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(54) Title: A METHOD FOR DETECTION OF CANCER USING A THERMAL ENHANCEMENT AGENT, AND NON-INVASIVE THERMAL MONITORING

(57) Abstract: A method for detecting a malignant lesion within a human tissue, comprising: (a) administering a thermal enhancing agent, and said thermal enhancing agent generates heat upon activation from an external energy source, to a human; (b) submitting the human tissue to a predetermined amount of energy emitted from an external energy source; (c) monitoring the temperature or other thermal magnitude on the skin on a plurality of points on the tissue; (d) analyzing the results of said monitoring; (e) detecting specific points on the tissue having abnormally higher temperatures or other thermal magnitudes, in comparison to other points on the tissue or to predetermined data.

A METHOD FOR DETECTION OF CANCER USING A THERMAL ENHANCEMENT AGENT, AND NON-INVASIVE THERMAL MONITORING

FIELD OF THE INVENTION

The present invention generally relates to a method for detection of malignant lesions within human tissue. The present invention is especially useful for detection of breast cancer.

BACKGROUND OF THE INVENTION

Non-invasive detection and assessment of malignancy, remains one of the great targets in the field of cancer, especially in breast cancer. Breast cancer is the most common malignancy in women affecting almost one in nine individuals. Early detection of breast cancer has been widely acknowledged as the key to the successful treatment of this disease in women. To date, the best way to cure women diagnosed with breast cancer is to detect the tumor in time. Studies of breast cancer identify several stages in the evolution of a tumor. The stage of the detection has a crucial effect on the survival chances and/or healing possibilities for the breast cancer patient. With present medical practices, early detection of breast cancer is considered to be detection in the period spanning from the end of stage one (tumors smaller than 2cm) through the beginning of stage two (tumors larger than 2cm, with one lymph node).

Today, breast cancer may be detected using several methods. Generally, an initial breast examination involves breast palpation, performed by the woman herself and/or her physician. If breast palpation uncovers a potential tumorous growth or another abnormality, a test such as mammography, MRI, or an ultrasound examination is advised. These are performed in a hospital or a large medical center. When a tumor is positively detected by any of these means, a biopsy or fine needle aspiration is utilized to determine whether or not the tumor is cancerous.

Mammography is the breast imaging technique most commonly used when an abnormality is suspected, and is also widely used as a preventative screening tool. Several western nations administer annual mass screening tests for women over 50 years of age using mammography, MRI, or ultrasound. Mammography is essentially an x-ray technique that locates dense spots or tiny specks of calcium in breast tissue,

that may be an early sign of cancer. Mammography necessitates administration of ionizing radiation, which can cause cumulative damages upon repeated exposure. Mammography testing is costly, since the equipment is expensive, a trained technician must be on hand to operate the equipment, and medical personnel must evaluate the results. Furthermore the accuracy of mammography with respect to primary detection capabilities and diagnosis of benign and malignant breast lesions is not considered to be high enough to rely on in the under 50 age group, for two main reasons. First, hormonal fluctuations present in women under the age of 50 affect the fibrous nature of the female breast, and may lead to erroneous interpretation of the diagnostic images, resulting in false positive or, even worse, false negative findings. Second, misdiagnosis may occur due to the unique ratio of glandular and adipose tissues in women under the age of 50. This makes mammography a less than ideal tool for breast imaging.

An optimal imaging tool for detection and diagnosis of breast cancer should be noninvasive and more widely available in gynecologic clinics, should not involve harmful irradiation and should be accurate for women in all age groups. A major goal of breast imaging is differentiation between benign and malignant lesions in a noninvasive and reliable manner.

Thermal monitoring has been considered for use in diagnosing cancer. Classical thermal monitoring makes use of the slight variations in temperature that exist in different tissues in order to generate a thermal map from which information can be gleamed. However, these internal temperature differences are so minor as to be difficult to detect non-invasively . One way of overcoming this problem is to chill the tissue undergoing evaluation, then allow it to re-perfuse, in order to create a dynamic situation. This enhances the temperature differences and may provide additional information. US Patent No. 6,077,228 discloses an array of thermoresistors and conductors which can be used to measure breast temperature after the breasts have been chilled, then re-perfused. Chilling and re-perfusion of tissues enhances the temperature differences, but does not improve the sensitivity of the method. In spite of the fact that re-perfusion creates a dynamic situation which is easier to measure, the measurements are too lengthy, and the thermal effect, which is slight to begin with, usually dissipates before it can be noted.

Neoplastic lesions are associated with an enhanced blood supply. The blood vessels at the lesion are dense and their permeability is different than that of the

vessels in normal tissue, so that there is leakage from the pathological vascular bundles into the tumor. In breast cancer specifically, vascularature has many characteristics not found in the microcirculation of normal tissues. These characteristics include:

1) A large extracellular fraction -a large fraction of volume which is not occupied by cells or vascularization and accessible for agent that cannot enter cells.
2) Increased permeability – rapid diffusion between the intravascular and the extracellular space due to leakiness of microcapillaries.
3) High vascular density - high vascular surface area associated with the angiogenesis process that takes place in a carcinoma.

These characteristics result in accumulation of a material injected into the bloodstream, in a tumor, at a level higher than that which it accumulates in the surrounding tissue. This has been put to use in various imaging techniques to diagnose cancer; for example, when contrasting agents are injected into the bloodstream in preparation for MRI or ultrasound imaging, they tend to accumulate in a lesion due to the increased permeability as well as the large extracellular fraction. The high blood fraction enhances the amount of the agent which perfuses the lesion. All of these factors together offer better specificity of diagnosis and improved detection ability. The present invention similarly utilizes the circulatory abnormalities of blood vessels in a neoplastic lesion, to aid in detection.

Perfluorocarbon (herein PFC) compounds are common organic compounds, in which hydrogen atoms have been substituted by flourine atoms. Carbon-flourine compounds are highly inert, and are therefore bio-compatible and non-toxic. Perfluorocarbons have been used in implants and in drugs, and have been investigated for use as blood substitutes. PFC's have a high affinity for gasses, and are able to dissolve 20 times more oxygen that water, for example. Gas-loaded perfluorocarbons absorb sound energy due to the presence of the dissolved gas, and this results in heating of the area that contains the compounds. US Patent No. 5,149,319 discloses a method for destroying a tumor by heat, in which a gas or a perflourocarbon compound is first administered to a patient and then ultrasonic energy is applied to the tissue, causing the temperature in the tissue to rise to 43°C, at which temperature, cell death is assured. US Patent No. 5,158,536 discloses a similar method for treating lung cancer, in which a patient's lungs are temporarily filled with a perfluorocarbon liquid,

then ultrasound is applied until a temperature of 41-50°C is reached and the tumor cells are assumed to have been killed. Thus, attempts have been made to utilize perflurocarbons for treatment and eradication of cancer; surprisingly, the applicants have discovered PFC's can be utilized in detection of cancer.

It is the object of the present invention to provide a method for detecting malignant lesions in humans, which is extremely inexpensive and does not involve harmful radiation. This method is especially useful for breast cancer, but can be used for other types of cancer as well. When this method is used to detect breast cancer, it is applicable for women of all age groups. The method disclosed in the present invention does not require trained personnel to administer testing, and so may be made available in any outpatient clinic. It is the object of the present invention to provide a method for detection of malignant lesions in humans, which utilizes thermal monitoring, yet has improved sensitivity and success over prior art methods.

These and other objects of the present invention will become more apparent from the summary of the invention and the detailed description of the drawings that follow.

DEFINITIONS

In the present invention, the term "thermal magnitude" refers to the temperature, heat flux, or radiance. Thermal measurements include for example, temperature measurements, heat flux, or radiance measurements

In the present invention, the term "a thermal enhancing agent" refers to a material which, when injected into human tissue, absorbs energy from an external energy source, and releases heat in response. The amount of heat released is considerably greater than the amount that would have been released by the tissue alone, should the thermal enhancing agent not have been present. This phenomenon is based on the ability of thermal enhancing agents to convert the energy absorbed to heat which enhances the thermal magnitude and therefore the sensitivity of the thermal monitoring and detection.

In the present invention, the term "gaseous precursors" refers to materials that form a gas after being triggered to do so. The trigger can be, for example, a change in pH, such as is achieved, upon injection of the material into the bloodstream, causing modification and breakdown of the precursor, resulting in release of a gas.

SUMMARY OF THE INVENTION

The present invention is based on the ability of thermal enhancing agents to produce heat upon absorption of energy, emitted from an external energy source, for thermal monitoring and detection of malignant lesions in human tissue. The method of the present invention is especially useful for detection of breast cancer.

In the present invention, a thermal enhancing agent, (for example a gas-loaded perfluorocarbon compound, or a solution containing a precursor to a gas), is injected into a patient's peripheral vein. The material injected accumulates in a tumor, should such a lesion be present, at a higher concentration than in the normal tissue, due to the above-mentioned circulatory abnormalities associated with tumors. A beam of an external energy source is directed towards the area undergoing evaluation, such as the breast. The thermal enhancing material that was injected, absorbs this energy and generates heat, which can be measured externally on the skin. The surrounding normal tissue emits less heat than the tumorous area, due to the differences in the concentration of the thermal enhancing agent in each of these areas. Thus, thermal monitoring can be used to generate a map of non-invasive thermal magnitude measurements which correspond to different areas on the tissue, and this map reflects the presence or absence of a neoplasm.

The present invention provides a method for detection of malignant lesions in humans, which utilizes thermal monitoring, yet has improved sensitivity and success over prior art methods.

More specifically, the present invention relates to a method for detecting a malignant lesion within a human tissue, comprising:

a) administering a thermal enhancing agent, and said thermal enhancing agent generates heat upon activation from an external energy source, to a human;
b) submitting the human tissue undergoing evaluation, to a predetermined amount of energy emitted from an external energy source;
c) monitoring the temperature or other thermal magnitude, on the skin, in a plurality of points on the tissue;
d) analyzing the results of said monitoring;
e) detecting specific points on the tissue having abnormal thermal magnitudes (such as temperatures or other thermal magnitudes), in comparison to other points on the tissue or to predetermined data.

Various thermal enhancing agents can be utilized, along with any external energy source appropriate for activation of said thermal enhancing agents.

In accordance with a preferred embodiment of the present invention, the thermal enhancing agent is a perfluorocarbon.

Further, in accordance with a preferred embodiment of the present invention, the perfluorocarbon is selected from cis-perfluordecaline, trans-perfluorodecaline, perfluorohexane, or perfluoro-2-butyl-tetrahydrofurane.

Still further in accordance with a preferred embodiment of the present invention, prior to administration the perfluorocarbon is loaded with a gas selected from carbon dioxide or oxygen.

Moreover, in accordance with a preferred embodiment of the present invention, the thermal enhancing agent is a gaseous precursor.

Further, in accordance with a preferred embodiment of the present invention, the gaseous precursor is selected from sodium bicarbonate, aminomalonate, diazonium or methylactete.

Additionally, in accordance with a preferred embodiment of the present invention, the human tissue is the female breast.

Still further, in accordance with a preferred embodiment of the present invention, the predetermined amount of energy to which the tissue is submitted, is emitted from the external energy source at a plurality of levels of intensity, and wherein said emission is constant or time-dependant.

Moreover, in accordance with a preferred embodiment of the present invention, the amount of thermal enhancing agent administered and the amount of energy the tissue is submitted to are such that will produce a maximal internal tissue temperature of 41°C. In the present invention, the thermal magnitude of the tissue is measured non-invasively on the skin.

In certain embodiments of the present invention, the agent injected is enclosed within liposomes.

Still further, in accordance with a preferred embodiment of the present invention, the agent injected is in the form of an emulsion. In certain embodiments, the emulsion has a particle size of 10-100nm.

In accordance with a preferred embodiment of the present invention, the energy to which the tissue is submitted, is ultrasonic energy.

Still further, in accordance with a preferred embodiment of the present invention, the ultrasonic energy to which the tissue is submitted to, has a frequency of 0.3-10MHz.

Additionally, in accordance with a preferred embodiment of the present invention, the external energy is emitted in several pulses having predetermined intervals between said pulses. In one embodiment, at least one of the pulses is characterized by a varying level of pulse intensity within said pulse.

Moreover, in accordance with a preferred embodiment of the present invention, the external energy source is activated in a continuous manner.

Further, in accordance with a preferred embodiment of the present invention, the method further comprises the step of comparing results of said monitoring, with an image obtained using an imaging technique other than thermal magnitude monitoring.

Moreover, in accordance with one embodiment of the present invention, the thermal magnitudes, (such as the temperature), are monitored using an infrared-based camera. In another embodiment, the thermal magnitudes, (such as the temperature), are monitored using at least one temperature-sensing probe, a sensor array, or a plurality of thermistors. If the temperature or other thermal magnitudes are monitored in a plurality of points, these readings can be taken simultaneously. In certain embodiments, a temperature-sensing probe or a thermal magnitude-sensing probe (such as a probe measuring the heat flux or the radiance), is used. In certain embodiments, the thermal magnitude-sensing probe is located within or on the external energy source in general, and on an ultrasonic transducer specifically.

Additionally, in accordance with one preferred embodiment of the present invention, analyzing of the results of said measurements is performed using an prediction algorithm. This computation aids in mapping of the thermal monitoring results, and correlating them with specific areas on the tissue. Another algorithm can also be used to shorten the length of the thermal monitoring; by calculating and predicting the steady-state temperature value after only a brief amount of time. This prevents premature dissipation of the thermal effect before it can be measured.

Further, in one preferred embodiment, administration of the thermal enhancing agent is performed by intravenous injection.

BRIEF DESCRIPTION OF THE DRAWINGS

The present invention is herein described, by way of example only, with reference to the accompanying drawings, wherein:

Figure 1 illustrates a graph of temperature elevations obtained in Example 1.

Figure 2 illustrates a schematic presentation of the experiment protocol of Example 2.

Figure 3 illustrates thermal images captured after bovine tissue was injected with perfluorodecalin and subjected to ultrasound, as performed in Example 2.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

It is appreciated that the detailed description that follows is intended only to illustrate certain preferred embodiments of the present invention. It is in no way intended to limit the scope of the invention, as set out in the claims.

The present invention discloses a method of detecting malignancies within a human, especially within the human breast. In the following description, a gas-loaded perfluorocarbon compound is used as an example of the thermal enhancing agent, and the external energy source described is an ultrasound transducer. However, various thermal enhancing agents may be used other than gas-loaded perfluorocarbons or gaseous precursors, and various external energy sources may be utilized. Upon selection of a specific thermal agent, an external energy source must be selected as well, so that the energy source selected is one that is capable of activating the specific thermal enhancing agent.

In a preferred embodiment, a perfluorocarbon compound is loaded with a gas, for example, carbon dioxide gas or oxygen, and emulsified into a water-soluble micro-emulsion. The emulsion is administered intravenously to a patient undergoing screening or detection of breast cancer. The emulsion tends to accumulate in a neoplastic lesion, if one is present, due to the abnormal vasculature present in such lesions, as described above. Ultrasound energy is directed towards the breast area, the energy is absorbed by the gas in the perfluorocarbon emulsion, and heat is generated as a result. An array of sensors is brought in contact with the skin in the breast area,

and the temperature is measured on a plurality of points on the breast. Alternatively, rather than the temperature being measured on the skin, the radiance and/or the heat flux on the skin can be measured. These thermal magnitude measurements are taken either after the application of the external energy is completed, or while it is being applied.. The operation mode of the external energy source, can be continuous or pulsed. In the continuous mode the energy source is switched on for a predetermined time period. During this time, the intensity might be constant or time dependent. In the pulsed mode the energy source is switched ON and OFF alternately. The duration of time in which the energy source is switched "ON" and the duration of time in which the energy source is switched "OFF", can be controlled and is changeable. The "ON" time period followed by the "OFF" time period is defined as a cycle. In the pulsed mode, the number of cycles can be controlled. In the pulsed mode the intensity of energy can be controlled and may vary during the application period. One or more pulses may have a higher level of intensity than the remainder of the pulses, or the level of intensity can vary even within a single pulse, so that for example, the pulse may begin at one intensity level, and end at another intensity level. Cumulatively all the parameters such as operation mode (continuous or pulsed), duration times, intensity form (constant or time dependent) comprises the operation profile. The control unit of the energy source may contain many operation profiles. The method of the present invention grants control over the dynamics of the thermal effect, by controlling the duration and the timing of application of the external energy source. The timing of the monitoring is controllable in the present invention, more so than in prior art. Use of a thermal enhancing agent, and controlling the dynamics of the process, enhances the differences in thermal magnitude on the one hand, and avoids dissipation of the thermal effect on the other hand, by improving the timing of the monitoring.

The temperatures or other thermal magnitude measurements, are plotted and a thermal map is generated and analyzed by computer. A point of abnormally elevated thermal magnitude corresponds to a suspected lesion in that area on the breast. In one embodiment, thermal magnitude measurements are compared to data previously accumulated from the same patient. In another embodiment, the thermal magnitudes are monitored over a period of time, so that several measurements are taken for each point on the breast.

The amount of material injected is calibrated to be sufficient enough to receive a detectable change the thermal magnitude reading on the skin, from material accumulated in a tumor at a typical depth of 2.5cm within the breast. The temperature reached within the breast should not be higher than 41°C, a maximum temperature suited for diagnostics. This is assured by injecting the proper amount of material, by calibrating the intensity of the energy administered towards the breast, and the length of time for which it is applied.

The thermal magnitudes are measured in one embodiment with an array of sensors, (which are, for instance, thermistors), and the distance between the sensors determines the resolution of the thermal map which is generated. The method of the present invention aims to detect lesions of a minimum size of 0.4cm (which correlates to a developmental stage of malignancy of up to stage 1), and thus in a preferred embodiment, the maximum distance between the sensors in the array is 0.2cm . In an alternative embodiment, the thermal magnitudes are measured using a thermal camera, from which a gray scale, or a colored scale, thermal map is generated. The infrared-based camera is directed towards the breast, or the sensor array is brought in contact with the breast, either before, during or after the external energy is applied. Thermal magnitude measurements can then be taken before, after, or in parallel to application of the external energy, or in any combination of timing thereof.

The amount of time necessary to measure the thermal magnitudes of the breast may be shortened if a prediction algorithm is used. The algorithm can aid in shortening the measurement time by calculating the steady-state temperature value instead of waiting for skin temperature to reach steady state.

In one embodiment, the material to be injected is enclosed within liposomes. In another embodiment, it is emulsified using a carrier, until it is a water-soluble micro-emulsion with a particle diameter <100nm, so that the emulsion can diffuse out of the blood vessels and into a lesion, should a lesion be present.

In one embodiment, the material to be injected is a gaseous precursor, for example sodium bicarbonate, aminomalonate, or methylactete. These materials will form a gas after a change in pH, such as is achieved, for example, upon injection into the bloodstream, or when they reach a hypoxic, acidic tumor.

EXAMPLES

The aim of the following examples was to prove two basic principles underlying the method of the present invention:

1) A temperature rise can be generated when a thermal enhancing agent (at concentrations as low as are expected in tumors) is activated by an external energy source.
2) The temperature rise generated deep within the tissue, in the presence of a thermal enhancing agent, can be measured on the skin.

Example 1

Two test tubes were chosen, containing saline (0.9M NaCl). Perflourodecalin was repeatedly added to one of the test tubes so as to obtain ten-fold increases in perflourodecalin concentration. After each new concentration was reached, the test tube was subjected to ultrasound energy, having a frequency of 1MHz, with an intensity of 100 mW/cm^2 for a period of three minutes. The temperature was then read via a temperature probe inserted into the test tube. The temperature was similarly measured in the remaining test tube , which contained saline only, and functioned as a control. The results are depicted in Figure 1.

Referring to Figure 1, the temperature is shown in both test tubes over the course of the experiment. The upper line on the graph represents the test tube to which perfluorodecalin was added in increasing amounts, and the lower line represents the test tube which contained saline. Each peak on the graph represents a rise in temperature at a specific time in the experiment. The first peak on the left (peak 0) represents a time-point where both test tubes contained only saline, and application of ultrasound raised the temperature in both test tubes to 33°C. Subsequently, the concentration of perfluorodecalin was continuously raised in one of the test tubes, represented by the upper line on the graph. The temperature rise after application of ultrasound was always higher in this test tube compared to the test tube containing saline, as can be seen by comparison of the upper line on the graph with the lower line, at each peak. For example, at a concentration of 0.01%perfluorodecalin (upper line of peak 1), the temperature was 38°C in this test tube, compared with 33.5°C in the control tube containing saline (lower line, peak 1).

Results were similar for 0.1%perfluorodecalin (upper line, peak 2). At 10% perfluorodecalin (upper line, peak 3) and at 100% perfluorodecalin (upper line, peak 4), the temperature rise was greatly enhanced by the presence of perfluorodecalin. This can be seen as a difference of approximately 8°C between the two test tubes (peaks 3,4). Thus, perfluorodecalin amplifies the rise in temperature associated with application of ultrasound.

Example 2

Bovine tissue was subjected to several cycles, in which in each cycle the tissue was injected with a ten-fold increased concentration of a perfluoro- decalin solution, then immediately subjected to ultrasonic energy having a frequency of 1MHz, with an intensity of 100 mW/cm^2 for a period of three minutes. Then the tissue was imaged using an infrared-based camera. Between each injection and subsequent application of ultrasound, the tissue was allowed to return to the baseline temperature.

Referring to Figure 2, a schematic presentation of the experiment protocol is shown. The bovine tissue was first injected with saline (0.9M NaCl) (0) at a depth of 2.7 cm within the tissue. This depth was chosen since it represents a typical depth at which a tumor can be found within a human breast. Ultrasound was applied to the tissue, at the intensity described above, for three minutes, after which thermal mapping was performed using an infrared-based camera. A delay of five minutes allowed the tissue to return to the baseline temperature, then 0.01% perfluorodecalin (1) diluted in saline was injected, and after three minutes of ultrasonic energy was applied, the tissue was imaged once again. 0.1% perfluorodecalin (2) was injected subsequently, followed by 1% perfluorodecalin (3), 10% perfluorodecalin (4) and 100% perfluorodecalin (5). Only 0.01%-0.1% of the amount of material injected into a human will accumulate within a tumor, which explains the choice of these appropriate ranges of concentrations within the model of this example. The resultant thermal images captured after injection of each of these concentrations, and application of ultrasound, can be seen in Figure 3.

Refer now to Fig. 3, which depicts images taken by an infrared-based camera after injection of various concentrations of perfluorodecalin to bovine tissue. The percentage of injected perfluorodecalin is noted in the left-hand corner of each box

within the figure. Light-colored areas in the gray scale represent higher temperatures, while darker areas represent lower temperatures.

When saline was injected instead of perfluorodecalin (box 3a), the application of ultrasound lead to a minimal rise in temperature at the site of injection, which is represented by a light-colored area on the dark gray background. Even the lowest percentage of perfluorodecalin used in this experiment, 0.01% (box 3b), enhances the rise in temperature obtained when ultrasound is applied to the tissue. At 0.1%perfluorodecalin (box 3c), the rise in temperature is greatly enhanced. This concentration, and concentrations greater than it, are shown to significantly intensify the thermal effect that application of ultrasound has on tissue (see boxes 3c, 3d, 3e and 3f). Therefore, perfluorocarbons can be administered to a tissue and after application of ultrasound, a diagnostic thermal image can be obtained that clearly depicts areas of perfluorocarbon accumulation.

The results of Examples 1 and 2 strongly indicate a temperature rise was caused upon interaction of the ultrasound energy with the thermal enhancing agent. Moreover the temperature rise which was generated deep within the tissue could be clearly sensed on the surface of the tissue. Cumulatively these data confirm the validation of the two basic principles underlying the method of the present invention. Hence, this method can enhance the slight variations in temperature that exist in different tissues in order to generate a thermal map useful for detection of breast cancer non-invasively.

CLAIMS

1. A method for detecting a malignant lesion within a human tissue, comprising:
   a) administering a thermal enhancing agent, and said thermal enhancing agent generates heat upon activation from an external energy source, to a human;
   b) submitting the human tissue to a predetermined amount of energy emitted from an external energy source;
   c) monitoring the temperature or other thermal magnitude on the skin on a plurality of points on the tissue;
   d) analyzing the results of said monitoring;
   e) detecting specific points on the tissue having abnormally higher temperatures or other thermal magnitudes, in comparison to other points on the tissue or to predetermined data.
2. A method according to claim 1, wherein the thermal enhancing agent is a perfluorocarbon.
3. A method according to claim 2, wherein the perfluorocarbon is selected from cis-perfluordecaline, trans-perfluorodecaline, perfluorohexane, or perfluoro-2-butyl-tetrahydrofurane.
4. A method according to claim 2, wherein prior to administration the perfluorocarbon is loaded with a gas selected from carbon dioxide or oxygen.
5. A method according to claim 1, wherein the thermal enhancing agent is a gaseous precursor.
6. A method according to claim 5, wherein the gaseous precursor is selected from sodium bicarbonate, aminomalonate, diazonium or methylactete.
7. A method according to claim 1, wherein the human tissue is the female breast.
8. A method according to claim 1, wherein the energy to which the tissue is submitted, is ultrasonic energy.
9. A method according to claim 8, wherein the ultrasonic energy to which the tissue is submitted has a frequency of 0.3-10MHz.
10. A method according to claim 1, wherein the external energy source is activated in a continuous manner.
11. A method according to claim 1, wherein the external energy source is activated in several pulses having predetermined intervals between said pulses.
12. A method according to claim 11, wherein at least one of said pulses is characterized by a varying level of pulse intensity within said pulse.

13.A method according to claim 1, wherein the predetermined amount of energy to which the tissue is submitted, is emitted from the external energy source at a plurality of levels of intensity, and wherein said emission is constant or time-dependant.

14.A method according to claim 1, further comprising the step of comparing results of said monitoring, with an image obtained using an imaging technique other than thermal magnitude monitoring.

15.A method according to claim 1, wherein the amount of thermal enhancing agent administered and the amount of energy the tissue is submitted to are such that will produce a maximal internal tissue temperature of 41°C.

16.A method according to claim 1, wherein the agent injected is enclosed within liposomes.

17. A method according to claim 1, wherein the agent injected is in the form of an emulsion.

18. A method according to claim 17, wherein the emulsion has a particle size of 10-100nm.

19. A method according to claim 1, wherein the temperature or other thermal magnitudes are monitored using an infrared-based camera.

20. A method according to claim 1, wherein the temperature or other thermal magnitudes are monitored using an array of sensors or a plurality of thermistors.

21.A method according to claim 1, wherein analyzing of the results of said measurements is performed using a prediction algorithm.

22.A method according to claim 1, additionally comprising the step of calculating the steady state temperature value using a prediction algorithm.

23.A method according to claim 1, wherein administration of the thermal enhancing agent is performed by intravenous injection.

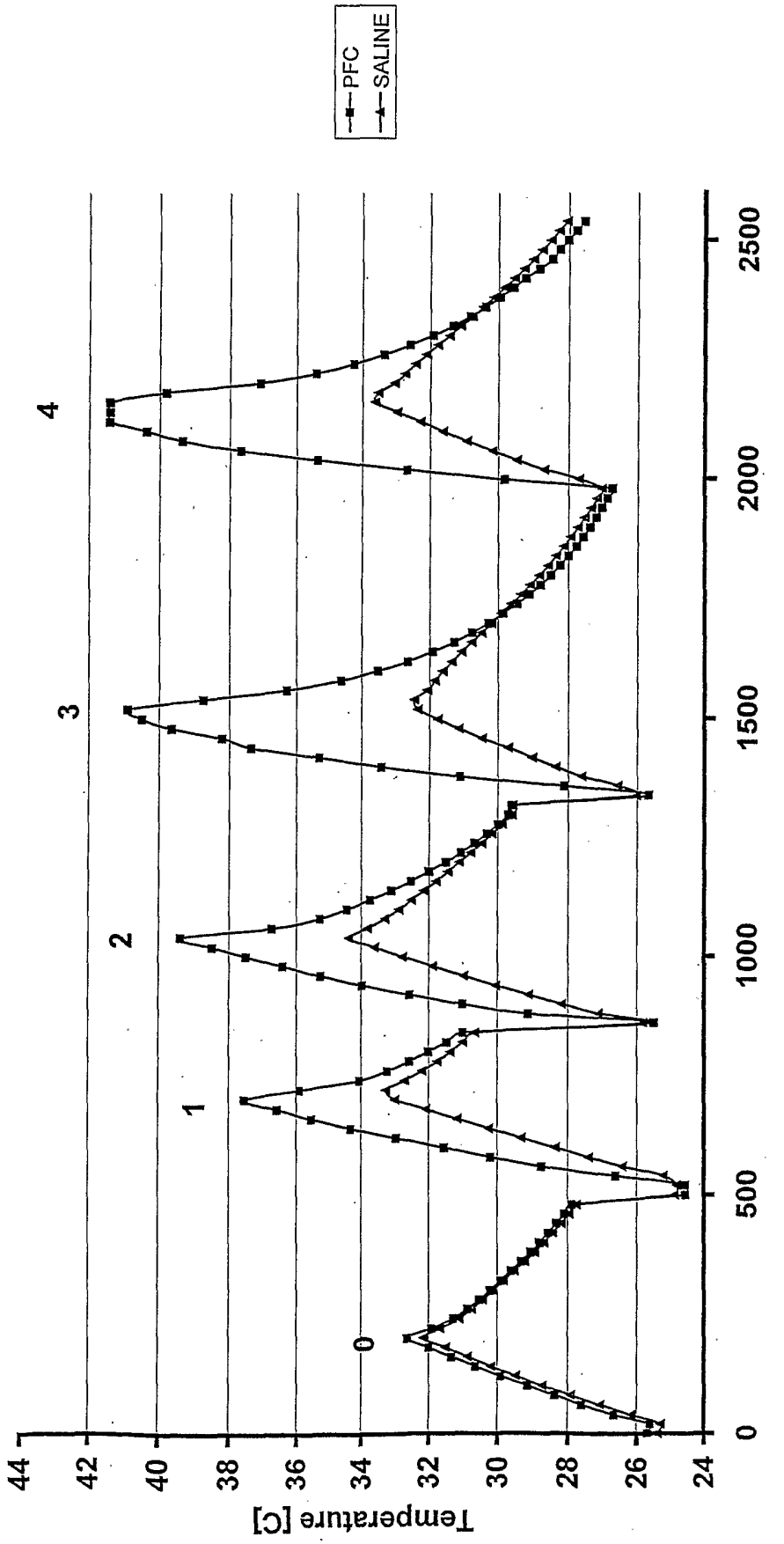
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FIGURE 1

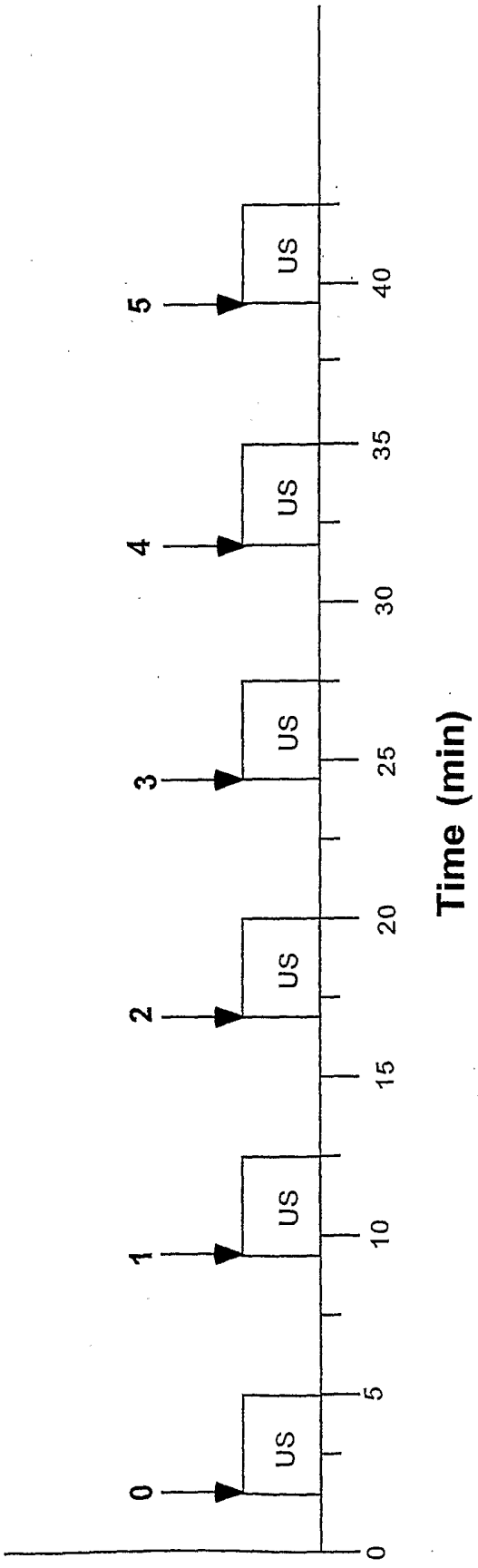

FIGURE 2

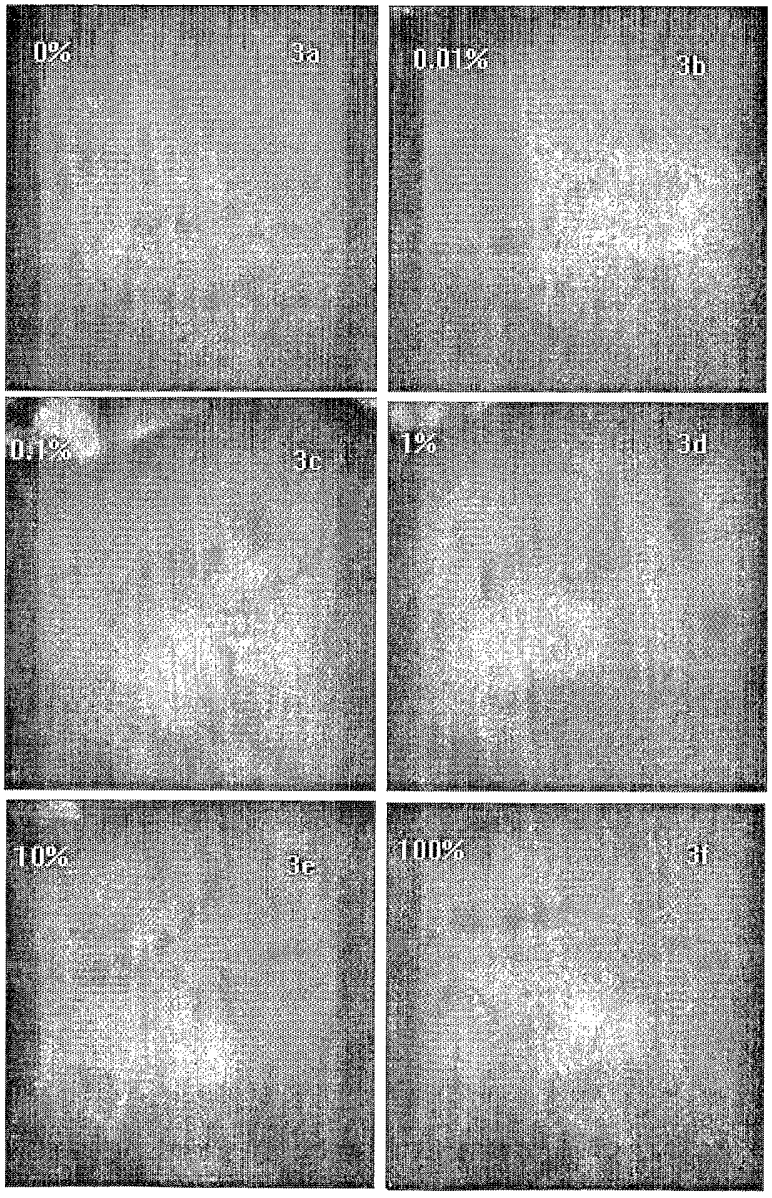

FIGURE 3