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What is This?
Whole-body hyperthermia: a review of theory, design and application

Roger A Vertrees, Angela Leeth, Mark Girouard, John D Roach and Joseph B Zwischenberger

The intentional induction of elevated body temperature to treat malignant lesions has its origins in the 18th century. The mechanism of heat-induced cell death is not clear; however, heat induces a variety of cellular changes. For heat to exert a therapeutic effect, pathogens (bacteria, viruses, or neoplastic tissues) need to be susceptible within temperature ranges that do not exert deleterious effects on normal tissues. Hyperthermia has been used successfully to treat isolated neoplastic lesions of the head and neck, regional tumors such as melanoma of the limb, and is under investigation as either an adjunct to, or therapy for, locally disseminated and systemic diseases. The clinical utility of perfusion hyperthermia has evolved into three approaches – isolated organ or limb, tumorous invasion of a cavity, and systemic or metastatic spread. When whole-body hyperthermic treatment has been tried, it has been induced in the patient by submersion in hot wax or liquid, wrapping in plastic, encasement in a high-flow water perfusion suit, or by extracorporeal perfusion. Our group has developed an extracorporeal method, veno-venous perfusion-induced systemic hyperthermia, that was used first to safely heat swine homogenously to an average body temperature of 43°C for 2 h. More recently, a Phase I clinical trial has been completed in which all patients were safely heated to 42 or 42.5°C for 2 h and survived the 30-day study period. We have been sufficiently encouraged by these results and are continuing to develop this technology. Perfusion (2002) 17, 279–290.

Introduction

The use of heat to treat disease is not a new concept. In fact, the idea has been around almost as long as recorded history. The very earliest reports, by Hippocrates, were about the use of red-hot irons to treat nonulcerating lesions. More reports on the therapeutic use of heat surfaced after the Renaissance; these reports described the disappearance of tumors in patients who had, for one reason or another, sustained a prolonged elevation of temperature. Coley reported beneficial effects associated with fever induced by injections of Streptococcus erysipelas toxins in humans with cancer. In 1927, Wagner-Jauregg received the Nobel Prize for achieving a 30% remission rate in syphilis patients intentionally infected with Plasmodium falciparum (malaria), which induced a high fever. In 1955, Nauts and Fowler repeated Coley’s ‘febrile therapy’ of earlier years and realized a significant therapeutic advantage in patients with tumors. The therapy was abandoned, however, because of side effects of the inoculations. The mechanism of heat-induced cell death is not clear; however, heat induces a variety of cellular changes. These include changes in the membrane, nuclear and cytoskeletal structures, cellular metabolism, macromolecular synthesis, intracellular signal transduction in hormone–receptor interactions, and expression of the heat shock genes. For heat to exert a therapeutic effect within an achievable dose range, pathogens need to be more susceptible than normal tissues. This range of susceptibility is often called a therapeutic window. The thermal therapeutic window has three measurable borders – maximal and minimal temperatures and duration at the elevated temperature.

Maximal temperature is defined as the point past which living normal nontarget tissue is susceptible to destruction by heat and is 45°C. Core temperatures elevated much above 40°C, however, can have adverse effects as evidenced by elderly patients with heat stroke who survived body temperatures up to 47°C, but with some impairment, manifested as a persistent confusional state. The effect of temperature on the brain of monkeys was studied; it was determined that a brain temperature > 43°C for more than 60 min resulted in irreversible brain damage.
Elevated core temperatures (>43°C) may have detrimental effects, ranging from denaturation of proteins, neuronal damage, edema formation, and hemorrhage to cell death.

The minimal temperature of the therapeutic window falls at the maximum of normal physiologic fever. An elevated body temperature, or fever (between 37.5 and 41°C), does have a beneficial effect on the outcome of infections.13 has been conserved across evolution, and is present throughout the animal kingdom. In order to have a ubiquitous biological presence, fever must play a beneficial role since it extracts a high metabolic cost.14

The duration of the therapeutic thermal exposure ends when target tissue is either destroyed or protected from further thermal destruction, or normal tissue becomes threatened. A normal response of cells to thermal stress is the production of heat shock proteins (HSPs), which act as chaperones and have a protective effect on cellular ultrastructure, shielding essential proteins from thermal disruption.15

Theory for the therapeutic value of hyperthermia

The therapeutic value of heat can be divided into two parts. One value is the beneficial effect on the body, such as enhanced immune surveillance, including increased mobility and activity of white blood cells,16,17 stimulation of interferon production18 (an anti-viral and anti-tumor protein), activation of T lymphocytes,19 and hypoferremia.20

The second aspect of the therapeutic effect of heat is the deleterious effect on the invading agent. Most pathogenic bacteria are mesophiles with a normal physiologic range of 33–41°C.21 When the temperature is elevated, the growth rate decreases,22 autolysis increases,23 mobility is decreased,24 and the cell wall is damaged.4 All of these factors result in an increased inability of the bacteria to prevent environmental insults.

Viruses also show sensitivity to environmental heat. Elevated temperatures result in a large decrease in the propagation of many types of viruses, such as poliovirus,25 influenza virus,26 herpes simplex virus,26 rabies virus,27 and transmissible gastroenteritis virus.28 Additionally, virus-infected cells are more susceptible to destruction from heat; viral budding increases the permeability of the infected cell,29 which can result in an altered intracellular Ca²⁺ level.30–32 Other studies have shown that virally infected cells are more susceptible to destruction due to an accumulation of unintegrated DNA, viral RNA, and protein.33 Other factors related to heat probably play roles in the effect on pathogens as well. Changes in pH, oxygen content, and ionic makeup are just a few of these variables.34

Specific diseases treated with hyperthermia: human immunodeficiency virus (HIV) and tumors

Hyperthermia has been used successfully to treat isolated neoplastic lesions of the head and neck,35 regional tumors such as melanoma of the limb,36 and is under investigation as either an adjunct to,37 or therapy for, systemic diseases.36–40

HIV and hyperthermia. An early study suggested the therapeutic potential of hyperthermia when it was realized that HIV could be inactivated by heat sterilization of 100°C.26 Pasteurization of plasma derivatives subjected to 60°C for 10 h results in a high margin of safety by eradicating infectious agents.41 Other studies have demonstrated that HIV replication is completely inactivated at 56°C after 30 min of exposure.26,42,43 For HTLV-III, it was determined that the rate of thermal decay was consistent with first-order kinetics: 60°C for 32 min resulted in no detectable infectious virus.44 Another purported effect of hyperthermia on the HIV virion is the inactivation of the HIV enzyme reverse transcriptase at 56°C after 30 min.42,44

In cell lines chronically infected with HIV, it was found that response varied with the temperature. Exposure of longer than 15 min at 45°C resulted in 90% of the cells dying, 43.7°C yielded no increase in expression, exposures at 41.6–42.5°C resulted in up to a sixfold increase in activity, and temperatures below this range, but above 37.5°C, led to an 8- to 16-fold increase in viral production.45 An additional aspect that responds to an elevated temperature is the increased activity of the HIV long terminal repeat, resulting in increased transcription of proviral DNA.46 HIV infection of a human T cell line increased the sensitivity of the cell to heat and radiation toxicity.47 At 42.8°C, an increase in viral activity occurred at 25 min (183%); at 75 min of exposure, the activity had returned to baseline values (97%); and, at 135 min of exposure, had declined to only 16% of baseline values.48

The length of time of exposure to the elevated temperatures has a direct bearing on virus production. As the temperature increases, the time needed to inactivate HIV decreases.49 Therefore, the effect of temperature on HIV activity appears to be a function of the thermal dose (Temperature differential × Duration of exposure) delivered to the virion as well as that of an absolute temperature.50
Hyperthermia as a treatment for tumors. The literature suggests that the therapeutic utility of hyperthermia may result from factors that affect tumors at the molecular, cellular, and tissue levels of organization. Perhaps the most fundamental is that of the molecular response — either normal or malignant. Next, the type of cancer cell present (e.g., squamous cell) will govern the cellular response. Finally, the response of the tumor to hyperthermia depends on the size of the tumor, its composition, physical location within the host tissue, and its vascularity.51

At the molecular level, the loss of regulation of cell proliferation, a process thought to be controlled by apoptosis (programmed cell death), may be a contributing factor in cancer.52 Hyperthermia has been shown to be a pathological insult that is a stimulus for apoptosis.53 In cells with irreparable levels of DNA damage (as might occur from hyperthermia), apoptosis is the means of elimination; however, if the apoptotic mechanism is missing or functioning weakly, these cells with damaged DNA may proliferate. Regulatory proteins such as p53, BAX, and Bcl-2 have all shown altered responses in heated cells and have been the subject of a recent review.54 The spectrum of tissue susceptible to apoptosis induction by hyperthermia essentially is similar to that described for radiation and anti-cancer drugs (e.g., rapidly proliferating normal cell populations, lymphoid organs, and tumors).55,56

All mammalian cells respond to heat stress by a rapid synthesis of evolutionarily highly conserved proteins, called HSPs, that confer survival to the heat-stressed cells.54,57,58 resistance to apoptosis,59 and cell death when the HSP is defective or absent.60,61 Therefore, HSPs play an important role in modulating cellular responses to heat shock.60

At the tissue level, blood flow is critical in determining the capability to reach and maintain therapeutic temperatures62 and, therefore, is also critical in establishing the effectiveness of hyperthermia. The temperature within tissue and tumor is, in large part, determined by the blood flow away from the site (increased blood flow, increased removal of heat).62 In general, tumor blood flow rates lie between those of resting peripheral tissues and several highly perfused organs.63 Song et al. have determined that during hyperthermia, the tumor bed does not vasodilate; therefore, blood flow does not increase and heat is retained in the tumor tissue at temperatures that would have caused normal capillary beds to vasodilate.64 Vaupel et al. have determined that even brief periods at 41.5–43°C have been shown to concentrate heat in the tumor as opposed to normal tissue.65

Growth of solid tumors is associated with the incorporation of fluid within the tumor mass as a result of nutrient deprivation, which can constitute up to 60% of the tumor volume. This fluid is deficient in oxygen and glucose, and contains increased concentrations of carbon dioxide and the products of glycolysis, including lactic acid. These necrotic foci are observed in tumors as the radial distance from functioning capillaries increases. Between the nutrient-rich capillaries and the necrotic zone, viable cells reside within a gradient of decreasing oxygen and glucose concentration. The presence of this fluid may be responsible for the large gradient in oxygen, glucose, and pH within the tumor. Under conditions of extreme nutrient deprivation, cell death occurs rapidly at 37°C and even more rapidly at higher temperatures. An increase in the temperature of this fluid may lead to an increase in the hydrostatic pressure due to the increase in molecular motion. When the supply of both glucose and oxygen is reduced sufficiently to bring about a reduction in intracellular adenosine triphosphate levels, cell thermal sensitivity is enhanced markedly.65 Decreasing oxygen and glucose concentration prolongs the cell generation time and causes a redistribution of cells in their cell cycle. As a consequence, the therapeutic anti-neoplastic effect of cell cycle-specific agents may be modified substantially. In addition, local tissue hypoxia may severely limit the toxicity of drugs, the effect of which is mediated by activated oxygen species.66

Clinical design and application of hyperthermia

The clinical utility of hyperthermia can be assessed at levels depending upon the extent of the disease: isolated tumor mass, localized spread, tumorous invasion of a cavity, and systemic or metastatic spread.

For primary and recurrent localized tumors or tumorous masses without localized spread, current methods of hyperthermic treatment include application of heated needles, circulating water baths, radio frequency, electromagnetic waves, and homemade devices often used in conjunction with such chemotherapeutic agents as tumor necrosis factor-α (TNF-α), melphalan, interferon-γ (IFγ), and mitomycin C. Response has varied somewhat according to histology and anatomical site of treatment.35 Shibamoto et al. report using direct intraoperative radiotherapy heating of the pancreas,67 and Matsuda et al. employed an intraluminal heat exchanger for the treatment of submucosal carcinoma of the esophagus with a 3-year survival of 83%.58 Often the goal of this therapy is to gain local control of the tumor through heating and concomitant therapy.

More extensive localized involvement consists of tumors invading an organ or limb where localized
control is questionable. This technique requires cannulation of afferent and efferent vessels, and connection to a venoarterial circuit, with the treated area isolated from the general circulation because the amounts of chemotherapeutic agents administered would otherwise be lethal if released in the systemic circulation. Extracorporeal devices used for this type of intervention are infant oxygenators and heat exchangers with a roller pump. Most centers use a radioactive tracer and Geiger counter to monitor leakage into the systemic circulation. Tumors show various degrees of response, from adenocarcinoma with a 40% complete remission to squamous cell carcinoma with a 7.7% complete remission. The incidence of side effects and severe complications is low, limited only to cutaneous necrosis. Isolated limb perfusion (Figure 1) is a treatment of soft tissue tumors that is restricted to limbs and has enjoyed a measure of success when regional hyperthermic perfusion has been employed. Eggermont et al. used isolate limb perfusion and TNF-α, IFγ, and melphalan for nonresectable sarcomas and achieved a major tumor response in 87% of patients with a 36% complete response and 84% limb salvage rate at 50 months. Recent interest has also been directed toward hyperthermic chemotherapy for either primary or metastatic hepatic tumors. Isolation of the liver is achieved by cannulation through the gastroduodenal artery and an isolated segment of the vena cava and, again, radioactive tracers are used. Libutti et al. achieved 75% incidence of melanoma regression and Alexander et al. achieved a 62% regression using this method.

The newest modality is regional hyperthermia used for metastatic disease confined to either the pleural or peritoneal cavities. This technique is basically a heated lavage of the affected cavity with a crystalloid solution that contains a high concentration of a chemotherapeutic agent. The rationale is, that by using this approach, it should be possible to deliver a higher concentration of the agent to the tumor without the lethal systemic effects. The time of treatment is usually between 1 and 2 h at 41°C. Using an extracorporeal circuit and collapsed lung on the affected side (Figure 2), Matsuzaki et al. had no serious clinical complications in heating the pleural space for 2 h with 43°C saline/cis-platinum solution. They achieved a median survival of 20 months (concurrent control median survival was 6 months). Refaely et al. used this technique in conjunction with maximal surgical debulking for thymic malignancies and realized a survival benefit.

Intraperitoneal chemohyperthermia, another form of regional hyperthermia, is used in conjunction with chemotherapeutic agents such as mitomycin C for treating patients with peritoneal carcinomas. Again, an extracorporeal circuit is used with both inflow and outflow cannulae placed in the operative field after surgical debulking. Loggie et al. used this method in patients with peritoneal carcinomatosis of gastrointestinal origin where the perfusate was heated to 40.5°C for 120 min, which resulted in a 6%
30-day mortality with a 14.3-month median survival (untreated survival for this group is <6 months). \textsuperscript{78} Witkamp \textit{et al.} employed intraperitoneal chemohyperthermia therapy (41°C for 120 min plus mitomycin C and surgical debulking for colorectal carcinomatosis and pseudomyxoma peritonei. They showed a 9% operative mortality and achieved a survival rate (Kaplan–Meier) of 81% at 3 years. \textsuperscript{79,80}

When whole-body hyperthermic treatment has been tried, it has been induced by submerging the patient in hot wax or liquid, \textsuperscript{81,82} wrapping in plastic, \textsuperscript{83,84} or encasing in a high-flow water perfusion suit. \textsuperscript{85} These methods induce hyperthermia by restricting body heat loss and by the application of heat directed from the skin and peripheral tissue inwards to the body core. These methods are associated with heterogeneous heat distribution due to a redistribution of blood flow that favors peripheral tissue in an attempt to shed heat.

A possible alternative method for the inducement of heat to the body is \textit{via} an extracorporeal circuit, and has proved to be a safe and efficient means of manipulating the patient’s blood temperature. \textsuperscript{86} Regulation of blood temperature using an extracorporeal circuit allows for safe and precise control of blood temperatures over a wide range (4–42°C). \textsuperscript{87} During extracorporeally induced hyperthermia, the elevated blood temperatures transfer heat uniformly throughout the body, eliminating the effects of peripheral cooling. In two papers discussing the clinical application of whole-body extracorporeal hyperthermia, the bladder temperature, interpreted as core temperature, was maintained at 42°C for 2 h at high blood flows (1000–1200 ml), \textsuperscript{88} or 42°C for 1 h at low (300–400 ml) flows \textsuperscript{37} using an arterio-venous circuit orientation. In both studies, the patients experienced few adverse side effects. \textsuperscript{88} Parks \textit{et al.} reported on patients with stage III bronchogenic carcinoma who were heated with conventional cardiopulmonary bypass under general anesthesia to an infusion blood temperature of 45°C with a resultant ‘body’ temperature (indwelling bladder temperature) of 41.5–41.8°C. This therapy lasted for 6 h and was repeated at 7-day intervals for four treatments. This group experienced a 64% incidence of an anti-tumor effect defined by histologic study as extensive disruption and necrosis of malignant cells that were attributed to hyperthermia; however, regressions were typically incomplete. The authors suggested that for hyperthermia to be effective against advanced lung cancer, temperatures over 41.5°C must be achieved and maintained. \textsuperscript{89} Frazier reported on 16 patients with tumors in whom 55 perfusion-induced hyperthermia treatments were carried out at 41.5–43°C for 4 h using arterio-venous cardiopulmonary bypass. A mid-esophageal temperature probe recorded their target temperature. The authors concluded that the patients achieved an ‘objective’ regression or stabilization of disease during the period of treatment. \textsuperscript{90} Eisler \textit{et al.} reported on treating 28 cancer patients using arterio-venous cardiopulmonary bypass by elevating their temperature to 41.8°C (esophageal) with few sequelae. \textsuperscript{91}

### The University of Texas Medical Branch whole-body hyperthermia experience

Our investigations into the therapeutic utility of whole-body hyperthermia started with development in a large animal model. The initial animal study was a concept feasibility study aimed at determining: 1) if a therapeutic thermal dose could be delivered; 2) what the maximum safe temperature and time were; and 3) the associated pathophysiology in surviving animals. Heat was delivered by an extracorporeal circuit in an arterio-venous orientation (Figure 3). Systemic anti-coagulation was produced with a constant infusion of heparin titrating the activated clotting

![Figure 3](image-url)

*Figure 3 UTMB arterio-venous hyperthermia in swine. Blood was withdrawn from femoral artery through roller pump into heat exchanger and back to femoral vein. Additional fluids were added through the reservoir. Swine were perfused at 43°C for 2 h.*
time (ACT) >600 s. Temperatures were monitored in the esophagus, rectum, tympanic canals, and bladder; however, the rectal temperature was used to determine both adequacy of heat delivery and duration of the hyperthermic interval. From these experiments, we found that either 43°C for 120 min or 42°C for 180 min resulted in a 60% survival. An additional finding was that, in animals that were heated the fastest, there were less arrhythmias and hypotension. This model needed further refinement because the animals suffered from dysrhythmias and hypotension, tissue temperature heterogeneity (Figure 4), inefficient heating (bone marrow and muscle did not reach the therapeutic window whereas the kidney and brain got too hot), bleeding, electrolyte imbalance, and a death rate that exceeded 30%.

Sufficiently encouraged by these early results, the next set of experiments was designed to eliminate the dysrhythmias and hypotension. The standard thermal dose was 43°C for 120 min. Believing that the arterio-venous shunt might be causing the hemodynamic instability and because neither gas exchange nor cardiac support is necessary, we changed to a veno-venous circuit orientation. Blood was withdrawn from a catheter placed or inserted in the femoral vein, passed through the circuit and heat exchanger, and was returned through a catheter in the jugular vein (Figure 5). Results of these experiments showed that we were unable to eliminate the dysrhythmias and hypotension noted earlier. However, we were able to prevent anuria, severe tachycardia, and significantly reduce end-organ temperature heterogeneity (Figure 6). HSP70 analysis showed a 100-fold increase in heart, lung, liver, kidney, gut, and brain compared to a control sample. This series of animals proved that veno-venous perfusion delivered a more homogenous heating and caused a redistribution of blood flow favoring the thoracoabdominal organs. However, there was still significant bleeding, electrolyte shifts, anuria, hemolysis, destruction of platelet function, and such significant pathological changes of myocytolysis, pyknosis in the adrenals, and focal hemorrhage in the heart and lungs. We termed this technique veno-venous perfusion-induced systemic hyperthermia (VV-PISH).

We designed the next set of experiments aimed at reducing the bleeding and death rate. We used our

![Figure 4](Image)

**Figure 4** Tissue temperature heterogeneity. Graph showing 6°C temperature differential during therapeutic interval – the result of arterio-venous perfusion.

![Figure 5](Image)

**Figure 5** UTMB veno-venous perfusion in swine. Blood removed by roller pump from femoral vein, pumped through heat exchanger into jugular vein and through a catheter directed toward the right atrium. Therapeutic hyperthermic interval was 3 h at 43°C.

![Figure 6](Image)

**Figure 6** Variance in tissue temperature. Graph depicting significantly greater variance in measured temperature sites; occurred when animals were heated with arterio-venous perfusion (p<0.05).
now standard thermal dose (43°C for 120 min) and VV-PISH. We also placed a catheter through the carotid artery retrograde across the aortic valve into the left ventricle to measure left ventricular end diastolic pressure. Since we were monitoring so many temperatures, we decided to create an average core temperature and use this to guide heat transfer (Figure 7). In addition, continuous heparin infusions were replaced with boluses of heparin titrated to maintain the ACT at approximately 300 s; additionally, anti-coagulation was monitored with a thromboelastogram. The anesthesia regimen was changed from halothane to a narcotic-based anesthesia with isoflurane used as needed, fluid delivery was increased (animals were found to be suffering from heat-induced dehydration), and pump blood flow changed from 10 to 30 ml/min/kg. Results from these animals were encouraging: we had significantly reduced tissue temperature heterogeneity (Figure 8), experienced no deaths, and eliminated the problem of bleeding. On the other hand, we were still plagued with dysrhythmias, low systemic vascular resistance, and abnormal electrolyte serum levels.

The next set of experiments was aimed at reducing the amount of electrolyte imbalance we were experiencing by tailoring pump prime solutions by adding Mg²⁺, Ca²⁺, glucose, lidocaine, albumin, and red blood cells in quantities sufficient to normalize these values. Mid-way through these experiments, we became aware of a study on patients with HIV infections who were heated by extracorporeal methods. Ash et al. had integrated a dialysis circuit into the heating circuit (Figure 9). We then employed this device in these study animals. The BioLogic-DT portion of the circuit contains a sorbent suspension and cellulosic plate dialyzer through which blood flows. Within the dialyzer, diffusion causes chemicals to

Figure 7 Profiles of heat transfer. Graph showing VV-PISH heat transfer profiles; temperature of blood out of heat exchanger (HE) is controlled to <46°C; average core temperature does not exceed 43°C.

Figure 8 Tissue temperature profiles of VV-PISH. Graph showing that during therapeutic interval, 75–235 min, all measured temperatures attain therapeutic level; variance <2.5°C.

Figure 9 VV-PISH circuit in swine. This shows a push–pull dialysis circuit added in an anti-parallel configuration. This addition helped to stabilize the animal’s electrolyte shifts during hyperthermia by removing excess amounts of some chemicals and the delivery of other chemicals necessary to maintain homeostasis.
pass from the blood into the sorbent suspension. Inclusion of certain chemicals in the sorbent suspension composition can result in the return of these chemicals to the blood during the procedure. When we used this device in our model, the results were compelling. We no longer had significant electrolyte imbalance (Table 1) and had eliminated much of the hemodynamic instability seen in earlier experiments.97

Our last animal study was undertaken to help develop clinical protocols for surgery, anesthesia, nursing, and perfusion for the expressed purpose of preparation of a US Food and Drug Administration (FDA) Phase I submission. To this end, we used a hyperthermia delivery device developed by HemoCleanse (West Lafayette, IN), which had previously been used to induce hyperthermia in patients with HIV infection in FDA trials. From these animal studies and computer modeling of heat transfer for VV-PISH with FDA approval, the HemoCleanse device was modified for the clinical trial. The following changes were made: increased blood flow rate using a larger bore tubing in the roller pump head; removed the bubble trap and some smaller connectors, thus reducing the resistance to blood flow; and increased the water flow rate and the surface area in the heat exchanger, thus increasing the overall efficiency of the machine.

Development of the concept of target tissue thermal sensitivity was also conducted in tissue culture, focused on defining limits for thermal cytotoxicity in both normal and cancerous cells in vitro. Studies were carried out in a cancer laboratory where human lung cells were heated to 41, 42, 43, 44, and 45°C for 120 or 180 min. In our initial studies, we determined that the maximum safe thermal dose was 43°C for 120 min. In another experiment, which compared thermal sensitivity between cancerous and normal lung cells, we were able to show an increased cell kill in lung cancer cells compared to normal lung cells when exposed to temperatures within the therapeutic window. The mechanism of cell death was determined to be apoptosis – the result of a depressed and delayed heat shock response in the cancer cells.98 Other cell culture work suggests that hyperthermia may influence apoptosis-inducing cell surface receptors, thus initiating cell death.99

We also studied the effectiveness of heat on human lung tumor xenografts in athymic nude mice. Xenograft tumors were produced ectopically or orthotopically by either subcutaneous injection into the back, or endotracheal instillation directly into the lungs. The cells were allowed to establish themselves in the nude mice, where tumor growth occurred in both models. Experiments revealed that 1) when lung cancer cells were preheated, then implanted, cells did not form tumors; 2) subjecting mice with tumors to hyperthermia resulted in a significantly smaller tumor; and 3) the timing between hyperthermia and drug therapy had a significant effect on tumor growth.100

Our next venue was the use of perfusion hyperthermia in an FDA-approved Phase I clinical trial. This initial trial was a Phase I clinical trial of 10 patients with stage IIIIB/IV non-small cell lung cancer and was designed to test safety and concept feasibility in this population of patients.

To qualify for this trial, the patient had to have either failed or refused conventional therapies. We divided the 10-patient cohort into two groups of five patients each. Each group received a different thermal dose. Patients in the first group were heated to 42.5°C and maintained at this level for 120 min by VV-PISH. Patients in the second group were heated to 42°C for 120 min, again with VV-PISH (Figure 10). Percutaneous access of the right internal jugular (3/10) or left common femoral vein for drainage (7/10) and right common femoral vein (10/10) for reinfusion allowed extracorporeal blood flow of 16 ml/min/kg with VV-PISH. Six monitored sites were used to

### Table 1 Blood components

<table>
<thead>
<tr>
<th>Component (normal ranges)</th>
<th>Perfusion only</th>
<th>Perfusion and dialysis</th>
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<tr>
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<td>137</td>
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<td>K⁺ (3.5–5.0) mg%</td>
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<td>Cl⁻ (98–108) mg%</td>
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<td>Ca²⁺ (6–13) mg%</td>
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<td>Mg²⁺ (1.2–10) mg%</td>
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<td>PFH⁺ (5) mg/dl</td>
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*pSig=differences significant (p<0.05) using paired t-test. **PFH=plasma-free hemoglobin.
and somnolence, with full recovery. Average length of hospital stay was 5.4 days. In the second group, by reducing the thermal dose, we were able to reduce the length of stay to 3.6 days, and time to extubation to 6–12 h. All patients survived the 30-day study period, and there were no permanent patient or circuit complications detected. Tumor response for group I patients revealed a 64.5±18% decrease in tumor size in two patients, no change in one, and enlargement in one. Median survival after hyperthermia was 172 days (range 40–271 days). Outcome data for group II are unavailable because the study is still in progress.

We have been sufficiently encouraged by the results of our Phase I trial, which shows that patients with far-advanced lung cancer can safely withstand high thermal doses when it is administered by VV-PISH. However, although it appears that the thermal dose that can be delivered is insufficient by itself to totally eliminate these tumors, it is evident that heat does have a therapeutic effect in some patients. Optimization of this effect is currently not known, but is thought to be in conjunction with other anti-neoplastic strategies. We are currently exploring the therapeutic effectiveness of heat in combination with other anti-neoplastic strategies.

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