Percutaneous Venovenous Perfusion-Induced Systemic Hyperthermia for Lung Cancer: A Phase I Safety Study

Joseph B. Zwischenberger, MD, Roger A. Vertrees, PhD, Eric A. Bedell, MD, Christopher K. McQuitty, MD, Jill M. Chernin, RN, and Lee C. Woodson, MD, PhD

Departments of Surgery and Anesthesia, The University of Texas Medical Branch, Galveston, Texas

Background. Veno-venous perfusion-induced systemic hyperthermia (VV-PISH) homogeneously raises core body temperature potentially improving outcomes from metastatic lung cancer.

Methods. Patients (n = 10) with stage IV lung cancer, received VV-PISH ($\geq 42°C$ to $\leq 42.5°C$) for 120 minutes. General anesthesia, spontaneous ventilation, and heparinization allowed for percutaneous central venous access. The ThermoChem HT system provided extracorporeal blood flow (1000 to 1340 mL/min), used a calculated average core temperature for feedback control of blood heating, and included a charcoal-based sorbent for electrolyte homeostasis.

Results. The first three patients helped in refining the technique and reflect an evolutionary process, therefore their data are not included as part of the VV-PISH cohort. Venovenous perfusion-induced systemic hyperthermia (n = 7) had a preoperative weight loss of 4.4 ± 2.8 Kg, and a Karnofsky score of ≥ 70. Time to target temperature was 47 ± 2 minutes, as electrolytes remained normal, without patient or circuit complications. Extubation occurred between 6 and 18 hours. Hospital stay was 4.6 ± 1.1 days; median length-of-survival after hyperthermia was 271 days. For concurrent controls (n = 16, stage IV lung cancer), median length-of-survival from time of diagnosis to death was 96 days, but for the VV-PISH patients it was significantly longer at 450 days ($p < 0.05$). All patients returned to pretreatment status following treatment and died from progression of lung cancer.

Conclusions. Venovenous perfusion-induced systemic hyperthermia is safe, technically feasible, and achieves target temperature. Survival may be enhanced in stage IV lung cancer.

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Non-small cell lung carcinoma (NSCLC) remains the leading cause of cancer death in both men and women in the United States [1]. The majority of patients with NSCLC present with advanced regional (stage III) or metastatic disease (stage IV). Survival without treatment for stage IV is 6 months; with current treatment options including radiation therapy, chemotherapy, and surgery for palliation, average survival is extended to only 9 to 12 months [2].

All known mammalian cells and tissues are thermosensitive, as manifested by protein denaturation and tissue destruction at critically elevated temperatures [3]. Neoplastic tissues are vulnerable to destruction by heat at 41°C to 43°C, a temperature tolerated by normal cells [4–7]. Exogenously induced heat (hyperthermia) has attained a measure of success in the treatment of localized tumors [8, 9]. Systemic or whole-body hyperthermia (WBHT) is currently under investigation as a treatment for patients with metastatic cancer [10, 11]. Whole-body hyperthermia for metastatic disease is controversial [12] because of the difficulty in administering and monitoring the thermal dose and an incomplete knowledge of thermal pathophysiology [13]. Previous techniques of WBHT have demonstrated substantial morbidity and mortality (approximately 12%), especially in debilitated elderly cancer patients [14, 15].

We have developed an extracorporeal method of WBHT, venovenous perfusion-induced systemic hyperthermia (VV-PISH) with multipoint temperature monitoring, in which the core body temperature is raised to 42.0°C to 42.5°C for 2 hours [11, 16, 17]. VV-PISH delivers a predictable thermal dose that exceeds published data from all other methods [18].

In our initial report of this clinical experience, five patients with advanced (stage IV) non-small cell lung carcinoma (average 4.4 ± 1 months after initial diagnosis) received VV-PISH to assess technical issues and patient risks [19]. Results of the first three patients revealed hemodynamic instability, large fluid shifts, and inotropic requirements; all required prolonged intubation. For the next two patients, we altered the anesthesia technique, changed venous cannulation sites, reduced the target temperature to 42°C, and selected patients with Karnof-

sky 70 or greater. The knowledge gained from the first three patients allowed for standardization in the next seven patients (#4–#10), who comprise our data set for this report.

The purpose of this investigator initiated, phase I clinical trial was to evaluate the feasibility as well as immediate technical and patient-related risks of VV-PISH at 42.0°C to 42.5°C core temperature for 120 minutes in patients with stage IV NSCLC. All patients achieved the target core temperature for 2 hours with no 30-day mortality. For the seven study patients, the mean survival post diagnosis for VV-PISH was 504 ± 91 days and the median survival 450 days. Sixteen patients, who met all entry criteria but declined VV-PISH or had exclusion criteria, served as concurrent controls with a mean survival of 171 ± 194 days and median survival of 96 days.

Material and Methods

Experimental Design

The Institutional Review Board of The University of Texas Medical Branch, as well as the U.S. Food and Drug Administration, approved this study for 10 patients with histologic or cytologic documentation of stage IV (metastatic) NSCLC (squamous cell, adenocarcinoma, or large cell carcinoma) for a phase I study. Both agencies were notified of and approved the protocol changes that resulted from the first three patients. Patients were reviewed by The University of Texas Medical Branch multiple disciplinary lung cancer working group consisting of attending faculty from Thoracic Surgery, Medical Oncology, Radiation Oncology, Pulmonary Medicine, Radiology, Pathology, and Medical Ethics. For informed consent of the VV-PISH protocol, the principal investigator (JBZ), a disinterested physician, and a nurse coordinator (JMC) explained standard and alternate treatment modalities independently. Additionally, all patients received a neuropsychological evaluation before VV-PISH.

Both cognitive and psychosocial functioning were assessed to determine if the patient had neuro or cognitive changes due to the hyperthermia procedure and to insure variations were within normal expectations for this population. The psychological assessment was administered individually to the patient over a 3-hour period. Neuropsychological assessment was collected one day before the hyperthermia treatment and again at one-month posthyperthermia procedure. The information gained from the neuropsychological evaluation was used to determine if any additional or extraordinary psychosocial and cognitive changes occurred in patients.

The following instruments were used together to determine if a neuropsychological change occurred: Demographic Data Form (10 minutes); Beck Depression Inventory II (5 minutes); Wechsler Adult Intelligence Vocabulary Scale (WAISIII) including Block Design, Similarities, Digit Span, and Digit Symbol (60 minutes); the European Oncology Research Treatment Center (EORTC

10 minutes); Controlled Oral Word Association Test (5 minutes); Luria Motor Tasks (5 minutes); Wechsler Memory Scale (WMS III) Logical Memory & Visual Reproduction (10 minutes); Grooved Pegboard (10 minutes); Trails A&B (5 minutes); and the Token Test (10 minutes).

From October 1997 to November 2001, 89 patients with stage IV non-small cell lung cancer were screened for the VV-PISH phase 1 trial. Of this group, thirty-one patients satisfied both inclusion and exclusion criteria. Ten patients gave informed consent and received VV-PISH. Sixteen patients who met inclusion criteria either declined VV-PISH (the patient did not want to participate in hyperthermia) or elected conventional medical therapy (the patient specifically chose this therapy over hyperthermia) and served as the concurrent control group. The remainder (n = 5) failed to meet inclusion or exclusion criteria because of progression of disease before entry into the trial or refused(failed) follow-up. All patients who received VV-PISH underwent one hyperthermia treatment in the UTMB General Clinical Research Center (GCRC) induced by the ThermoChem System (ViaCirQ Corp., Pittsburgh, PA). Venovenous perfusion-induced systemic hyperthermia elevated average core temperature to 42° to 42.5°C and maintained this temperature for 120 minutes followed by cooling to return the patient's temperature to normal. All patients were followed in clinic weekly for 30 days, then monthly until death. For this report, the first three VV-PISH patients were deleted (as our learning curve) then all remaining patients were divided into two groups: the first group consisted of seven sequential VV-PISH patients and were the focus group of this report as the VV-PISH cohort, the second group was the matched concurrent controls (n = 16).

Patient Selection

INCLUSION CRITERIA. Inclusion criteria were: (1) stage IV NSCLC after conventional therapy failed or refused; (2) one focus of measurable disease (in two dimensions); (3) Karnofsky score $\geq$ 70 and performance status 0 to 2; and (4) informed consent.

EXCLUSION CRITERIA. Exclusion criteria included: (1) congestive heart failure, coronary disease, cardiomyopathy, severe chronic obstructive pulmonary disease; (2) brain metastasis; (3) within 3 weeks of surgery or 30 days of chemotherapy and radiation; (4) white blood count less than $4000 \cdot \mu L^{-1}$, platelet count less than $75,000/\mu L^{-1}$, creatinine clearance less than 60 mL $\cdot$ min^{-1}, serum bilirubin and serum glutamic oxaloacetic transaminase (SGOT) more than 2 times normal; (5) concurrent hormonal, biological, and radiation therapy; and (6) pregnant or nursing women.

Treatment

PRETREATMENT PREPARATION. Patients were pretreated with intravenous glycopyrrolate (0.2 mg). General anesthesia was induced using thiopental (3 to 5 mg $\cdot$ kg^{-1} IV) and incremental fentanyl (500 to 1000 μg/dose). Succinylcholine (1 to 1.5 mg $\cdot$ kg^{-1} IV) facilitated endotracheal intubation. Anesthesia was maintained with isoflurane (0.5%

to 1.0% inspired) in nitrous oxide-oxygen and mechanical ventilation was utilized briefly until the patient established a spontaneous breathing pattern. Arterial access allowed continuous pressure monitoring and blood sampling. A urinary bladder catheter with a temperature probe was inserted. A pulmonary artery thermodilution catheter measured continuous mixed venous oxygen saturation (SvO_2) (Opticath, Abbott Labs, Mountain View, CA). Cefazolin (1 gm), heparin, and solumedrol (100 mg IV) were given.

Immediately before VV-PISH, isoflurane was discontinued and the patient placed on assisted ventilation (Puritan-Bennett 7200). The FiO_2 maintained PaO_2 85 to 110 mm Hg. Infusions of thiopental (3 mg · min^{-1}), fentanyl (5 to 10 μg · kg^{-1} · h^{-1}), and lorazepam 1 mg/dose (max 6 mg) were titrated to achieve a respiratory rate of 14 to 20 breaths · min^{-1}. Volume administration was limited to albumin (5%) solution and packed red blood cell transfusion to maintain central venous pressure (CVP), pulmonary artery diastolic (PAD), and pulmonary capillary wedge pressure (PCWP) within normal limits. Transesophageal echocardiograph (TEE) was used intraoperatively for evaluation of cardiac function and detection of regional wall motion abnormalities. Norepinephrine infusion was titrated to maintain mean arterial blood pressure within 30% of baseline.

Arterial blood samples were obtained every 30 minutes. Systemic heparin was infused before cannulation (10,000 to 20,000 U of beef lung heparin, Upjohn), and 1,000 to 2,000 U were administered to titrate the activated clotting time (ACT) above 300 seconds. For VV-PISH, a 15F perfusion cannula (15 Fr. Arterial, 96530—15, Biomedicus, Eden Prairie, MN) was percutaneously inserted by Seldinger technique into the left common femoral vein and positioned in the distal inferior vena cava (IVC) for drainage of blood. A 15-Fr. cannula was positioned in the proximal IVC (immediately below the diaphragm) via the right common femoral vein for reinfusion of blood in all patients. A sheet of aluminized Mylar was wrapped around the patient to minimize radiant heat loss. All pressure points on the skin were padded to avoid injury.

Temperature was monitored and recorded from the distal esophagus, bilateral auditory canals, rectum, bladder, airway, pulmonary artery blood, and skin. Core body temperature was defined as the mean value of the temperatures measured from the esophagus, right and left auditory canals, rectum, pulmonary artery blood, and bladder.

VV-PISH. The hyperthermia extracorporeal circuit consisting of the ThermoChem system (ViaCirQ Corp., Pittsburgh, PA) was connected to the cannulas. Blood was withdrawn, heated, then pumped back into the proximal IVC at blood flows up to 1500 mL · min^{-1} (20 mL · kg^{-1} · min^{-1}) (Fig 1). During the initial heat-induction phase, the maximum water bath temperature did not exceed 52°C and maximum blood temperature did not exceed 48°C. The ThermoChem system machine contains a heat exchanger and a cellulose plate dialyzer with membranes that expand and contract (in response
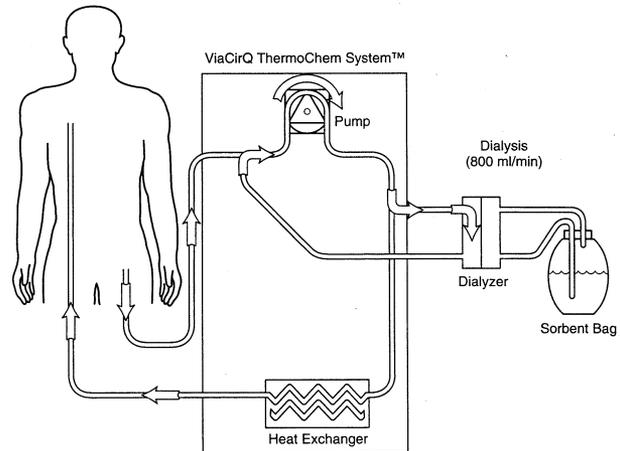

Fig 1. Schematic diagram of the venovenous perfusion-induced systemic hyperthermia circuit.

to dialysate pressure changes) to propel blood through the dialyzer [20]. The heat exchanger was regulated by a computer program feedback loop based on the five measured temperatures, which determined core body temperature. The dialysate side contained a 2 L suspension of powdered sorbents (charcoal and cation exchanger): (1) 200 gm of cation exchanger preloaded with sodium, calcium, potassium, hydrogen, and magnesium (maintains equilibrium with normal blood concentrations); (2) 140 gm of powdered activated charcoal with 80 mmol/L of calcium phosphate precipitated on the surface to dissociate when the surrounding solubility product was lower than normal; (3) sodium bicarbonate and sodium chloride in physiologic concentrations; (4) flow-inducing agents; and (5) glucose absorbed to the powdered charcoal (maintained normal or slightly elevated blood glucose). Additional calcium chloride was infused into the venous return line of the ThermoChem system to maintain normal blood-calcium concentration. A norepinephrine infusion was utilized to control the peripheral vasodilatation seen upon initiation of VV-PISH; and fluid administration was titrated to maintain a target systolic blood pressure of more than 100 mm Hg. When the target core body temperature of 42°C was achieved, the water temperature was reset to 30°C until the average body temperature was below 37°C. Venovenous perfusion-induced systemic hyperthermia was terminated; systemic heparin reversed with protamine sulfate (1:1); then the venous access catheters were removed.

FOLLOW-UP. At completion of VV-PISH, the patient received intermittent propofol infusion for sedation. Diuresis was initiated with Lasix (40 mg IV q 8 to 12 hours) and mannitol (50 gm). All patients recovered in an intensive care unit (ICU) setting, monitored by radial arterial catheter, Foley catheter, and pulmonary artery catheter. The patients remained in the ICU for at least 24 hours until they were extubated and responsive. Patients were discharged from the ICU after they were alert enough to protect their airway. They were discharged from the floor

Table 1. Pretreatment Demographics

Patient Number	M/F	Age (Yrs)	% Wt Change	Karnofsky Score	Functional Class	Diagnosis	Stage IV	Previous Disease Treatments	Comorbidities
VV-PISH									
4	M	56	6	70	1	Adeno	Bone marrow	RT, taxol/carboplatin, platinum/etoposide	Hypertension, peptic ulcer
5	M	61	0	90	0	Adeno	Liver	None	None
6	M	61	35	80	1	Squamous	Spine	None	Hypertension, hip replaced
7	M	67	0	100	1	Squamous	Bone	RT	Hypertension, PVD
8	M	63	0	90	0	Squamous	Lung	Surgery, taxol/carboplatin	Hypertension
9	M	64	0	80	1	Squamous	Liver, lung	Surgery, taxol/carboplatin	None
10	M	51	22	90	1	Adeno	Adrenal	RT, taxol/carboplatin X3	None
Ave: 4–10		60 ± 5	9 ± 14	85.7 ± 3					
Control									
1	M	57	25	80	1	Adeno	Adrenal	RT	SVC syndrome
2	M	63	12	90	0	Adeno	Spine	RT × 10	Hypertension
3	M	51	15	80	1	Adeno	Lung	None	PVD
4	M	57	17	90	0	Adeno	Adrenal	None	Hypertension
5	F	63	10	90	0	Adeno	Lung	RT × 8	None
6	M	63	0	80	1	Squamous	Lung	RT × 15	DOE
7	F	54	2	90	0	Squamous	Lung	Taxol/carboplatin	Hypertension
8	M	76	9	70	1	Squamous	Kidney	RT × 20	S/p AVR
9	M	49	4	90	0	Adeno	Bone	RT × 7	Hypertension
10	M	63	18	70	2	Adeno	Spine	RT	Hypertension
11	M	52	0	100	1	Squamous	Adrenal	Carbo/Taxol	None
12	M	49	0	100	1	Adeno	Bone	RT	None
13	M	65	10	80	1	Squamous	Adrenal	None	SOB, Fatigue
14	F	50	—	80	1	Adeno	Lung	None	SOB
15	F	57	6	80	1	Adeno	Adrenal	RT	None
16	M	60	—	80	1	Squamous	Adrenal	Carbo/Taxol	Fatigue
ave		58 ± 7	9 ± 2	84.4 ± 2					

Following VV-PISH standardization patients (4–10) used for comparison with concurrent controls.

when they were tolerating solid food and all intravenous access had been removed. All patients were returned to the care of an attending oncologist who managed the patient with best therapy for the duration of their illness.

All patients were followed in clinic weekly for 30 days then monthly. A follow-up computed tomographic scan was performed at three to six months to reevaluate tumor size. Patients in both the VV-PISH group and the control group were followed until death.

Statistics

Values are expressed as mean ± standard error of the mean. Significance was determined when *p* was less than 0.05 in all comparisons. Between group comparison was accomplished with Student's *t* test; comparison before and after hyperthermia treatment was done with a paired *t* test; and analysis of variance (ANOVA) was used for repeated measures.

Results

Demographics

From October of 1997 to November of 2001, 89 patients with stage IV NSCLC were screened for inclusion in this VV-PISH trial. Thirty-seven patients met inclusion criteria, and 51 did not. Of these 51 patients, reasons for not meeting inclusion criteria included; additional information was needed that was not available (n = 14), declined hyperthermia (n = 12), lung disease (other than lung cancer, n = 7), metastasis to the brain (n = 6), acquired heart disease (n = 3), no site of measurable disease (n = 3), small-cell component of primary disease (n = 2), died before entry (n = 1), and multifactorial reasons (n = 3). Of the 37 patients that met inclusion criteria, three were excluded due to subsequent pathology findings of a small-cell component, and three were determined to have brain metastasis on further evaluation. The remaining 31 patients all met inclusion criteria and had no exclusion criteria. Ten patients consented to receive VV-PISH and 21 served as a group of concurrent controls (nonrandom) of which 5 were lost to follow up. Demographics of these two study groups, VV-PISH (n = 7) and control (n = 16) are included in Table 1.

In the group exposed to VV-PISH the first three patients helped refine our technique and reflected a learning curve where none were treated in the same manner. After patient #1, we refined fluid management and our anesthesia protocol; after patient #2, the infusion cannula
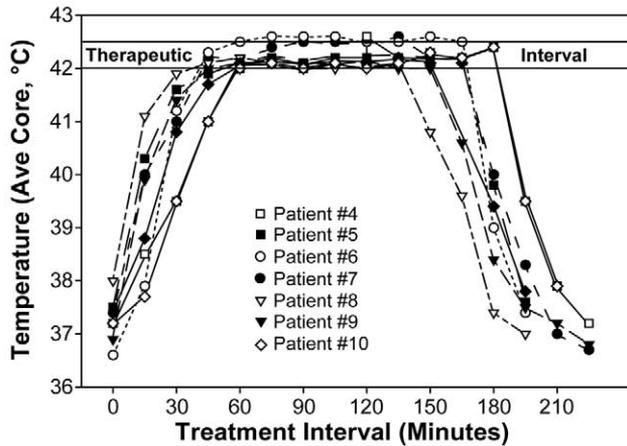
Fig 2. Time course to the target average (Ave) core temperature during venovenous perfusion-induced systemic hyperthermia.

Fig 3. Time course of average temperature change by measured site during venovenous perfusion-induced systemic hyperthermia. (L = left; R = right).

position was changed from external jugular to the contralateral femoral vein; and, after patient #3, the target temperature was reduced from 42.5° to 42°C. Additionally, we elevated the minimum Karnofsky score from 60 to 70. In aggregate, these three patients (2 males and 1 female) had a weight loss of 19.3 ± 5.6 Kg, Karnofsky score of 60 to 70/100, age of 53.7 ± 5.8 years, all were stage IV (spleen, adrenals, adrenals), 2 had failed conventional medical treatment and 2 had no known comorbidities. All developed severe systemic vasodilation requiring norepinephrine, fluid resuscitation, vigorous diuresis, and more than 24 hours of intubation for pulmonary edema and somnolence. Hospital stay was 7.3 ± 1.3 days and median length-of-survival was 57.5 days. Because of the evolving technique, these three patients are not included in the VV-PISH group.

Following standardization of the VV-PISH protocol, the study cohort (#4–#10) had a weight loss of 4.4 ± 2.8 kg and a Karnofsky score of more than 70/100. Extubation occurred between 6 and 18 hours, hospital stay was 4.6 ± 1.1 days, and median length-of-survival was 271 days. Time to target temperature was 47 ± 2 minutes, electrolytes remained normal, without patient or circuit complications. There were no significant differences between the VV-PISH and control groups by cell type, sites of remote metastasis, and the use of other disease related treatments and comorbidities. Additionally, the percentage change in weight, quality-of-life scores (Karnofsky and Functional Class), and patient age were not different ($p > 0.05$).

Therapeutic Effects

TEMPERATURE PROFILES. Figure 2 displays the time course for the average core temperature for all seven patients in VV-PISH group 2. The average time to heat the patients to the target core temperature was 49.9 ± 4 minutes, and the average amount of time to return the patients to a normal temperature (37°C) after 120 minutes at target temperature was 40 ± 4 minutes. Figure 3 displays the time course of average temperature change by measured
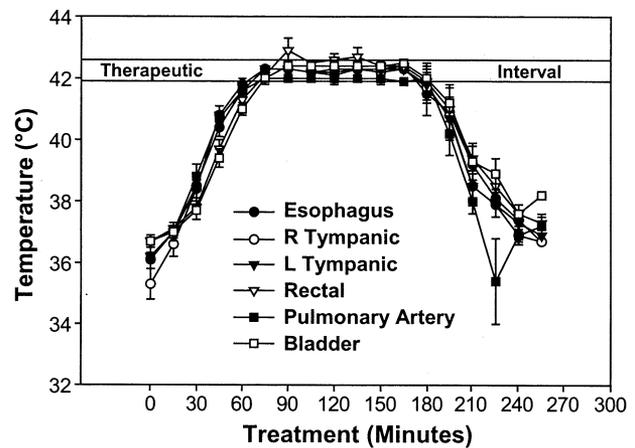
temperature per body site. There was a 120-minute period where all measured temperatures were within the therapeutic range. Figure 4 shows the dynamics of heat exchange between the heat exchanger water bath, the extracorporeal circuit blood temperature, and the core body temperature required to produce the level of homogenous hyperthermia we observed in these patients.

HEMODYNAMIC VARIABLES. Clinically and statistically significant ($p < 0.05$) changes occurred in both heart rate (HR) and cardiac output (CO) during VV-PISH (HR = 126 ± 5 bpm; CO = 12.0 ± 5 L/min) compared to pretreatment levels (HR = 84 ± 6 bpm; CO + 6 L/min) with both returning to normal values in the posttreatment interval (HR = 109 ± 4 bpm; CO = 8 ± 2 L/min). Both the CVP and capillary wedge pressure show clinically notable but statistically insignificant ($p > 0.05$) increases during treatment (CVP = 7 ± 1 to 14 ± 1 Torr; PCWP = 11 ± 1 to 17
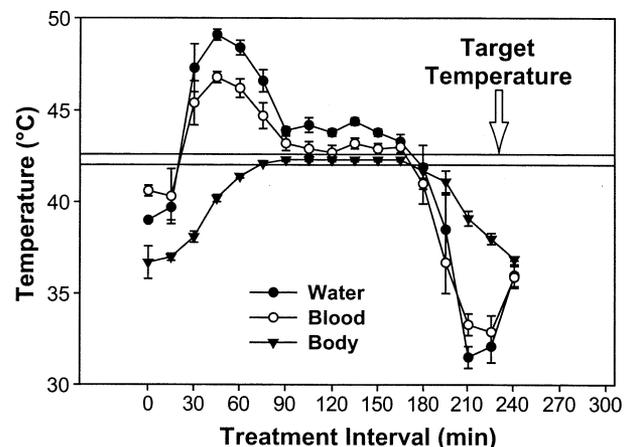

Fig 4. The dynamics of heat exchange between the heat exchanger water bath, the extracorporeal circuit blood temperature, and the core body temperature.

Table 2. Treatment-Related Problems VV-PISH

Patient Number	Intraoperative Complications	Posttreatment Morbidities	Ventilator-Dependent Time	Hospitalization
4	ECG, precordial ST elevation[a]	Mild confusion (48 h)	1 day	6 days
5	None	Mild confusion (48 h), stage I decubitus on sacrum	1 day	4 days
6	SVC syndrome[b]	Mild confusion (36 h), hip pain from old hip replacement	1 day	3 days
7	None	Mild confusion (24 h)	18 hours	2 days
8	None	Mild confusion (24 h), atrial fibrillation	1 day	3 days
9	None	1° burn right thigh	12 hours	3 days
10	None	Mild confusion (2–3 h), nausea and vomiting (6–8 h)	9 hours	2 days

[a] TEE verified no cardiac dyskinesis.   [b] Occurred during cooling phase alleviated by partial withdrawal of cannula.

ECG = electrocardiogram;   SVC = superior vena cava;   VV-PISH = venovenous perfusion-induced systemic hypothermia.

± 2 Torr) that remained elevated 2 hours later. These are the result of both anesthesia and perfusion management during VV-PISH. Experience from the first three patients taught us that hyperthermia caused a relative period of hypotension that could be successfully managed with adequate volume resuscitation [19]. Urine output dropped (ANOVA, $p < 0.05$) from 4.9 ± 1 mL/min to 0.7 ± 1.7 mL/min during hyperthermia and increased to 25.3 ± 8 mL/min 2 hours later after implementation of diuretics. The hematocrit showed a treatment related change from 33.3 ± 2 to 30.3 ± 1 to $27.2\% \pm 3\%$.

COMPARISON OF SOLUTE VARIABLES. A comparison between pretreatment and posttreatment variables shows moderate but clinically insignificant changes for K+, glucose, aspartate aminotransferase, alanine aminotransferase, lactate dehydrogenase, and fibrin split products. Prothrombin time and partial thromboplastin time were still elevated immediately following heparin reversal, but no bleeding complications were noted. The electrolyte changes still reflect values within normal limits and confirm normalization of electrolytes during the dialysis portion of VV-PISH.

Toxicities and Complications

Table 2 lists both intraoperative and posttreatment complications and morbidities associated with VV-PISH. The most significant posttreatment morbidity was mental confusion or somnolence (6 of 7) that persisted for up to 48 hours following VV-PISH. All patients returned to baseline before discharge from the hospital. Patient number 6 developed superior vena cava (SVC) syndrome during the procedure presumably due to swelling of metastatic nodes surrounding the SVC that caused restriction of venous return. The SVC syndrome resolved within 48 hours following completion of VV-PISH. All patients required critical care management in the intensive care unit for 2 to 3 days, were discharged with an

average length of stay of 4.6 ± 1.1 days, and survived longer than 30 days. In the five VV-PISH patients in whom neuropsychic testing was completed before hyperthermia and at 30 days afterward, no central nervous system abnormalities were detected [21].

Outcomes

Table 3 compares outcomes of VV-PISH to control with respect to additional therapies. The VV-PISH group survived a significantly longer period of time after original diagnosis with stage IV non-small cell lung cancer (VV-PISH, 504 ± 102 days, vs the concurrent control group, 171 ± 194 days, $p < 0.05$) (Fig 5). Median survival was also remarkably different between the groups (VV-PISH, 450 days, vs control, 96 days).

Comment

This phase I clinical trial evaluated VV-PISH for safety and feasibility in patients with stage IV NSCLC. We demonstrated that (1) VV-PISH is technically feasible, (2) the targeted core temperature was achieved, and (3) electrolyte balance was maintained. All patients exhibited systemic vasodilation and temporary somnolence, yet all patients experienced full recovery to pretreatment activity. Standardization of the selection process (Karnofsky ≥ 70), anesthesia management, perfusion technique, and target temperature (core temperature ≥ 42.0°C) was necessary to achieve the most favorable risk/benefit during this limited trial.

The rationale for hyperthermia in cancer treatment is predicated on a differential thermal response between normal and cancerous tissue. At the molecular level, hyperthermia has been shown to be a stimulus for apoptotic cell death in cancer cells [22]. Cellular effects include damage caused by heat-induced lipid peroxidation, reduced mitotic rate [23], destabilized cellular mem-

Table 3. Outcomes

Patient Number	Additional Therapies	Survival After VV-PISH (Days)	Survival After Diagnosis (Days)
VV-PISH			
4	Taxol/carboplatin Platinum/ etoposide XRT, navelbine	270	450
5	Taxol/carboplatin × 6, gemcitabine	271	331
6	RT, taxol/carboplatin	262	322
7	Taxol/carboplatin	139	199
8	RT, radio ablation	294	901
9	Taxotere, gemzar	277	857
10	RT, aredia	278	469
Ave (4–10)		255 ± 18	504 ± 102[a]
Median	Patients 4–10	271	450
Control		Reason for Assignment to Control Group	
1	RT	Metastatic diffuse disease	43
2	RT × 10	Recurrent CVAs	107
3	none	Pericardial and pleural effusions (no metastasis)	35
4	None	Chose conventional therapy	34
5	RT × 8	Declined VV-PISH	19
6	RT × 15	Chose conventional therapy	56
7	Taxol/carboplatin	Mixed cell type	424
8	RT × 20	Declined VV-PISH	87
9	RT × 7	Chose conventional therapy	744
10	RT	Epidural nerve involvement	103
11	Carbo/taxol	Died prior to treatment	40
12	RT	Chose conventional therapy	360
13	None	Declined VV-PISH	180
14	None	Refused staging	273
15	RT	Chose conventional therapy	150
16	Carbo/taxol	Chose conventional therapy	89
ave			171 ± 194[a]
median			96

[a] Statistically significant difference ($p < 0.05$).

Following VV-PISH standardization, patients (4–10) used for comparison with concurrent controls.

branes [24], and increase in tumor necrosis factor-α and IL-1β [25]. Within the tumor, hyperthermia causes decreased blood flow, an elevated rate of glycolysis, acidosis, and oxygen utilization [26]. Heat also has a well-known stimulatory effect on the immune system, causing both increased production of interferon-γ and increased immune surveillance [27].

Complications from hyperthermia are attributable to both the physiologic response to the elevated temperature and the technique of inducing elevated temperature. Core temperatures greater than 41.8°C cause increased vascular compliance [28], increased intrinsic heart rate (7.1 beats min^{-1} · C^{o-1}) [29], decreased afterload [30], and increased cardiac output [31]. Additionally, hypovolemia results from vasodilation and electrolyte concentrations become altered, resulting in arrhythmias, further impairing cardiac performance [30]. Using our VV-PISH technique, electrolyte concentrations were maintained within normal ranges throughout the treatment period, and no

arrhythmias were seen. Our patients showed an immediate increase in heart rate and cardiac output and decrease in afterload during hyperthermia as previously noted [19]. Central venous pressure increased steadily throughout the treatment period; however, phenylephrine, norepinephrine, and vigorous diuresis returned these values to normal in the early postoperative period.

Whole-body hyperthermia is also associated with a consumptive coagulopathy [32, 33]. However, Parks and associates [15], when using perfusion-induced systemic hyperthermia with systemic anticoagulation, reported no hemolysis, clotting, or bleeding, although they experienced a 32% drop in platelet count. No hemostatic derangements were experienced from perfusion-induced systemic hyperthermia in the HemoCleanse human immunodeficiency virus clinical trials [34]. Alterations in coagulation profiles with WBHT are probably the result of hyperthermia combined with the primary disease state without the protection offered by heparin used in perfu-
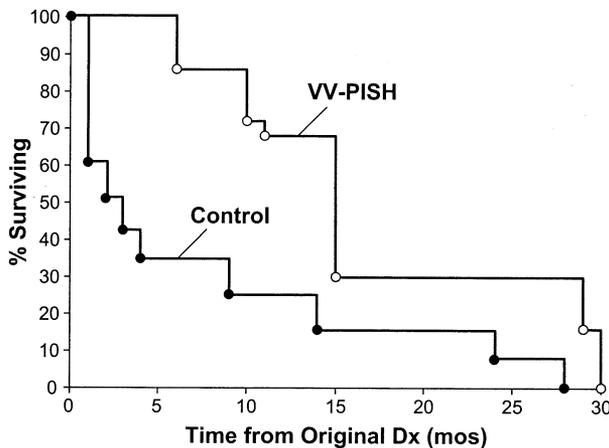
Fig 5. Survival following original diagnosis (DX) with stage IV NSC lung cancer (VV-PISH+, 504 ± 102 days versus control, 171 ± 194 days, p < 0.05). *Median survival was* VV-PISH, *450 days versus control, 96 days. (NSC = non-small cell; VV-PISH = venovenous perfusion-induced systemic hyperthermia.)*

sion-induced systemic hyperthermia studies. In our studies, thrombotic complications were avoided by systemic heparin anticoagulation during VV-PISH, after which activated clotting times approached normal following heparin reversal with protamine. We also observed a 44% decrease in platelet count, but the resultant number was still greater than 110,000/dL. Likewise, no bleeding complications were noted throughout the study.

Our VV-PISH technique has three unique aspects in delivering heat to the body. First, we use a venovenous approach, where heated blood is reinfused into the venous circulation and mixed in the pulmonary circulation, and then the heat is evenly distributed by the systemic circulation [17]. Our technique allows us to deliver blood at 42.0°C in a more rapid and homogeneous manner than other methods. Second, the rate of heat induction is of critical importance because the faster the rate, the better the cancer cell kill [35]. Venovenous perfusion-induced systemic hyperthermia requires only 50 ± 4 minutes (Fig 2) to reach target temperature, whereas other methods of WBHT may require up to 2.8 hours [15]. Third, VV-PISH allows for homogeneous distribution of heat and precise control of temperature gradients. The heterogeneous temperature distribution seen with other techniques may explain the inconsistent results in previous clinical trials using hyperthermia for the treatment of tumors. We have documented a redistribution of blood flow favoring the thoracoabdominal organs resulting in homogeneous temperature elevation [18].

Our technique of VV-PISH involves multipoint temperature monitoring and use of average body temperature for feedback control of heat induction [17]. Excessive temperature elevations or excessive time at an elevated temperature may damage nontarget tissue, whereas insufficient temperature or thermal dose may have no therapeutic effect on the targeted cancer tissue. Veno-

venous perfusion-induced systemic hyperthermia delivers a thermal dose that is both predictable and substantial [17]. We previously measured intratumor temperature directly (two patients with accessible tumor burden, supraclavicular nodes) [19]. The measured thermal dose exceeded that received by the body. Venovenous perfusion-induced systemic hyperthermia incorporates a sorbent-based plate-membrane dialyzer system [20], which controls the chemical composition of the dialysate and helps to maintain normal electrolyte values [16]. We experienced no arrhythmias during this trial.

All study patients had stage IV NSCLC and had failed or refused other therapeutic trials. All patients had multiple solid-organ metastases with cachexia on entry into the trial. In the VV-PISH group, the target temperature of 42.0°C for 2 hours was achieved and 42.0 ± 0.2°C was measured at all monitored sites. Percutaneous cannulation, hyperthermia induction, maintenance, and cooling were free of significant complications. All patients required critical care management in the intensive care unit for 2 to 3 days, were discharged with an average length of stay of 4.6 ± 1.1 days, and survived longer than 30 days. In the five patients in whom neuropsychic testing was completed before hyperthermia and at 30 days afterward, no central nervous system abnormalities were detected [21].

During this safety trial, no assessment of therapeutic efficacy is possible; however, the time of survival of patients in the VV-PISH group after VV-PISH (median of 271 days) is an interesting finding. Likewise, median length-of-survival from diagnosis to death for the concurrent controls was 96 days, but for the hyperthermia patients, was remarkably longer at 450 days. Selecting a concurrent control group, from the initial cohort of stage IV patients introduces bias, which can only be eliminated in a prospective, randomized, controlled study. The survival data for our control group are less than what are currently published in other clinical trials, where various regimens are being compared [36]. A possible explanation is that in our control group, therapy is not homogenous; in fact, several of the patients elected no therapies after their initial diagnosis, whereas in many other published reports, control groups received standardized treatments.

In summary, our technique of percutaneous VV-PISH provides potential advantages over other external methods both in terms of safety and efficiency of thermal delivery [5, 37, 38]. Venovenous perfusion-induced systemic hyperthermia provides precise control of a target core temperature, maintenance of electrolyte homeostasis, and manageable side effects (vasodilation and somnolence) in properly selected patients. Our results using VV-PISH to 42.0°C to 42.5°C core temperature with stage IV lung cancer also imply potentially improved outcomes for a favorable risk/benefit. Required future studies include prospective, randomized, controlled, multicenter trials of VV-PISH compared to conventional therapy and evaluating the therapeutic efficacy of combining VV-

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PISH with chemotherapeutics, to establish synergistic antineoplastic effects.

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DISCUSSION

DR JOSHUA R. SONNETT (New York, NY): I enjoyed your talk, Dr Zwischenberger, and appreciate the opportunity to discuss your presentation. You and your whole team are to be congratulated on bringing a difficult experimental concept to clinical evaluation, a concept that you systematically studied in animal models, successfully reported these experimental results, and then in a controlled IRB manner went from the laboratory to the clinical arena. I have some questions.

With the rapid rewarming and the need for significant inotropic support, did your patients experience significant tachyarrhythmias?

On your inclusion criteria was measurable disease. Do you have evidence of measurable tumor response to this therapy?

The nature of this phase I trial was that of safety and temperature dosing. You report all patients returning to pretreatment status. However, your patients required an average of 5 days of hospitalization, significant intensive care support with inotropes, and extended ventilation. I am worried that as you try to apply this strategy to larger cohorts of patients that you will see further morbidity. Thus, do you see this as a concept that can expand beyond the realms of your institution and your experience?

Finally, the medical oncology literature indicates that in advanced disease, one of the most important prognosticators of how patients fare and ultimate survival with chemotherapy is their initial performance status and weight, their Karnofsky score. Thus, by selecting patients with good performance status and lack of weight loss in your study, you essentially selected patients who would have longer survivals with standard chemotherapy. Thus, with this phase I study of seven patients, I would be careful about claiming any survival advantage at this date.

Again, I congratulate you on your beautifully run study and an excellent presentation. Thanks.

DR ZWISCHENBERGER: Thank you, Dr Sonnett, for your insightful comments. As you can imagine, this trial was an adventure. In the first three patients we did see tachyarrhythmias, but once we standardized our technique of anesthesia and fluid resuscitation—literally in one hand a norepinephrine bag and intravenous fluid in the other—hemodynamics smoothed out, arrhythmias resolved, and sinus tachycardia was very well tolerated at a rate of about 110 to 120.

The length of stay reported is unusual because this study was through a General Clinical Research Center (GCRC). Patients had to be admitted the day before, then received perfusion-induced systemic hyperthermia in the GCRC, which we set up as a temporary procedure unit. For recovery, they had to go to an intensive care unit for ventilator management and extubation; then they had to be ambulatory before they could be released for discharge. If you have ever worked with a GCRC, you know the nurses are not experienced with ill patients. I estimate with a little practice the whole procedure and postoperative care would require about 2 days, which I think compares very favorably to the hours spent by patients undergoing chemotherapy.

Patient selection is critical. The patient should be ambulatory, which we agree is a major factor. The concurrent control group was interesting because we did screen all of these patients for entry criteria, discussed options with them, and then tried to obtain informed consent for the study. As you can imagine, when you educate a patient on something this unusual, many of them opted out. So we retrospectively reviewed the outcomes of that group as concurrent controls. Of course, a retrospectively selected group has bias and does not allow valid statistical comparison, but I thought it would be interesting to see how this group fared.

I know it is "soft science" when you start talking about how a patient feels, but every single patient had a period of euphoria and enhanced performance for 3–9 months after hyperthermia. We actually had a number of patients begging for additional therapy. Because this was a tightly controlled phase I study, we couldn't offer additional treatments.

I look forward to prospective randomized controlled studies and I also look forward to the idea of exploiting synergistic efforts of hyperthermia with chemotherapeutics.

If anyone wants to try perfusion-induced systemic hyperthermia, be sure and call me because there are several issues regarding the perfusion and the anesthesia management our team could share.