dissipate accumulated heat. The low surface
temperature also alters the patient's perception of temperature. The temperature
sensors are located in the subcutaneous area and their cooling down reduces the
perception of high temperature, which could lead to adipose burn due to the
patient not accurately sensing the increased temperature.

The present invention discloses that increasing the blood circulation in or around
(in the case of bone near to the surface) the low dielectric constant tissue is
effective to prevent the overheating of this tissue. The increase of blood circulation
changes four parameters for better treatment conditions, namely: increases the
real part of the complex dielectric constant and at the same time increases the
conductivity (imaginary part) of the complex dielectric constant of the skin area
due to the increased blood-flow; and as well the circulatory cooling and the higher
specific heat of the blood changes the area to be more accurately matched to the
deep-tissue energy target.

The prior art discloses lowering the temperature of surface tissue to prevent
overheating as described, for example, in US 4,633,875 and US 4,884,580.

US 4,633,875 discloses an electromagnetic radiation hyperthermia device for use
in the ultrahigh frequency radio wave range. The device is provided with
temperature sensors to monitor the surface tissue temperature and the
temperature of the targeted internal tissue. Methods proposed for cooling the
surface tissue are flowing room temperature or cooler air directly onto the surface
tissue or providing cooled liquid in the hyperthermia device applicator that directly
contacts the surface tissue.

US 4,884,580 discloses an electromagnetic radiation hyperthermia device for use
in the microwave range. The device is also provided with temperature sensors to
monitor the surface tissue temperature and the temperature of the targeted
internal tissue and a feedback mechanism to control the device based on the
sensed temperatures. The method proposed for cooling the surface tissue is
providing cooled liquid in the hyperthermia device applicator that directly contacts
the surface tissue.

However, the prior art does not disclose the use of increased blood circulation as
described in the present application to prevent the overheating of tissue having a
low dielectric constant and does not disclose any hyperthermia device or
thermotherapy device capable of increasing the blood flow in the effected tissue during hyperthermia or thermotherapy treatment, respectively.

It is the object of the present invention to provide a hyperthermia device that reduces the undesirable side effect of overheating or discharging of tissue of low dielectric constant.

The object of the present invention is solved by the teaching of the independent claims. Further advantageous features, aspects and details of the invention are evident from the dependent claims, the description, and the examples of the present application.

**Description of the invention**

The complex dielectric constant of a material can be correlated with the electric potential (voltage) drop through the material. Materials having a low dielectric constant have a higher voltage drop, whereas materials having a high dielectric constant have a lower voltage drop. The voltage drop acts as one of the factors determining how much energy can be released into the tissue. A tissue having a higher potential energy drop will absorb more energy from the energy passing through that tissue than a tissue having a lower potential energy drop. Therefore materials having a low dielectric constant will heat more quickly under the electric field, than materials having a high dielectric constant. When using electromagnetic hyperthermia devices to heat biological tissue the differing dielectric constants of different tissues must be taken into consideration.

The problem of low complex dielectric constant is not really significant when the area of low dielectric constant is localized and is entirely surrounded by high complex dielectric constant material. In this case the low complex dielectric portion generating a high potential difference does not participate in the absorption process as the adjoining high complex dielectric constant material acts as bridge and shunts the absorbed energy around the area of low complex dielectric constant.

However, the situation is different in the case of stratified areas of low complex dielectric constant, for example, skin or subcutaneous adipose tissue layers or the skull, where there is no possibility for the absorbed energy to be the shunted around the area of low complex dielectric constant when using only external electrodes. Because of the low complex dielectric constant and higher potential
drop a large amount of energy is transferred to the skin and subcutaneous adipose tissue layers leading to overheating of the low complex dielectric constant tissue and causing discomfort and possibly burns, as well as suppressing the amount of energy delivery possible to the deep seated tissues.

In the language of resistive loads we may introduce the real resistance (ohmic, inverse of the conductance), and the capacitive resistance (frequency dependent, virtual). The ohmic resistance is roughly

\[ R_\Omega = \frac{1}{\sigma} \frac{d}{A} \]

where \( \sigma \) is the specific conductivity, \( d \) is the thickness of the tissue and \( A \) is the area where the current flows through. The capacitive resistance is:

\[ R_C = \frac{1}{\omega \epsilon} \frac{d}{A} \]

where the \( \omega = 2\pi f \) (the \( f \) is the actual frequency) and \( \epsilon \) is the dielectric constant. From the conduction point of view when the low complex dielectric constant tissue is limited to an area and can be "bypassed", then the picture corresponds to the parallel connections of the resistive loads. Then the absorbed power has to be calculated by the equipotential layers and the absorbed power of these would be

\[ P_i = \frac{U^2}{R_p} \]

where \( U \) is the actual potential difference between the given layers, \( R_p \) is the actual sum of the parallel resistors, irrespective their origin:

\[ R_p = \left( \sum_i \frac{1}{R_i} \right)^{-1} \]

where \( i \) runs through all the resistive components. This means, that in the case of the "bypassed" structures the energy will be absorbed in the region where \( \sigma \) and \( \epsilon \) are both high.

In the case of layered dielectric materials, when no "bypass" is possible (skin, skull, etc.) the absorbed power must be calculated from the equal current conditions. Hence, the absorbed power is:

\[ P_p = I^2 R_s \]

where \( I \) is the actual current flows through the given layers, \( R_s \) is the actual sum of the serial resistors, irrespective their origin:

\[ R_s = \sum_j R_j \]
where \( j \) runs through all the resistive components. This means, that in the case of the layered structures we need both the \( \sigma \) (permittivity) and \( \varepsilon \) (conductivity) high, to go through these isolators.

The dielectric constant of a material slightly changes with temperature. Increasing the temperature of a material increases the dielectric constant of the material whereas decreasing the temperature of a material decreases the dielectric constant of the material. However, to avoid the unwanted side effect of overheating of the body surface, the surface tissue is cooled using cool air or fluids, which consumes a part of the useful energy, but protects the skin and the adipose tissue from the damage. If the desired energy delivery is higher and/or the adipose layer is thicker, the preventive cooling has to be increasingly more intensive. Therefore, the conventional hyperthermia methods, which apply intensive cooling for these safety reasons, waste an increasing amount of the delivered energy on this process.

However, cooling of the tissue also leads to constriction of capillaries and as a consequence also to a decrease in the blood circulation in the cooled tissue. Circulating blood is an effective way to dissipate heat from a defined area, and the decrease in circulation caused by local cooling of low dielectric tissue inhibits this loss of absorbed heat via blood circulation. Therefore, the cooled tissue has the opposite physiological effect to that expected: the natural heat-exchanger and the natural electric conductivity (imaginary part of the complex dielectric constant) are blocked, requiring more cooling and causing positive feedback in the wrong direction.

Blood has a high permittivity (real part of the complex dielectric constant) and thus enhanced blood circulation in a low dielectric constant tissue area effectively increases the overall dielectric constant of this low dielectric constant tissue area. This decreases the overall voltage drop in this tissue and therefore less energy (heat) is absorbed by the low dielectric constant tissue having enhanced blood circulation than by a low dielectric tissue area having decreased blood circulation, as is the case in cooled tissue.

Figures 1 and 2 demonstrate tissue temperature profiles of tissue having a skin surface with low blood-perfusion and Figures 3 and 4 demonstrate tissue temperature profiles of tissue having a skin surface with high blood-perfusion after identical hyperthermia treatments. Comparing Figure 1 and Figure 3 it can be
seen that the tissue of the high blood-perfusion skin sample is maintained at a consistently higher temperature throughout the sample whereas for the low blood-perfusion skin sample the heat is transferred mainly to the upper and lower surface tissue. Comparing Figures 2 and 4 again it can be seen that in the low blood-perfusion skin surface tissue sample the upper and lower surface tissue absorbs significantly more heat than the tumour tissue, whereas in the high blood-perfusion skin surface tissue sample the tumour absorbs more heat than both the upper and the lower surface tissue. The upper and lower surface tissue can also be cooled sufficiently to eliminate the temperature gain on the upper and lower surface. The surface cooling can be regulated so that it does not significantly reduce the blood-perfusion, but is still sufficient to prevent surface burns. In this way the cooling provides increased safety and the increased blood perfusion provides increased efficacy.

In the present invention the aim is opposite to that of whole-body hyperthermia treatment. In whole-body hyperthermia treatment, the near-surface capillary bed is heated up to provide this heat into the body interior and to heat up the whole body equally. In whole-body hyperthermia the blood acts as the heat-carrier and the heat-source for heating the tumour.

In contrast, in the present invention the electromagnetic effects (mainly the impedance heating) generate heat in the target tissue and the whole body preferably remains at its usual body temperature. In this case the blood-flow in the tumour is kept as low as possible to prevent the loss of the electromagnetic energy generated heat from the tumour. The purpose of the enhanced blood circulation in the surface tissue (i.e. low complex dielectric tissue) is not the heating of the surface tissues or heating of the whole body, but instead the cooling down of surface tissues to avoid surface burn due to the massive energy flow into the body across the surface tissue and to the deep-seated tumour region.

The prior art methods of surface cooling by applying a cooled applicator to the skin surface are very useful to reduce the heat-sensing of a patient (i.e. that is the perceived burn-pain) and so provide conditions where more energy can be delivered through the actual surface area without causing patient discomfort. However this cooling has important disadvantages: 1.) a large amount of the energy delivered to the tissue is lost in the cooled tissue and thereby not delivered to the target tumour tissue, 2.) the cooled down surface which has reduced blood perfusion acts more and more as an isolator (due to increasing permittivity of
adipose tissue), and the voltage drop becomes higher than optimal in this layer. This high voltage drop causes an electric burn of the surface tissue, which therefore has to be further cooled, and so a positive feedback can lead to the use of an applicator cooled to below 0 °C to maintain a surface tissue temperature of approximately 20 °C.

In the present invention the blood flow in the surface tissue (i.e. low complex dielectric tissue) is maintained at the patient's normal physiologically controlled level or at a higher level than the normal physiological controlled level for that patient. The normal physiologically controlled blood flow (blood perfusion) of a patient can be measured and changes in blood flow can be monitored during treatment using a variety of methods as outlined below. Thermal burn is avoided by keeping the surface tissue temperature under the patient tolerance limit (approximately < 42 °C) during the delivery of electromagnetic energy to the target (tumour) tissue. This is achieved by increasing the blood perfusion by thermal, and/or mechanical, and/or chemical, and/or electric etc. methods, and thus keeping the surface temperature under approximately 42 °C. This method successfully prevents the physiological loss of the blood-perfusion in the low complex dielectric surface tissue and therefore reduces the voltage drop across the surface tissue and prevents electric burn due to increased voltage drop across the surface tissue.

The present invention wherein the hyperthermia device significantly enhances blood circulation in the skin tissue and subcutaneous adipose tissue increases the dielectric constant and the conductivity (imaginary part of the complex dielectric constant) of the tissue without the disadvantage of preventing dissipation of accumulated heat due to poor circulation.

Furthermore the present invention reduces the need for excessive cooling of the surface tissue to prevent overheating. Therefore a double saving of energy can be realized: a large cooling energy is not required, and a large additional heating energy is not needed to achieve the desired energy delivery to the target tissue depth. Using the hyperthermia device of the present invention which incorporates a blood circulation enhancement means, the surface tissue need not be cooled and held at a temperature near approximately 20 °C.

The scientific literature provides measured values for the complex dielectric constants (real part is the permittivity and the imaginary part is the conductivity) of
various biological tissues, but these values vary for the same tissue due to differences in temperature at measurement, differences in measurement methods and of course the variable nature of biological tissue. However, it is still clear that skin, subcutaneous tissue and adipose tissue have a dielectric constant significantly lower than the dielectric constant of the desired target tissues, for example, muscle tissue or tumour tissue. For the purposes of this application we will define tissue having a low complex dielectric constant (complex dielectric constant A), for example skin, subcutaneous tissue and adipose tissue, and target tissue having a high complex dielectric constant (complex dielectric constant B), for example tumour tissue and muscle tissue, as follows. Basically the complex dielectric constant A of the tissue having a low complex dielectric constant is less than the complex dielectric constant B of the tissue having a high complex dielectric constant (A<B). The complex dielectric constant ratio of high complex dielectric constant tissue to low complex dielectric constant tissue is at least 2:1. That is the high complex dielectric constant tissue has a complex dielectric constant that is at least double the complex dielectric constant of the low complex dielectric constant tissue. Thus, the ratio of the dielectric constant B and dielectric constant A has a typical range of values between 1.5:1.0 to 10.0:1.0 (1.5<B/A<10), preferably between 2.0:1.0 to 5.0:1.0 (2.0≤B/A≤5.0), and most preferably between 2.5:1.0 to 3.5:1.0 (2.5<B/A≤3.5). However the imaginary part (conductivity) could change 2 - 50 fold, typically 3 - 20 fold. The absorption ratio with these data could be normal but can be as high as 130 as well. Realistic calculations show a power-ratio of about 5.

Thus, the present invention is directed to a hyperthermia device comprising an electromagnetic radiation means for directing electromagnetic energy to a target tissue, wherein the target tissue is a high complex dielectric tissue, and a blood circulation enhancement means for increasing blood circulation, wherein the blood circulation enhancement means maintains the blood flow or increases the blood flow by a factor of 1 - 10 in low complex dielectric constant tissue. The blood circulation enhancement means of the hyperthermia device of the present invention reduces the amount of electromagnetic energy absorbed by the low complex dielectric tissue due to the enhanced blood flow in the low complex dielectric tissue.

The skin blood supply regulates the heat-exchange of the body. The regulation can be regarded as a mechanical controlling system.
The skin in a cold environment represents a good heat insulator (and together with this a low complex dielectric constant), while in a high temperature environment the blood perfusion makes this layer a good heat-conductor (heat-exchanger) as well as transforming it to a high complex dielectric constant material. The blood perfusion may be changed by different methods, not only by increased temperature.

The blood perfusion in the cold for human skin is approx. 0.02 [ml/min/g] while in hyperthermic conditions (around 38°C environment) it is more than 0.2 [ml/min/g], a ten fold increase. The vasodilatation (allowing the increased blood perfusion) increases the heat conductance by a large value.

The important point is the heat conduction is dependent on the vasodilatation, and that the heat conductivity and the electric conductivity are proportional. Thus the enhancement of blood circulation is defined as the volume of the blood per time unit and per mass of the tissue, circulating in the given tissue part.

There are different methods to measure the blood flow, including measurement of the Doppler-effect, thermal camera observation and bioimpedance measurement (complex impedance measurement). Bioimpedance measurement can be performed simply by using two pairs of electrodes. A current is applied by one electrode pair and detected by a second electrode pair. The change in the voltage detected by the second electrode pair allows the measurement of the impedance of the tested tissue. A decrease in the impedance denotes an increase in blood flow (blood perfusion). Real time measurement of blood flow by the Doppler method is performed by ultrasound or by laser techniques. Thus the normal physiologically determined blood flow (blood perfusion) in the low complex dielectric surface tissue of a patient can be determined and the level of blood flow monitored by well known prior art methods during hyperthermia treatment with the device of the present invention.

The blood thermal conductivity as whole blood is 0.492 [W/mK] while for plasma is 0.570 [W/mK]. The complex dielectric properties of the fatty tissue, muscle and bone at 70 MHz are collected in the table below (from Gabriel S, Lau RW, Gabriel C: The dielectric properties of biological tissue: II. Measurements in the frequency range 10 Hz to 20 GHz, Phys. Med. Biol. 41:2251-2269, 1996). The permittivity of
blood is 140 (at least ten times higher than the fatty tissue) and its conductivity is 1.1 [S/m], (at least also ten times higher than the fatty tissue).

**Low, average and high values of dielectric parameters at 70 MHz based on literature (Gabriel et al. 1996)**

<table>
<thead>
<tr>
<th>Tissue type</th>
<th>Conductivity $\sigma$ (Sm$^{-1}$)</th>
<th>Relative permittivity $\varepsilon_r$</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>low     avg     high</td>
<td>low     avg     high</td>
<td></td>
</tr>
<tr>
<td>Fatty</td>
<td>0.025   0.06    0.095</td>
<td>7       10       13</td>
<td></td>
</tr>
<tr>
<td>Muscle-like</td>
<td>0.6     0.75     0.9</td>
<td>60      75       90</td>
<td></td>
</tr>
<tr>
<td>Bone</td>
<td>0.025   0.05    0.075</td>
<td>7       10       13</td>
<td></td>
</tr>
</tbody>
</table>

Specifically the hyperthermia device of the present invention increases blood circulation to low complex dielectric constant tissue, for example, skin tissue, adipose tissue and subcutaneous tissue or the surrounding area of the bone, near to the surface of the body. The ratio of the blood volume increase will determine the complex dielectric constant of the tissue. This means that on average the original average permittivity will change from 10 to about 35 and the conductivity from 0.06 S/m to 0.25 S/m. Figure 5 shows the increase of permittivity and conductivity as blood perfusion ratio increases. The conductivity, permittivity and blood perfusion ratio in Figure 5 were calculated using the following equations:

The blood-volume ratio:

$$v_b(x) = \frac{v_{b0} + x}{v_{b0} + 150} \quad [1 < x < 100]$$

The conductivity and permittivity would be:

$$cond(x) = \sigma_i \left[ v_b(x) - \frac{\sigma_s (1 - v_b(x))}{\sigma_b} \right]$$

$$perm(x) = \varepsilon_i \left[ v_b(x) - \frac{\varepsilon_s (1 - v_b(x))}{\varepsilon_b} \right]$$

where:

$v_{b0}$ (starting volume of blood) = 10

$v_b(x)$ = volume of blood when constant x is a value between 1 and 100

Conductivity and permittivity at 13.56 MHz

$\sigma_b$ = conductivity of blood in Siemens per metre [S/m]

$\sigma_s$ = conductivity of skin in Siemens per metre [S/m]

$\varepsilon_b$ = permittivity of blood in Siemens per metre [S/m]

$\varepsilon_s$ = permittivity of skin in Siemens per metre [S/m]
Further the hyperthermia device of the present invention directs electromagnetic radiation to target high complex dielectric tissue, for example, all kinds of tumour tissues and healthy muscle tissue, or healthy organs having high complex dielectric properties, such as for example, liver, lung, heart, kidney, spleen, brain, ovary, uterus, prostate, pancreas, larynx, most of the gastrointestinal tract, most of the gynaecological tract (except the fat-enriched breast, where the only the tumour is attacked).

The electromagnetic radiation means of the present invention can be any electric field coupled energy transfer means (capacitive coupling device), magnetic field coupled energy transfer means (inductive coupling), or radiative energy transfer means (radiative coupling or antenna array).

Preferably the electromagnetic radiation means of the present invention is an electric field coupled energy transfer means (capacitive coupling device).

As shown in Figure 6 the electromagnetic radiation means of the present invention comprises at least an electromagnetic radiation generator (1), a tuning/matching unit (2), a treatment bed (3), an electromagnetic radiation applicator (5) and a blood circulation enhancement stimulation means (6). Preferably the blood circulation enhancement means is integrated with the electromagnetic radiation applicator (5).

The blood circulation enhancement means can be a mechanical stimulation means, for example, mechanical stimulation provided through the electromagnetic radiation applicator of the electromagnetic radiation means of the hyperthermia device.

The mechanical stimulation means can be a vibration means, for example, mechanical vibration (the alternating pressure induces blood-perfusion) provided through the electromagnetic electrode applicator of the electromagnetic radiation means of the hyperthermia device. For example the electrode can have a mechanical vibration of 1-20 Hz, and 0.5 to 5 mm depth (depending on the electrode bolus applied). The vibration could be caused by the vibration of the electrode, or could be caused by pressure changes inside of the water-bolus.

Other mechanical stimulation methods are the well known massages, acupressure, and skin-brushing. The widely applied "Jet therapy" is a water (air)
jet-massage, increases vasodilatation by up to 22%. Also the negative pressure (suction) therapy increases the blood-flow by 7-30 times.

Acupuncture can also stimulate the microcirculation, which could be measured by thermal cameras. Also spinal cord stimulation and vasodilatation by neural control (due to inhibition of vasoconstrictor nerve traffic) influences the blood-perfusion on the surface skin area.

The blood circulation enhancement means can be an electrical stimulation means, for example, electrical stimulation provided through the electromagnetic radiation applicator of the electromagnetic radiation means of the hyperthermia device.

The blood flow could be controlled by electro-physiological means, like for example by iontophoresis. Using iontophoresis a blood circulation enhancing agent can be delivered transdermal by repulsive electromotive force using a small electrical charge applied to an iontophoretic chamber containing a similarly charged blood circulation enhancing agent provided on the electromagnetic radiation applicator.

The blood circulation enhancement means can be a physical material, for example, wherein the electromagnetic radiation applicator of the electromagnetic radiation means of the hyperthermia device comprises a heat insulator which generates physiological congestion.

The blood circulation enhancement means can be a physical means, for example, a heat means increasing surface temperature to the pain/tolerance limit (for example local heat can increase blood flow by 70-160 %).

The blood circulation enhancement means can be a chemical stimulation means, for example, the oleoresin capsicum (pelegrin-acid-vanillilamid:PV) which increases the skin blood flow 3-4 fold.

The hyperthermia device of the present invention can also comprise a cooling means for cooling the low complex dielectric tissue. One example of a cooling means is a bolus electrode applicator containing a circulating cooled liquid as known in the art. This cooling means is able to cool the low complex dielectric tissue to maintain the normal physiological temperature of the low complex dielectric tissue during hyperthermia treatment. Alternatively the cooling means is
able to cool the low complex dielectric tissue to reduce the temperature of the low complex dielectric tissue to below normal physiological temperature during hyperthermia treatment.

The hyperthermia device and method of the present invention provides the following significant advantages over prior art hyperthermia devices and methods.

The present invention provides a device for regulation surface tissue conditions to solve the contradiction between the need to transfer the maximum amount of energy and at the same time prevent an unpleasant or possibly harmful effect of heating of the surface tissue. Cooling the surface tissue decreases the undesired effects of the heating of the surface tissue, however it also also limits the amount of energy transferred through the surface tissue due to the decrease in blood flow in cooled tissue. The present invention provides a device for maximising the blood flow in surface tissue and thus increasing the dielectric constant of the surface tissue and maximising the amount of energy that can be delivered across the surface tissue to a target tissue while at the same time minimizing the amount of heat generated in the surface tissue.

With the hyperthermia device of the present invention having a blood circulation enhancement means the occurrence of overheating is prevented. Consequently, the problem of patient discomfort due to skin tissue overheating during hyperthermia treatment is solved, and also the problem of tissue damage (burns) and necrosis due to overheating of skin tissue and subcutaneous tissue is solved.

Also with the hyperthermia device of the present invention having a blood circulation enhancement means excessive cooling of surface tissue is not required. However the blood circulation enhancement means of the inventive device can also maximise the blood circulation in cooled surface tissue. The blood circulation enhancement means of the inventive device is able to maximise the blood flow in surface tissue regardless of the temperature of the surface tissue.

Further the hyperthermia device of the present invention having a blood circulation enhancement means allows for the optimal energy transfer to the target tissue, as the level of energy transfer is no longer limited by occurrence of overheating of low dielectric constant tissue. Also the applied energy can be significantly increased and therefore higher temperatures attained and/or target tissue at deeper sites
effectively treated in comparison to the use of the same hyperthermia device without a blood circulation enhancement means.

The hyperthermia device of the present invention also allows for the more effective use of electric field coupled energy transfer devices (capacitive coupling devices). Efficient energy generation by electric field coupled energy transfer devices (capacitive coupling devices) is much more simple and more efficient than for the magnetic field coupled energy transfer devices (inductive coupling device), or radiative energy transfer devices (radiative coupling or antenna array device). These latter devices require more complicated device engineering and energy coupling methods.

Further electric field coupled energy transfer devices can be used at low commercial electromagnetic wave frequencies and therefore require no special shielding for safe operation.

Thus the present invention provides a method for preventing damage to low complex dielectric tissue during hyperthermia treatment of high complex dielectric tissue comprising directing electromagnetic energy to a high complex dielectric tissue sufficient to damage the high complex dielectric tissue, and maintaining the blood circulation of low complex dielectric tissue or increasing the blood circulation of a low complex dielectric tissue by a factor of up to 10, wherein the maintained or increased blood circulation in the low complex dielectric tissue prevents overheating of the low complex dielectric tissue.

In the inventive method the blood circulation enhancement means of the hyperthermia device of the present invention reduces the amount of electromagnetic energy absorbed by the low complex dielectric tissue due to the enhanced blood flow in the low complex dielectric tissue.

In the inventive method the temperature of the low complex dielectric tissue can also be reduced by a conventional cooling means, such as by the use of a bolus electrode containing a cooling fluid.

Another aspect of the present invention is the use of the inventive hyperthermia device to provide an improved method of hyperthermia treatment for cancer. Tumour cells are preferentially sensitive to heat in comparison to normal tissue.
Thus, the hyperthermia device of the present invention can be used for prophylaxis and treatment of cancer and proliferative diseases.

All types of cancer can be treated using hyperthermia such as adenocarcinoma, choroidal melanoma, acute leukemia, acoustic neurinoma, ampullary carcinoma, anal carcinoma, astrocytoma, basal cell carcinoma, pancreatic cancer, desmoid tumour, bladder cancer, bronchial carcinoma, non-small cell lung cancer (NSCLC), breast cancer, Burkitt’s lymphoma, corpus cancer, CUP-syndrome (carcinoma of unknown primary), colorectal cancer, small intestine cancer, small intestinal tumours, ovarian cancer, endometrial carcinoma, ependymoma, epithelial cancer types, Ewing’s tumours, gastrointestinal tumours, gastric cancer, gallbladder cancer, gall bladder carcinomas, uterine cancer, cervical cancer, cervix, glioblastomas, gynecologic tumours, ear, nose and throat tumours, hematologic neoplasias, hairy cell leukemia, urethral cancer, skin cancer, skin testis cancer, brain tumours (gliomas), brain metastases, testicle cancer, hypophysis tumour, carcinoids, Kaposi’s sarcoma, laryngeal cancer, germ cell tumour, bone cancer, colorectal carcinoma, head and neck tumours (tumours of the ear, nose and throat area), colon carcinoma, craniopharyngiomas, oral cancer (cancer in the mouth area and on lips), cancer of the central nervous system, liver cancer, liver metastases, leukemia, eyelid tumor, lung cancer, lymph node cancer (Hodgkin’s/Non-Hodgkin’s), lymphomas, stomach cancer, malignant melanoma, malignant neoplasia, malignant tumours gastrointestinal tract, breast carcinoma, rectal cancer, medulloblastomas, melanoma, meningiomas, Hodgkin’s disease, mycosis fungoides, nasal cancer, neurinoma, neuroblastoma, kidney cancer, renal cell carcinomas, non-Hodgkin’s lymphomas, oligodendrogioma, esophageal carcinoma, osteolytic carcinomas and osteoplastic carcinomas, osteosarcomas, ovarian carcinoma, pancreatic carcinoma, penile cancer, plasmocytoma, squamous cell carcinoma of the head and neck (SCCHN), prostate cancer, pharyngeal cancer, rectal carcinoma, retinoblastoma, vaginal cancer, thyroid carcinoma, Schneeberger disease, esophageal cancer, spinalioms, T-cell lymphoma (mycosis fungoides), thymoma, tube carcinoma, eye tumours, urethral cancer, urologic tumours, urothelial carcinoma, vulva cancer, wart appearance, soft tissue tumours, soft tissue sarcoma, Wilm’s tumour, cervical carcinoma and tongue cancer. Particularly suitable for treatment are, for example, astrocytomas, glioblastomas, pancreatic cancer, bronchial cancer, breast cancer, colorectal cancer, ovarian cancer, gastric cancer, laryngeal cancer, malignant melanoma, oesophageal cancer, cervical cancer, liver cancer, bladder cancer, and renal cell cancer.
Another aspect of the present invention is the use of the inventive hyperthermia device to provide an improved method of hyperthermia treatment for inflammatory conditions. Examples of inflammatory diseases and conditions which could benefit from hyperthermia treatment are arthritis, rheumatoid arthritis, allergy-rhinitis, other allergic symptoms and bronchial asthma.

Another aspect of the present invention is the use of the inventive hyperthermia device to provide an improved method of hyperthermia treatment for upper respiratory tract disease. Upper respiratory tract infections are caused by viruses and bacteria that have an optimum growth and survival temperature lower than the core body temperature. Therefore these infections can also be treated using hyperthermia therapy. Thus the hyperthermia device of the present invention is also useful for the treatment of rhinitis and other upper respiratory tract infections. Examples of viruses that cause upper respiratory tract infections are rhinoviruses, coronaviruses, adenoviruses, myxoviruses, coxsackie viruses, echoviruses, parainfluenza viruses, respiratory syncytial virus and influenza viruses. Examples of bacteria that cause upper respiratory tract infections are Mycoplasma pneumoniae, Chlamydia pneumoniae, Streptococcus pneumoniae, Corynebacterium diptheriae, and Haemophilus influenzae.

Another aspect of the present invention is the use of the inventive hyperthermia device to provide an improved method of cosmetic treatment, for example, medical face lift and medical cosmetic slimming by adipose tissue reduction.

The hyperthermia device of the present invention can also be used in combination with other forms of cancer therapy, for example, chemotherapy, radiotherapy and surgery.

In particular it is known that hyperthermia treated tumours demonstrate a higher sensitivity to chemotherapy drugs due to increased blood circulation to the tumour and increased cellular metabolism rates in the tumour. Therefore, the hyperthermia device of the present invention can be used in combination with chemotherapy treatment with cytostatic and/or cytotoxic drugs. Example of some cytostatic and/or cytotoxic drugs are actinomycin D, aminoglutethimide, amscarin, anastrozol, antagonists of purine and pyrimidine bases, anthracycline, aromatase inhibitors, asparaginase, antiestrogens, bexaroten, bleomycin, buselerin, busulfan, camptothecin derivates, capecitabin, carboplatin, Carmustine, chlorambucil, cisplatin, cladribin, cyclophosphamide, cytarabin,
cytosinarabinoside, alkylating cytostatics, dacarbacin, dactinomycin, daunorubicin, docetaxel, doxorubicin (adriamycin), doxorubicin lipo, epirubicin, estramustine, etoposid, exemestan, fludarabine, fluorouracil, folic acid antagonists, formestan, gemcitabine, glucocorticoids, goselerin, hormones and hormone antagonists, hycamtin, hydroxy urea, idambicin, ifosfamide, imatinib, irinotecan, letrozol, leuprorelin, lomustin, melphalan, mercaptopurine, methotrexate, miltefosine, mitomycin, mitosis inhibitors, mitoxantrone, nimustine, oxaliplatin, paclitaxel, pentostatin, procarbazine, tamoxifen, temozolomide, teniposide, testolactone, thiotepa, thioguanine, topoisomerase inhibitors, topotecan, treosulfan, tretinoin, triptorelin, trofosfamide, vinblastine, vincristine, vindesine, vinorelbine, antibiotics with cytotoxic activities. All the present and future cytostatics, or other medicaments including gene therapy could be applied.

When used for treatment of inflammatory conditions the hyperthermia device of the present invention can be used in combination with an anti-inflammatory drug treatment such as a non-steroidal anti-inflammatory drug (NSAID), for example, alclofenac, aceclofenac, sulindac, tolmetin, etodolac, fenoprofen, thiaprofenolic acid, meclofenamic acid, meloxicam, tenoxicam, lomoxicam, nabumetone, acetaminophen, phenacetin, ethenzamide, sulpyrine, mefanamic acid, flufenamic acid, diclofenac sodium, loxoprofen sodium, phenylbutazone, indomethacin, ibuprofen, ketoprofen, naproxen, oxaprozin, flurbiprofen, fenbufen, pranoprofen, floctafenine, piroxicam, epirizole, tiaramide hydrochloride, zaltoprofen, gabexate mesilate, camostat mesilate, ulinastatin, colchicine, probenecid, sulfonpyrazone, benz bromarone, allopurinol, salicylic acid, atropine, scopolamine, levorphanol, ketorolac, tebufelone, tenidap, clofezone, oxyphenbutazone, prexazone, apazone, benzydamine, bocolome, cinchopen, clonixin, ditrazol, epirizole, fenoprofen, floctafeninl, glaphenine, indoprofen, niflumic acid and suprofen, or with a steroidal anti-inflammatory drugs, for example, dexamethasone, hexestrol, methimazole, betamethasone, triamcinolone, fluocinonide, prednisolone, methylprednisolone, hydrocortisone, fluorometholone, beclomethasone dipropionate, estriol, clobetasol, diflorasone diacetate, halbetosol propionate, amicinonide, desoximetasone, halcinonide, mometasone furoate, fluticasone propionate, flurandrenolide, clocortalone, predincarbate, aclometasone dipropionate and desonide.

Description of figures:
Figure 1 shows temperature versus depth for hyperthermia treatment of low blood-perfusion skin.
Figure 2 shows the rise in temperature over time for hyperthermia treatment of low blood-perfusion skin.

Figure 3 shows temperature versus depth for hyperthermia treatment of high blood-perfusion skin.

Figure 4 shows the rise in temperature over time for hyperthermia treatment of high blood-perfusion skin.

Figure 5 shows the relationship between relative permittivity and conductivity and blood perfusion.

Figure 6 shows a hyperthermia device useful in the present invention.

Example

A comparison of tissue temperature was modelled for a tissue sample having high blood perfusion rate and for a tissue sample having a low blood perfusion rate.

The model tissue sample comprised an upper surface tissue layer and a lower surface tissue layer both of 1 cm depth, an upper and lower healthy tissue layer both of 10 cm depth situated directly below the respective surface tissue layers and a target (tumour) tissue layer of 1 cm depth situated between the upper and lower healthy tissue layers.

In this model the electrical field coupled energy was provided by an electromagnetic radiation applicator applied to the upper surface tissue layer.

The temperature of the upper and lower surface tissue, healthy tissue and the target (tumour) tissue was calculated using an initial body temperature of 36.6 °C and an initial blood temperature of 37 °C. The perfusion rate of the upper and lower healthy tissue was set at $3 \times 10^{-9}$ for both the low blood perfusion rate sample and the high blood perfusion rate sample. The perfusion rate of the target (tumour) tissue was set at $1 \times 10^{-3}$ for both the low blood perfusion rate sample and the high blood perfusion rate sample.

The only variable between the low blood perfusion rate sample and the high blood perfusion rate sample was the blood perfusion rate of the upper and lower surface tissue. The relative blood perfusion rate (as kilogram blood per kilogram tissue per second) of the upper and lower surface tissue to a depth of 1 cm was set at $0.1 \times 10^{-3}$ for the low blood perfusion rate sample and $2.8 \times 10^{-3}$ for the high blood perfusion rate sample.
The results of the modelling calculation are shown in Figures 1, 2, 3 and 4.

Figures 1 and 3 show the heating of tissue at the upper surface (depth 0 m) and at the lower surface (depth 0.23 m) and of the target tissue (depth 0.1 1-0.12 m), as well as the healthy tissue separating the surface tissues from the target tissue after a treatment time of 0.01 hour, 0.1 hour and 1 hour.

Figure 1 shows the result for a tissue sample having a low blood perfusion rate in the upper and lower surface tissue of $0.1 \times 10^{-3}$. The temperature is highest in the upper and lower surface tissues and lowest in the healthy and target (tumour) tissue regardless of the time period of the treatment. Figure 3 shows the result for a tissue sample having a high blood perfusion rate in the upper and lower surface tissue of $2.8 \times 10^{-3}$. In this case the temperature is highest in the target (tumour) tissue at a depth of approximately 0.1 1-0.12 m for a treatment period of 0.1 hour or 1 hour. Also the heat on the lower surface tissue is greatly reduced in comparison to the same treatment period in low blood perfusion tissue. Although the upper surface tissue where the electrical field coupled energy is applied shows an increase in temperature, this could be controlled by moderate surface tissue cooling sufficient to cool the surface tissue but not reduce the blood perfusion.

Figures 2 and 4 show the increase in temperature over time in the upper surface tissue (upper skin), the lower surface tissue (under skin) and the target tissue (tumour).

Figure 2 shows the result for a tissue sample having a low blood perfusion rate in the upper and lower surface tissue of $0.1 \times 10^{-3}$. The temperature is highest in the upper and lower surface tissues and lowest in the target (tumour) tissue regardless of the time period of the treatment. Figure 4 shows the result for a tissue sample having a high blood perfusion rate in the upper and lower surface tissue of $2.8 \times 10^{-3}$. In this case the temperature is highest in the target (tumour) tissue at a depth of approximately 0.1 1-0.12 m. Again the heat on the lower surface tissue is greatly reduced in comparison to the same treatment period in low blood perfusion tissue, and although the upper surface tissue where the electrical field coupled energy is applied shows an increase in temperature, this could be controlled by moderate surface tissue cooling sufficient to cool the surface tissue but not reduce the blood perfusion.
Claims

1. A hyperthermia device comprising:
   an electromagnetic radiation means for directing electromagnetic energy
to a target tissue, wherein the target tissue is a high complex dielectric constant tissue,

   and

   a blood circulation enhancement means for increasing blood circulation in
low complex dielectric constant tissue,

   wherein the blood circulation enhancement means increases the blood flow by a factor of 1 to 10 in low complex dielectric constant tissue.

2. The hyperthermia device of claim 1 wherein the low complex dielectric constant tissue is skin tissue, subcutaneous tissue or adipose tissue.

3. The hyperthermia device of claim 1 wherein the high complex dielectric constant tissue is tumour tissue.

4. The hyperthermia device of claim 1 wherein the electromagnetic radiation means is an electric field coupled energy transfer means, a magnetic field coupled energy transfer means, or radiative energy transfer means.

5. The hyperthermia device of claim 4 wherein the electromagnetic radiation means is an electric field coupled energy transfer means.

6. The hyperthermia device of claim 1 wherein the blood circulation enhancement means is a mechanical stimulation means.

7. The hyperthermia device of claim 6 wherein the mechanical stimulation means is a vibration means.

8. The hyperthermia device of claim 1 wherein the blood circulation enhancement means is an electrical stimulation means.
9. The hyperthermia device of claim 1 wherein the blood circulation enhancement means is a chemical stimulation means.

10. The hyperthermia device of claim 1 wherein the blood circulation enhancement means is a physical material.

11. The hyperthermia device of claim 1 wherein the blood circulation enhancement means is a physical means.

12. The hyperthermia device of claim 11 wherein the physical means is a heat means.

13. The hyperthermia device of claim 1 wherein the blood circulation enhancement means reduces the amount of electromagnetic energy absorbed by the low complex dielectric tissue.

14. The hyperthermia device of claim 1 wherein the device also comprises a cooling means for cooling low complex dielectric tissue.
FIGURES

Figure 1

![Graph showing temperature vs. depth with different time markers: 1 h, 0.1 h, 0.01 h.](image)

Figure 2

![Graph showing temperature vs. time for tumor and tissue layers.](image)
Figure 5

Values of conductivity [S/m] and relative permeability vs. blood-perfusion (ratio)

- Relative permittivity
- Conductivity [S/m]
INTERNATIONAL SEARCH REPORT

A. CLASSIFICATION OF SUBJECT MATTER

INV: A61N5/06

According to International Patent Classification (IPC) or to national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

A61N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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D Further documents are listed in the continuation of Box C

See patent family annex

* Special categories of cited documents

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Date of the actual completion of the international search 12 December 2007

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Chopinaud, Marjorie

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