Hyperthermia in Extracorporeal Technology

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Abstract
A review of the application of hyperthermia in the treatment of cancer is presented. The definition, historical background, biological rationale, indications and contraindications are discussed. The five basic methods of inducing hyperthermia as well as the five objective therapeutic modalities are reviewed. Hyperthermia for the treatment of cancer applied by extracorporeal circulation either alone or in conjunction with isolated regional perfusion is the specific target of the review. The published results demonstrating hyperthermic therapy as a "detrimental" therapy, an "indifferent" therapy or a "positive" therapy are explored (J. Extra-Corpor. Technol. 21(2): 65-72, 1989, 83 Ref).

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Hyperthermia is defined as: 1) an excessively high fever or 2) the treatment of disease by the induction of fever as by the inoculation with malaria, by injection of foreign proteins, or by some other physical means. We, as perfusionists, are certainly keen on the thermal concept of hypothermia; however, opposing this is hyperthermia.

The use of heat to treat disease is a therapeutic concept embraced and rejected by the medical community since the days of ancient Greece. The great physician Hippocrates is quoted from Aphorism 87: "Those diseases that medicines do not cure, iron cures; those that surgery cannot cure, fire cures; those that fire cannot cure are to be reckoned wholly incurable."

Certainly "fire" may have been one of the few therapeutic alternatives to Hippocrates' surgical "iron," but the concept remains a controversy today. Ramajamma in 2000 BC used red hot irons to treat tumor growth with suggestions of some degree of "success". The medical literature abounds with anecdotal material about tumor patients who experienced healing after having a high fever with an unrelated illness. Busch in 1866 reports the appearance of peripheral sarcoma regression in a patient suffering from a prolonged fever. Coley in 1893 reported anti-cancer effects of bacterial stimulants with the most notable manifestation being a fever. In 1927, he used "toxins" to stimulate febrile reactions yielding temperatures of 39 to 40 degrees Centigrade for several days implying that the fever was a tumoricidal agent by yielding several years of disease-free survival in one-third of the inoperable carcinomas and sarcomas he treated. In 1898, Westermark used hot-water circulating cisterns implanted in utero and demonstrated uterine cancer regression. Warren in 1933 was the first to apply heat via an infrared source with high frequency current and demonstrated neoplastic remission. Stehlin in 1957 began isolated limb perfusions using a nitrogen mustard agent melphalan and later increased muscle temperatures to 40 degrees Centigrade to demonstrate that tumor temperatures would increase 3 to 7 degrees Centigrade more. Whole body hyperthermia was first documented as a safe method in 1974. Since then several methods of inducing systemic hyperthermia have evolved. In 1979, Parks and associates documented the treatment of advanced malignancy by extracorporeal hyperthermia.

Fever is frequently thought synonymous with "brain damage." Extensive psychological and physiological testing has demonstrated no indication of cerebral cell death, seizures, memory loss, impairment of arithmetic ability or abstract thought or change in IQ. Extensive studies on the thermal tolerance of normal tissue generally recommends maintaining normal tissue temperatures between 41.5 and 43.5 degrees Centigrade. The optional levels of thermal maintenance have not been established. Temperatures in excess of 43.5 degrees Centigrade lead to a reduction in muscle high energy compounds with a concurrent increase in lactate production. The lactic acidosis...
causes a reduction in osmotic resistance of the erythrocyte and subsequent destruction. Neoplastic cellular thermal sensitivity doubles with each centigrade increase in temperature. Such extreme temperatures establish a need for extensive and sometimes redundant thermal monitoring to minimize complications. Heat itself is damaging to normal and tumor cells. Thermal damage is a function of both the heat absorbance of the tumor and the duration of the treatment. It is the object of thermal therapy to achieve cytotoxic temperatures within the tumor for a sufficient length of time without damaging the surrounding normal tissue. This "time-temperature" relationship encompasses the "thermal-dose" concept which is useful for planning treatments and comparing responses of patients and is currently under wide study. Detailed studies have investigated the mechanisms of hyperthermic action on biological systems, however the critical target or targets for its cytotoxicity and sensitization of radiation and drug response remains unknown. The use of hyperthermia in the treatment of cancer is based on a strong biological rationale which has been extensively reviewed. In summary, hyperthermia: (1) kills cells exponentially as a function of the time at temperatures above 42 degrees Centigrade due to the tumor's underdeveloped vascularity and inability to shed heat; (2) selectively kills S-phase and other radioresistant cells such as hypoxic tumor cells, which are also nutritionally deprived and often at a low pH due to the accumulation of lactic acid secondary to its hypoxic nature; (3) interacts synergistically with ionizing radiation; (4) interacts synergistically with certain chemotherapeutic agents; (5) limits vascularization and hemoconcentration; (6) is more effective when combined with radiation, chemotherapy, and surgery. Although heat by itself is cytotoxic, hyperthermia is used most often as an adjunct to other types of treatment.

There are five basic methods to induce hyperthermia: electromagnetic techniques, ultrasound, radiant light, thermal conduction, and extracorporeal circulation. The electromagnetic techniques have been widely used and are by far the most common. These methods have the ability to heat as deep as twenty centimeters. They are well tested, provide moderate focusing and allow only moderate interaction between differing tissues and the electromagnetic field, except for the excess heating of the surface fat layers and some bone absorption. Ultrasound methods have the advantage of increased depth with more highly focused heating than electromagnetics. This precision can be difficult to steer properly, since the heat patterns generally form an oblique ellipsoid with the long axis along the depth direction. Ultrasound techniques reflect on bone and air and cause some skin burning.

The method of radiant light is very simple to use and devices are simple to build; however, the penetration depth is limited to about three millimeters, which is not useful for most localized tumor sites. Thermal conduction also is simple in principle but only penetrates two millimeters into the tissue. This method requires uniform contact of tissues to a hot surface.

Extracorporeal circulation is the most invasive of the thermal therapies. Significant vascular access is needed to provide inflow and outflow for the system, systemic heparinization is necessary, hemodilution or the possible administration of blood products is unavoidable, and a team of individuals are required to provide the essential anesthesia, surgical access, and support of bypass. The costs are increased significantly thus making this approach less desirable.

The modalities of hyperthermia can be classified into five basic areas: deep-regional hyperthermia, superficial hyperthermia, interstitial hyperthermia, body orifice insertion hyperthermia, and whole-body hyperthermia. Deep-regional hyperthermia implies depths greater than five centimeters and has generally been performed using electromagnetic fields or ultrasound. This technique attempts to place a large deep heating field at the tumor site but it frequently heats surrounding tissues as well. The challenge with this modality of hyperthermia is to obtain sufficient depth and adequate localized heating in the full tumor volume with minimal heating of the surrounding tissues. Superficial hyperthermia has gained a much wider acceptance by clinicians. This modality involves the heating of body tissues from the surface of the body down to as deep as five centimeters. Generally electromagnetic fields have been used to accomplish this type of hyperthermia. Interstitial hyperthermia is also gaining increasing acceptance. This treatment modality involves placement of heating devices directly into the tumor. Most interstitial hyperthermia has involved the electromagnetic heating technique. The popularity of this modality has increased as

Many authors report a multitude of neoplasms responding to hypertherapeutic therapy. Those tumors include osteosarcomas, malignant fibrous histiocytomas, adenomas, fibrosarcomas, giant-cell sarcomas, malignant melanomas, liposarcomas, malignant schwannomas, leiomyosarcomas, and many more. Researchers have noted not only tumor response to hyperthermia, but pain relief as well. Wile reports a significantly greater response in pain relief than tumor response. Others have gone so far as to describe "thermal induced" increased plasma levels of opiate peptide beta endorphins.

Patients are candidates for hyperthermic therapy if their cancer resists standard therapy or it exists with no standard regime for treatment. The limiting organs in hyperthermia are the heart and liver. The heart must be able to meet the increased metabolic demands and the liver is sensitive as demonstrated by the measurement of serum enzymes.

II. Method to Employ Hyperthermia

Most recently hyperthermia has been added to the list of cytotoxic therapies for the treatment of cancer which includes radiation, chemotherapy, and surgery. Although heat by itself is cytotoxic, hyperthermia is used most often as an adjunct to other types of treatment.

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interstitial radiation therapy has become more widely practiced, since the needles or catheters used for the interstitial radiation therapy implant provide access portals for the hyperthermia applicators. The strong appeal of interstitial therapy is that the heating occurs primarily within the tumor volume. This enables higher tumor temperatures with lower normal tissue temperatures. Hyperthermia has also been accomplished by inserting heating devices into natural body orifices containing malignant growths. Electromagnetics has been the most common method for introduction of hyperthermia into these areas, though some have tried heated irrigations for bladder cancer. The rationale for this modality is much the same as in the interstitial techniques; even in deep sites, the heating can be localized to the tumor and heating of normal tissues can be avoided. A variation of this modality is peritoneal hyperthermia. It involves cannulation of opposite sides of the peritoneal cavity providing inflow and outflow for warm perfusate which consists of some isoelectrolytic solution.

Whereas local therapy may be used in isolated tumor sites, metastatic disease requires a systemic approach. Whole-body hyperthermia techniques include: immersion of the body in molten wax, hot water or hot air, thermally-controlled water circulating suits or blankets and extracorporeal circulation. Whole-body hyperthermia has as a theoretical goal, the elevation of the entire body to a uniform raised temperature. This is generally accomplished by thermal conduction, radiant light techniques, or extracorporeal circulation. Often this includes the thermal isolation of the body surfaces from the surrounding air.

Reports of using a radiant heat device demonstrate no significant "clinical toxicity," and no need for clinical intervention. Robins reports the device to be safe, efficient, and not labor intensive. He reports twelve patients with no general anesthesia or endotracheal intubation, but others report transient side effects including fatigue, hypotension, nausea, vomiting, and diarrhea.

Though no particular form of whole-body hyperthermia system has necessarily emerged as the dominant technique, extracorporeal circulation boasts the advantages of a rapid rate of heating and cooling, ease of control, avoidance of skin injury by burn, maceration, or pressure, and most of all, the patients remain accessible for ordinary care.

III. Hyperthermia by Extracorporeal Circulation

Utilizing extracorporeal circulation to deliver hyperthermia came not in the simplicity of that modality but by the ability to deliver high doses of cytotoxic chemicals to an isolated extremity: isolated regional perfusion. A 1950 study by Klopp documented that reduced tumor size occurred when small doses of nitrogen mustard were injected into tumor supplying arteries. He also notes that blocking the venous return from the area augmented tumor reduction. A study by Creech demonstrated limb isolation by an external tourniquet while sustaining circulation by means of extracorporeal circulation as he perfused the limb with high doses of L-phenylalanine mustard (L-PAM or Melphalan). This allowed the ability to administer the drug continuously at higher doses than could be tolerated systemically. Ten years later, Stehlin modified this technique by adding heat on the basis of the concurrent work by others who described marked tumor reduction of some neoplasms by the use of only hyperthermic blood. In the past, treatment for malignant neoplasms of the extremities have been associated with a high incidence of local or regional recurrence. The prognosis for recurrent in malignant melanoma is extremely grave. McNeer and others have reported a five-year survival rate to be between 14 and 20 percent. Treatments for both high risk and recurrent malignant melanoma of the extremity have included radical amputation, wide excision, and systemic chemotherapy with disfiguring results, major side effects, and no significant prolongation of life.

An ideal treatment for patients who have malignant disease confined to an extremity could then be isolated regional perfusion especially after unresponsive treatment with various antineoplastic agents. The aim of isolated regional perfusion is to achieve a high drug concentration in the target tissues maximizing tumor cell kill without producing serious systemic side effects in those organs not affected by cancer. When hyperthermia is combined with isolated regional perfusion, there is even greater cell kill and better results may be achieved.

Some have reported the use of extracorporeal circulation for the administration of hyperthermia without the use of antineoplastic agents. This has a reported benefit of providing systemic tumoricidal ability necessary for a tumor response without chemotherapeutic side effects. The only tumoricidal agent is the heated perfusing blood. Parks reports the technique of using a 100 centimeter loop of eight millimeter woven dacron graft anastomosed end-to-side to the common femoral artery and vein as a high flow shunt. As extracorporeal access, he exposes ten centimeters at a treatment, inserts an appropriate femoral cannula to provide circulatory assist with hyperthermia for four to six hour treatments. Koga states good response but no change in survival on seventeen patients with extracorporeal circulation induced hyperthermia for far-advanced gastro-intestinal cancer. Yokayama utilizes extracorporeal circulation induced hyperthermia for the treatment of pelvic tumors.

The majority of the literature reports the use of hyperthermia with extracorporeal circulation in conjunction with isolated regional perfusion. Cavaliere suggests better results utilizing the synergistic combination of heat and drugs. With hyperthermic extracorporeal circulation alone, he reports a 25 percent five year survival. Using amputation in conjunction with hyperthermic extracorporeal circulation, the five year survival improves to 50.9 percent. When hyperthermic isolated regional perfusion is used he reports a five year survival of 71.4 percent. Ghussen reported a prospective randomized study of 107 human patients with a highly significant difference (p = 0.0001) in hyperthermic isolated regional perfusion versus wide surgical excision alone.

Hyperthermic isolated organ perfusion has shown some
promise. The organ studied most and perhaps currently affected most by cancer is the liver. Several authors are reporting experience and success in regional chemotherapy of the liver. Some authors feel that isolated liver perfusion is better at least in animal models than whole-body hyperthermia. Vascular isolation certainly entails a much more complicated operative procedure than by systemic extracorporeal circulation. The use of hyperthermic isolated regional perfusion is not different than other forms of extracorporeal circulation with respect to certain basics of quality perfusion. The patient must be systemically anticoagulated with heparin at 300-400 IU per kilogram body weight before any form of extracorporeal circulation begins. Frequent monitoring of the anticoagulation level is necessary considering the hyperthermic state. An observance of a ten degree water to blood gradient should be maintained when warming the patient to the target temperature. Frequent blood gases may be necessary in whole-body hyperthermia and of lesser importance in isolated regional perfusion.

Studies have demonstrated the importance of maintaining a mean pressure in the isolated limb less than the mean arterial systemic pressure reducing leaks of the toxic chemotherapeutic agent. Since the clinician may not administer vasoactive drugs to control the limb arterial pressure, a perfusionist must rely on flow. Target flow rates should be 100-200 cc's per minute for the upper extremities and 150-250 cc's per minute for the lower extremities. Hyperthermia may lead to a compensatory vasodilatation that may require flows on the upper limits of normal. Limb pressures should be maintained to within 15 mmHg of that of the mean arterial pressure to assure adequate tissue perfusion. Transcutaneous oxygenation monitors have been shown to be a tool that reflects adequate muscle perfusion in the isolated limb.

No matter what the method of hyperthermic therapy used, diaphoresis causes large fluid losses from the patient. As body temperature rises, systemic vasodilatation occurs increasing volume uptake by the patient. This factor necessitates fluid replacement and electrolyte monitoring to compensate for the expected loss. Immediate post-treatment chemistries have revealed hypomagnesemia and hypophosphatemia. The catabolic effect of previous anticancer therapy and the nature of the disease process may place the patient in need of plasma protein replacement. Albumin should be used as the protein portion of the prime or replacement fluid during therapy. Herman documents severe generalized edema to be more prominent in a patient whose fluid replacement consisted of a high volume of crystalloid. Patients who were pretreated with colloid solutions and then given smaller amounts of crystalloid during treatment had less edema. His observation occurred irrespective of the method of hyperthermia treatment. He also reports less pulmonary edema when the use of colloid, net lower volumes of crystalloid, and positive end expiratory pressures of 5-10 cm H2O were used.

When utilizing extracorporeal circulation for hyperthermic isolated regional perfusion, generally one of four antiblastic drugs are used. Melphalan (L-phenylalanine, L-PAM, or nitrogen mustard) is the most common and requires temperatures of 40.5-41.5 degrees Centigrade to be activated. The use of actinomycin and imidazole carboxamide (DTIC) has also been shown to have "superimposable results" to L-PAM. More recently, Pommier has demonstrated cisplatin yielded a faster tumor response than melphalan; one to two weeks after perfusion versus four to five weeks.

IV. Results of Hyperthermia and Hyperthermic Isolated Regional Perfusion

Hyperthermia and hyperthermic isolated regional perfusion is by no means a benign therapy. This modality of treatment is a "toxic therapy" with a yet undefined role. A thorough review of the literature demonstrates that melanoma is clearly responsive to isolated regional perfusion and hyperthermia appears to increase that response. Unfortunately, most of the comparisons have been uncontrolled and retrospective subjecting many patients to the rigors of extremes for statistically insignificant results. The conclusions that hyperthermia is a detrimental therapy, an indifferent therapy, or a positive therapy in one form or another have been made.

Wile suggests that in fact hyperthermic extracorporeal circulation actually enhances tumor proliferation. Those studies involved carcinoma in rabbits. Wile recommends the use of local hyperthermia as opposed to whole-body hyperthermia because of results gathered on tumor pH. He feels that a more responsive tumor reaction can be made at higher tumor temperatures. Skibba has demonstrated a cause for thermal toxicity in the human liver. They have shown that proteolysis and lipid peroxidation are two inter-related factors causing heat toxicity.

When utilizing isolated regional perfusion in 158 patients being treated for malignant melanoma of the extremity, Schraffordt found no difference in results perfused in normothermia to those perfused in hyperthermia. Similar results were reported by Martijn in a series of 179 patients.

Positive results are reported more frequently. The salvage of an extremity is a benefit that some authors proclaim. A controversy exists in the reports of prolongation of survival. Cozad, Koops, Hoekstra and others report a significant prolongation of survival, while some report the merits of hyperthermia and hyperthermic isolated regional perfusion as a palliative procedure only. As with all forms of new and experimental therapy, clinicians tend to reserve it for when all other methods of therapy fail. Rege reports positive results using hyperthermic isolated regional perfusion as opposed to conventional surgical therapy and suggests that results are improved in patients under fifty years of age. Hartley feels that early application may be appropriate and the aggressive utilization of this therapy will in fact improve survival. Vaglini reports "impressive" clinical results using hyperthermic isolated regional perfusion, but also demonstrates...
The complications reported are many. Didolkar\textsuperscript{57} reports a significant incidence of deep venous thrombosis. Koga\textsuperscript{49} states a reversible extremity weakness occurs in most of the patients and the technique should be avoided in patients with hepato/renal dysfunction\textsuperscript{48,75}. Konits\textsuperscript{76} reports profound changes in the peripheral degradation of thyroxine persistant for several days after therapy. DeMoss\textsuperscript{15} reminds us of the seriousness that burns represent in our immunosuppressed patients secondary to chemotherapy, radiation, and malignant disease. Macy\textsuperscript{77} reports a possible diffusion barrier created in the lungs by hyperthermia. They reported diminished \( pO_2 \) and elevated \( pCO_2 \) values with no changes in serum chemistries, CBC's, or urinalysis. Stark\textsuperscript{78} reports significantly altered radiographic findings secondary to whole-body hyperthermia. He demonstrates intra- and postprocedural pulmonary edema, cardiomegaly, and pleural effusion in a statistically significant population of patients. Though most demonstrate marked increases in heart rate and cardiac output with no changes on mean arterial pressure, central venous pressure, mean pulmonary artery pressure, or pulmonary artery wedge pressure, Faithful\textsuperscript{79} shows serious cardiovascular complications in his series of thirty patients. He shows impairment of the right heart with elevated pulmonary vascular resistance and central venous pressures.

V. Directions

The raging controversy on the merits and demerits of hyperthermia as a functional therapeutic modality will continue. Modern cancer therapy has included surgery, radiotherapy, chemotherapy, immunotherapy, and hyperthermia\textsuperscript{80}. As neoplastic diseases are heterogeneous with regards to each cell's subpopulation response to a given therapy, a multimodality treatment approach should enhance the chance of all tumor cells being killed. Heat-induced vascular stasis alone may never be efficient enough to eliminate all tumor cells\textsuperscript{81}. Some malignant cells will inevitably have already infiltrated normal surrounding structures and will therefore not be affected by changes in the tumor vascular bed.

The hyperthermia literature is fraught with inconclusive data and is somewhat conflicting. It may be disconcerting to be involved in a treatment about which biological behavior and anticipated results are ambiguous. There is a serious need for quality research regarding hyperthermia, hyperthermic isolated regional perfusion and general hyperthermic extracorporeal circulation\textsuperscript{82}. Controlled, prospective, properly randomized studies are important to establish merit.

In the short-term, local-regional hyperthermia will dominate until this modality of treatment gains acceptance. If it does become established, then ultimately whole-body hyperthermia treatments will become more frequent. Cancer is a metastatic disease. Cancer is a disease that predominately involves the entire body, so it only makes sense that the direction is whole-body.

The Acquired Immunodeficiency Syndrome is only a recently recognized disease that is viral in nature. It is characterized by the deregulation of the cell-mediated immune function system and manifested by opportunistic infections and unusual neoplasms in previously healthy people. Late research has demonstrated positive results with hyperthermic isolated regional perfusion for Kaposi's Sarcoma\textsuperscript{83} in this population of patients.

Recent improvements in vascular access cannula and modifications in the extracorporeal circulation systems have allowed "percutaneous" femoral-femoral bypass for support of cardiovascular patients. Extracorporeal circulation can and in fact has been done on awake, alert, pain-free, extubated, talking patients for various cardiovascular procedures while they were ventricularly fibrillating. The simplicity of this technique will surely spill over to hyperthermic extracorporeal circulation.

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