BSD-2000 Hyperthermia System

Hyperthermia: another weapon in the fight against cancer

What is Hyperthermia

The BSD-2000 Hyperthermia System is used to deliver therapeutic heating (hyperthermia) to cancerous tumors using radiofrequency (RF) energy. During treatment, the cancerous tumor is heated to fever temperature (39°C -45°C). Hyperthermia damages cells in solid tumors without damaging surrounding healthy tissues. Higher temperatures selectively damage hypoxic and have low pH, a condition of necrotic tumor cells. Hyperthermia has been shown to inhibit cellular repair mechanisms, induce heat-shock proteins, denature proteins, induce apoptosis, and inhibit angiogenesis.

Hyperthermia and Radiotherapy

Hyperthermia increases the effectiveness of radiation therapy due to the independent cytotoxic effects of hyperthermia combined with its radiosensitizing effects. Hyperthermia increases blood flow, resulting in improved tissue oxygenation and thus increased radiosensitivity. Hyperthermia also interferes with cellular repair of the DNA damage caused by radiation. Hyperthermia damages hypoxic cells, cells with low pH and those damaged by radiation during the S-phase of division All conditions that make cells resistant to radiation therapy. The addition of hyperthermia does not usually increase the toxicity of radiation therapy.

Indication for Use

Humanitarian Use Device. In the U.S., the BSD- 2000 has a Humanitarian Device Exemption (HDE) approval for use in conjunction with radiation therapy in the treatment of cervical carcinoma patients who would normally be treated with combined chemotherapy and radiation but are ineligible for chemotherapy due to patient-related factors. The effectiveness of this device for this use has not been demonstrated.

What is Deep Regional Hyperthermia?

The BSD-2000 provides deep regional therapeutic hyperthermia to solid tumors by applying radiofrequency (RF) energy at an adjustable frequency range of 75 to 120 MHz. RF energy is delivered to the tumor site using a power source and an array of multiple antennae that surround the patient's body. The BSD-2000 is designed to provide an optimized heating zone targeted to the tumor region by utilizing the adjustment of frequency, phase, and amplitude from multiple power sources. The energy can be focused electronically to the tumor region, thus providing dynamic control of the heating delivered to the tumor region during treatment.

BSD-2000 Hyperthermia System

BSD-2000 System Description

The BSD-2000 consists of four major subsystems.

- RF power delivery subsystem.
- Proprietary, thermistor-based, thermometry subsystem.
- Monitoring and control subsystem.
- Applicator subsystem that includes an applicator and patient support system.
- Various accessories, including a tissue equivalent QA lamp phantom that provides verification of the energy focus, pattern steering, and system operations.

The BSD-2000 comes in two configurations, a standard power system that has a maximum power output of 1300 watts and an upgraded higher power system BSD-2000 3D that has a maximum power output of 1800 watts.

Power Delivery Subsystem

- Solid-state amplifier with 4-channel independent phase and amplitude adjustment capability.
- Maximum power output of 0 to 500 watts per channel.
- Phase accuracy within a 10 degree tolerance.
- Computer automatically monitors and controls forward and reflected power, phase, and power on each channel.
- Optimized treatment settings are calculated through the use of treatment planning software tools provided with the system.

Thermometry Subsystem

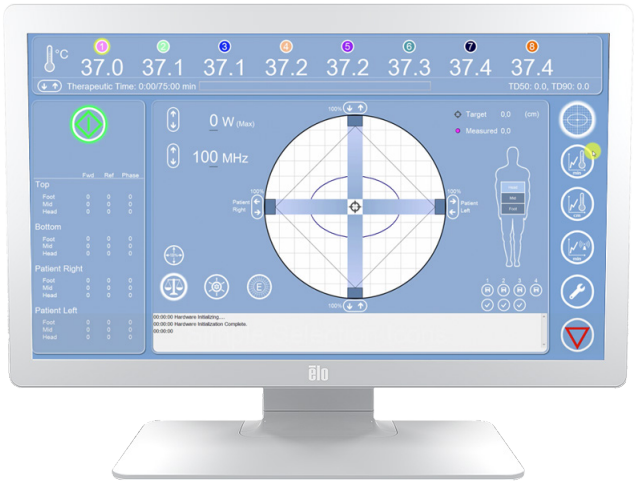
- Non-perturbing, electromagnetically insensitive, temperature sensors with an accuracy of ±0.2°C.

Amplifier

Sigma Treatment Base Unit with Applicator

Applicator and Patient Support System

- Optimized power coupling.
- Optimized patient comfort.
- Water system automatically fills the bolus and controls the bolus water temperature.
- Fabric sling comfortably supports patient inside the applicator.
- Easy patient access and handling.
- Quick drain capability allows fast access to the patient – 15 seconds for patient access and 30 seconds for a complete drain.



Computer System

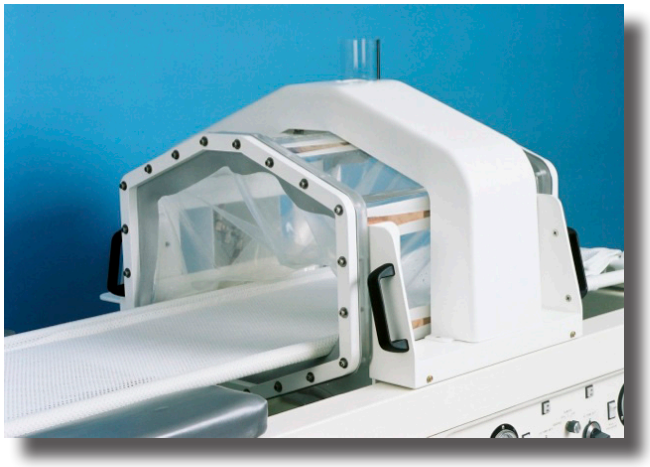
Computer Control System

- User friendly, intuitive, color graphics interface.
- Step-by-step guide for setup and treatment procedure.
- Icon selectable adjustments of the treatment parameters.
- Tabs allow operator to easily switch between screen displays.
- Closed -loop feedback system provides automatic monitoring and control of treatment parameters, including power output, frequency, amplitude and phase, tissue temperatures, core temperature, and treatment time.
- System automatically records, displays, and prints patient treatment data.
- Control of power and tissue temperature to within ±0.1°C.
- Data regarding temperatures, RF power level, and RF power control updated every 2 seconds.
- Control algorithms smoothly adjust heating and cooling rates.
- The system controls the applied power level in accordance with operator inputs and automatically adjusts the level of power to maintain the operator selected temperatures throughout the treatment.
- The computer automatically performs numerous safety checks to ensure proper operation of the system and ensure safety for the patient and the operator.

Applicator Subsystem

The Sigma applicators (Sigma 60 and Sigma Ellipse) are annular phased array applicators that are comprised of a clear plastic shell, 8 radiating dipoles, and a bolus membrane. The Sigma 60 uses a cylindrical shaped plastic shell to support the 8 radiating dipoles. The Sigma Ellipse is an elliptically shaped plastic shell used to support the same components used in the Sigma 60. The Sigma Ellipse provides improved comfort for smaller size patients.

Sigma 60



Sigma Ellipse

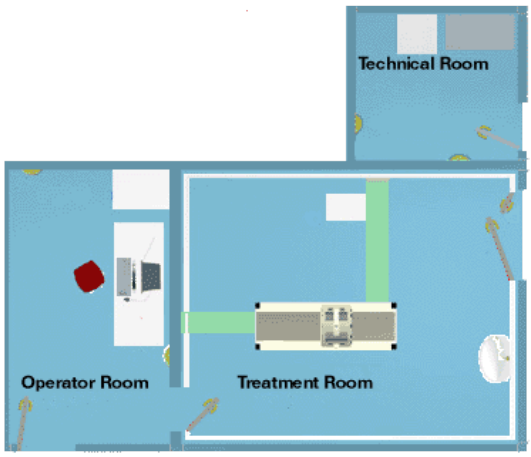
- Advanced annular phased array principles create a central focusing of energy, which significantly overcomes the penetration losses of the energy radiated into the body.
- Phased array applicators allow the operator to shape the heating pattern to the targeted treatment area and achieve selective power targeting at depth for treatment of deep tumors.
- Dipoles are covered by a thin dielectric layer to prevent contact with the bolus water.
- Water filled bolus dielectrically loads the individual antennas and provides an energy-confining medium that directs the RF energy into the body.
- Quick and easy patient setup.
- Plastic shell provides a clear view of the patient's surface to allow visual verification of the applicator positioning and to facilitate monitoring of any skin color changes, which would be indicative of surface hot spots.

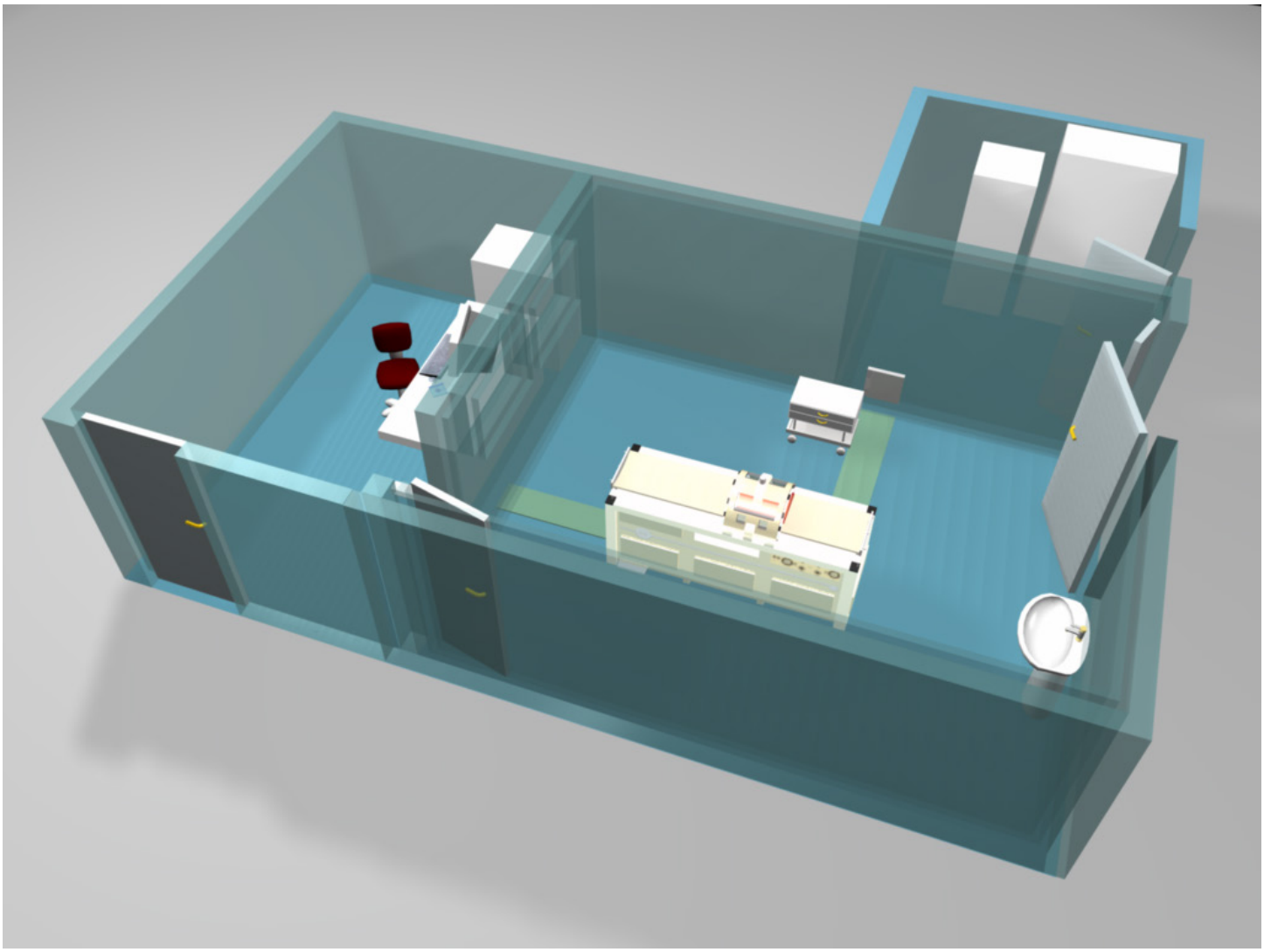
Site Planning

An enclosed RF shielded treatment area (not supplied by BSD as part of the BSD-2000) is required for use with the BSD-2000 in order to comply with FCC regulations. A standard hyperthermia treatment area consists of an RF shield enclosed treatment room (which contains the patient interface components), the operator room for installation of the RF power generator.

A standard hyperthermia suite consists of the treatment room, the operator room, and a small technical room. For convenient patient handling, the treatment room is equipped with electromagnetic shielding and typically requires floor space of 142.5 square feet. The adjoining operator room requires floor space of 78 square feet and an observation window looking into the treatment room. A small technical room of 34 square feet is required for installation of the amplifier.

Our site-planning specialists will be happy to assist you in finding the ideal layout for your environment. The installation manual includes specifications for building services, electricity, air conditioning, and other relevant factors.





Clinical Studies

A Phase III randomized study was conducted at Erasmus Medical Center – Daniel den Hoed Cancer Center (DHCC), Rotterdam, The Netherlands, to compare hyperthermia (HT) and radiation (RT) to RT only treatment of 65 advanced cervical cancer patients, referred to as the BSD Intent-to-Treat ("BSD ITT") population. 33 patients were randomized into RT combined with HT and 32 were randomized into RT alone. All patients had prognostic indicators that are associated with a poorer outcome for cervical cancer. The study met its primary endpoint of a 20% increase in complete response rates for cervical cancer patients receiving HT and RT as compared to RT alone. (Complete response [CR] was defined as disappearance of all viable tumor in the irradiated volume.) These data were a subset of the Deep Dutch Hyperthermia Trial data that were published in The Lancet. (Van der Zee J, Gonzalez-Gonzalez D, Van Rhoon GC, et al. Comparison of radiotherapy alone with radiotherapy plus hyperthermia in locally advanced pelvic tumours: a prospective, randomised, multicentre trial. Lancet 2000;355:1119-1125.)

The addition of HT to RT demonstrated a statistically significant improvement (p=0.006, Fisher exact test, BSD ITT Population) in local tumor control for cervical cancer. The CR rate for RT+HT was 88%, whereas it was 56% for RT. In the BSD ITT population, 14/33 (42%) of the RT + HT patients and 18/32 (56%) of the RT patients died prior to three years.

For the BSD ITT population, 29/33 (88%) of the RT+HT arm had CR, as compared to 18/32 (56%) of the RT arm with a CR, for an odds ratio=0.1773 (95% confidence interval 0.0504, 0.6235) and the difference between treatments was statistically significant (p=0.006, Fisher exact test). This result corresponds to a much lower failure rate in the RT + HT subjects.

The median survival times were 31.7 months for the RT + HT group and 23.2 months for the RT group. The addition of the HT increased the survival time by 8.5 months. Even though there was a trend towards increased survival for the patients treated with the BSD-2000, the difference was not statistically significant (p=0.71, log rank survival) for the BSD ITT Population. However, this lack of significance may be due to relatively low patient numbers, together with the high long-term mortality rate generally seen in patients with advanced cervical carcinoma.

The side effects observed in the pivotal study were generally self-resolving or managed conservatively. There were no unanticipated safety considerations reported from the pivotal study. There was no difference between the RT arm and the RT+HT arm for side effects. Twelve year follow-up data demonstrated that side effects for HT were few and generally self-resolving and mild for the study patients. There were no severe or unexpected toxicities or late effects that were attributed to the BSD-2000 treatment from the pivotal study

Restrictions

Federal (U.S.A.) law restricts this device to sale by or on the order of a physician trained in the use of this device.

The BSD-2000 System is to be used only by qualified operators upon the prescription and under the supervision of a physician who is experienced in clinical hyperthermia.

See **BSD-2000 Essential Prescribing Information** for complete information on the indications for use and side effects.

Indications and Use of the BSD-2000 Deep Regional Hyperthermia System

The BSD-2000 Deep Regional Hyperthermia System delivers therapeutic heat (hyperthermia) to certain solid tissue tumores by application of electromagnetic energy, and monitors the temperature of target and surrounding tissues by means of non-invasive and invasive temperature probes. In response to an operator-designated control probe, the BSD-2000 Hyperthermia System automatically adjusts power to maintain the operator-set therapeutic temperature, which typically is 42-44°C. The BSD-2000 Hyperthermia System also automatically limits power to prevent any detected temperature from exceeding the operator-set maximum, which cannot be greater than 59.9°C.

Tissue absorption of electromagnetic energy causes heating by molecular excitation. Living tissue dissipates accumulated thermal energy principally through transport by blood perfusing the tissue. Solid malignant tumors of significant size have less blood perfusion than surrounding normal tissue. For a given absorbed thermal dose, the reduced ability to dissipate heat causes tumor tissue to reach higher temperatures than normal tissue. Therefore, absorbed electromagnetic radiation will preferentially heat tumors present in normal tissue and cause them to reach higher temperatures than the normal surrounding tissue. Tumors heated repeatedly to higher temperatures (hyperthermia) for times approaching an hour sometimes exhibit regression and necrosis [Song, C.W., "Physiological Factors in Hyperthermia of Tumors" in Physical Aspects of Hyperthermia, G.H. Nussbaum, ed. American Institute of Physics (American Association of Physicists in Medicine, Medical Physics Monograph No. 8). New York, NY: 1982, p.43].

The BSD-2000 Hyperthermia System consists of the following components:

(1) A set of microwave applicators for deep regional application, as listed in the following table, where "MHz: signifies Megahertz and :W" signifies Watts:

Applicator Type	Model Number	Ranged Freq (MHz)	Per chan/ Power(W)
4-channel applicator	Sigma Ellipse	75-120	80
60cm 4-channel applicator	Sigma 60	75-120	80

(2) A set of non-perturbing, electromagnetically insensitive temperature probes.

(3) An operator console containing computer controls to obtain and display data from the temperature probes and to condition the power output of the applicators, and means to display and record relevant patient treatment parameters.

(4) Various accessories, including blind-end catheters for the insertion of probes, thermal well for probe calibration, probe driver for temperature mapping, patient sling a radiation leakage monitor, and various patient equipment and support.

INDICATIONS FOR USE

This device is indicated for use in conjunction with radiation therapy for the treatment of cervical carcinoma patients who normally would be treated with combined chemotherapy and radiation but are ineligible for chemotherapy due to patient related factors.

PROCEDURE FOR ADMINISTRATION OF HYPERTHERMIA IN CONJUNCTION WITH IONIZING RADIATION THERAPY

The standard therapy regimen for hyperthermia in conjunction with ionizing radiation therapy is a total of 10 hyperthermia treatments delivered two times per week at 72-hour intervals, with each heat treatment preceded or followed by a standard prescribed dose of ionizing radiation within 30 minutes of the heat treatment. During each heat treatment, an intra tumoral temperature of 42.5°C sustained for 60 minutes, or the equivalent thereof, entire course of treatment is 600, expressed in Thermal Equivalent Minutes (TEM) equal to 42.5°C, as calculated during treatment by the BSD-2000 Hyperthermia System.

Because the patient's ability to detect pain is an essential safety mechanism, hyperthermia is contraindicated in patients whose pain response has been significantly decreased by any means (previous surgery or ionizing radiation therapy, regional or general anesthetic, or other condition).

Since excessive heating of normal tissue is prevented by normal blood perfusion, it is imperative that adequate circulation be present and maintained in all tissues within the heating field. Treatment with the BSD-2000 Hyperthermia System is contraindicated in patients having known decrease in circulation in the heated area produced by any means (i.e., vasoconstrictive drugs, DIC, ischemia or other cause).

Because electromagnetic radiation from the applicators of the BSD-2000 Hyperthermia System may interfere with the operation of an electronic device, hyperthermia treatments are contraindicated in patients with cardiac pacemakers.

RESTRICTIONS

The sale, distribution, and use of the BSD-2000 Hyperthermia System are restricted to prescription use.

The BSD-2000 Hyperthermia System is to be used only by qualified operators upon the prescription and under the supervision of a physician who is experienced in clinical hyperthermia.

WARNINGS

Hyperthermia treatment can be safely and effectively administered only after careful placement of temperature probes as described in the Reference Manual and with alert monitoring of tissue temperatures during treatment.

Hyperthermia treatment presents a potential safety hazard in patients whose pain response has been decreased because of disease, previous surgery, ionizing radiation therapy, chemotherapy, or general or regional anesthesia.

The electromagnetic energy from microwave applicators may interfere with the operation of the cardiac pacemakers or other implanted electronic devices.

Large thermal doses (a continued elevation of moderately high temperature or a short extreme elevation of temperature) in normal tissues situated in the vicinity of the treated tumor or between the tumor and the body surface may result in regions of thermal aseptic necrosis that require medical intervention and that may not be apparent on inspection of the skin.

PRECAUTIONS

Adhere to recommended procedures for temperature probe placement and selection of control probe to minimize the probability of excessive temperature in normal tissue or of inadequate temperature in the tumor.

Observe strict adherence to aseptic techniques during the invasive placement of catheters to avoid localized infections, and instruct patients in the daily care of indwelling catheters and probe sites to prevent sepsis.

To ensure accurate temperature monitoring during treatments, verify calibration of temperature probes daily or as used.

Adhere to recommended applicator placement and bolusing practices to reduce the likelihood of surface burns and blistering from the subsequent delivery of therapeutic heat.

In patients with severely compromised pain response, monitor closely other physiological indicators of excessive heat delivery.

Monitor closely patients with metallic implants (joint prostheses, dental braces, etc.) during treatment because such metal objects may be excessively (and preferentially) heated.

ADVERSE REACTIONS

SIDE EFFECTS Although hyperthermia has the potential for producing a variety of adverse effects, those actually observed have been limited to direct effects of heating upon tissue and indirect effects related to tumor necrosis. Statistical analysis of clinical data obtained in Pyrexar Medical's studies has provided the following approximate figures for hyperthermia in general:

Burns. Patients have experienced in 9.7% of tumor sites studied, surface burns and blistering in the area of the delivery of therapeutic heat by local microwave applicators of the BSD-2000 Hyperthermia System. Adherence to recommended applicator placement techniques and bolusing practices greatly reduces the number of incidents.

Pain. Patients have experienced, in 8.4% of tumor sites studied, localized and temporary pain in the area of, and during delivery of, therapeutic heat by local microwave applicators of the BSD-2000 Hyperthermia System. The use of surface cooling techniques can diminish this pain.

Ulceration. Patients have experienced, in 3.6% of tumor sites studied, ulceration from rapid tumor necrosis following successful hyperthermia treatment with the BSD-2000 Hyperthermia System. Such ulceration may produce both fever through toxemia and patient discomfort through drainage and bleeding. Infection. Patients have experienced, in 1.8% of tumor sites studied, local and systematic infections resulting from the placement of the temperature probes of the BSD-2000 Hyperthermia System and from the ulceration related to rapid tumor necrosis. These infections have generally been local.

POTENTIAL ADVERSE HEALTH EFFECTS OF THE DEVICE

Hyperthermia has the potential for producing the conditions listed below, as a result of the delivery of therapeutic heat or of exposure to electromagnetic radiation. However, none of these adverse reactions was observed during the clinical investigation of local hyperthermia.

Cataracts. Inadvertent heating of the eye may occur during treatment of tumors in the head or neck. A single high dose of microwave radiation or repeated exposure over a long period of time may result in cataract formation which may not be observable for several weeks. [Clearly, S. F., "Microwave Cataractogenesis" in Proceedings of the IEEE 68: 4955.]

Male Sterility. A single high dose of microwave radiation to the testes, or testicular heating for a prolonged period of time, may result in temporary or permanent sterility. [Murca, G.J., E.S. Ferris. and F.L. Buchta. " A Study of Microwave Radiation of the Rat Testis" in Biological Effects of Electromagnetic Waves, C.C. Johnson and M. L. Shore, eds. HEW publ. (FDA 77-8010). Washington, D.C. 1976, pp. 484-494.]

Exacerbation of pre-existing disease. Patients having borderline cardiopulmonary function secondary to coronary atherosclerosis, emphysema, or other conditions, may not be able to tolerate the additional systematic stress of extensive or prolonged hyperthermia.

Enhanced drug activity. Elevated temperatures may be expected to affect the pharmacologic activity of some drugs, with unpredictable results. Altered vascular perfusion may dramatically affect the local tissue effects of systemic or infused drugs.

Thermal Stress. Significantly increasing the core temperature of the body or overheating the thermo regulatory center in the brain my result in thermal stress exceeding the patient's compensatory mechanisms. Reliable prediction of the consequences of thermal stress in patients with cardiovascular impairment is not possible. Signs of consequences of thermal shock or of local brain overheating may appear after several (up to 24) hours.

REFERENCES

1. Song, C. W., "Physiological Factors in Hyperthermia of Tumors" in Physical Aspects of Hyperthermia, G. H. Nussbaum, ed. American Institute of Physics (American Association of Physicists in Medicine. Medical Physics Monograph No. 8), New York, NY:

2 Clearly, S. F., "Microwave Cataractogenesis" in Proceedings of the IEEE 68: 4955.

3. Murca, G.J. E.S. Ferris, and F.L Buchta, "A Study of Microwave Radiation of the Rat Testis" in Biological Effects of Electromagnetic Waves, C.C. Johnson and M.L. Shore, eds. HEW publ. (FDA 77-8010). Washington. DC, 1976, pp. 484-494.

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PYREXAR MEDICAL
1825 West Research Way, Suite E
Salt Lake City, UT 84119 USA

Phone 844-797-3927
www.pyrexar.com

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