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Resolution of Pulmonary Hypertension Complication During Veno-Venous Perfusion-Induced Systemic Hyperthermia Application

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Abstract

We are developing a venovenous perfusion-induced systemic hyperthermia (vv-PISH) system for advanced cancer treatment. The vv-PISH system consistently delivered hyperthermia to adult healthy swine, but significant pulmonary hypertension developed during the heating phase. The goal of this study was to develop a method to prevent pulmonary hypertension. We hypothesized that pulmonary hypertension results from decreased priming solution air solubility which causes pulmonary gas embolism. Healthy adult sheep (n=3) were used to establish a standard vv-PISH sheep model without priming solution preheating. In subsequent sheep (n=7), the priming solution was preheated (42–46°C) and the hyperthermia circuit flushed with CO₂. All sheep survived the experiment and achieved 2 hrs of 42 °C hyperthermia. In the group lacking priming solution preheating, significant pulmonary hypertension (35–44 mm Hg) developed. In the sheep with priming solution preheating, pulmonary artery pressure was very stable without pulmonary hypertension. Blood electrolytes were in physiological range, and complete blood counts were unaffected by hyperthermia. Blood chemistries revealed no significant liver or kidney damage. Our simple strategy of priming solution preheating completely resolved the problem of pulmonary hypertension as a milestone toward developing a safe and easy to use vv-PISH system for cancer treatment.

Keywords

systemic hyperthermia; pulmonary hypertension; advanced cancer; whole-body hyperthermia

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INTRODUCTION

Hyperthermia is a potential new therapy for advanced lung cancer because it selectively kills thermo-sensitive lung cancer cells and enhances chemotherapy drug cytotoxicity.^{1–5} Whole body hyperthermia using infrared radiation has been developed for metastatic cancer treatment with promising clinical results.^{6–9} However, infrared radiation-induced whole body hyperthermia redistributes blood flow away from the visceral organs, the most common metastases site, to the skin and extremities, resulting in heterogeneous heating.^{10–12} Therefore, insufficient heat delivery to metastases compromises therapeutic efficacy.

We are developing a venovenous perfusion-induced systemic hyperthermia (vv-PISH) system to achieve homogeneous heating and efficient cancer treatment.^{13–14} It was tested in 10 advanced non small cell lung cancer patients in a phase I safety clinical trial with promising results. This vv-PISH system was very complicated with a dialysis unit, multiple pumps, and long tubing connections.¹⁴ Recently, a simplified vv-PISH system without the dialysis unit was developed. This simplified blood circuit consisted of a centrifugal pump, a heat exchanger, and a double lumen cannula. It was tested in adult healthy swine, showing consistent delivery of the therapeutic hyperthermia dose (42° C for 2 hrs). Unfortunately, a significant increase in pulmonary artery pressure occurred during the heating phase, causing hemodynamic instability. Although this pulmonary hypertension was temporary, it was severe enough to cause the death of one swine from circulatory collapse.¹⁵ In anticipation of long-term survival studies, we replaced the swine model with a sheep model for more practical post-procedure care. Pulmonary hypertension also developed during the heating phase in our sheep model. The possible reason for this effect is that fast heating decreases priming solution air solubility, generating micro air bubbles and causing pulmonary gas embolism with subsequent pulmonary hypertension.^{16–17} We hypothesized that preheating the solution to 42–46°C to release the air before priming would eliminate air bubble formation in the hyperthermia circuit, preventing the development of pulmonary hypertension. In this study, our hypothesis was tested and proven in seven sheep.

METHODS

All animal studies were approved by the University of Kentucky Institutional Animal Care and Use Committee (IACUC) and were conducted in accordance with the “Guide for the Care and Use of Laboratory Animals.”

Anesthesia and Instrumentation

Prior to surgery, adult female cross-breed sheep (34–87 kg, n=10) were fasted for 24 hours. Anesthesia was induced with ketamine (5mg/kg, i.v., Fort Dodge Animal Health, Fort Dodge, IA) and diazepam (0.25mg/kg, i.v., Hospira Inc. Lake Forest, IL). Sheep were intubated and connected to the anesthesia machine (Smiths Medical, Waukesha, WI). The sheep were then transferred to the operating room (OR) table in the supine position and connected to the OR anesthesia machine (Narkomed 2B North American DRAGER, Telford, PA). Maintenance anesthesia (1–3% isoflurane) was titrated to a normal range of arterial

blood pressure. Sheep were ventilated at 8–10 ml/kg tidal volumes with respiratory rates between 12 and 20 respirations per minute to maintain normal CO₂ levels.

Two 16 G catheters (Becton Dickinson, Sandy UT) were placed into the femoral artery and vein for blood sampling/pressure monitoring and fluid administration, respectively. A Swan-Ganz catheter (Edwards Lifesciences, Irvine CA) was placed percutaneously through the left jugular vein to the pulmonary artery (PA) for measurement of cardiac output, PA pressure (PAP), and central venous pressure (CVP). The catheters were connected to Tru-Wave transducers (Edwards Lifesciences Irvine, CA) for the monitoring of arterial blood pressure (ABP), CVP and PAP via a MP-50 monitor (Phillips, Boeblingen, Germany). Temperature probes were placed in the bladder (Foley catheter), right/left nasopharynx, blood in/out of animal, and pulmonary artery (Swan-Ganz catheter). After instrumentation, operative anesthesia was switched to either a propofol/remifentanyl (100–200 mcg/kg/min + 0.5–1.0 mcg/kg/min) or propofol/vencuronium (100–200 mcg/kg/min + 1mcg/kg/min) infusion to avoid the isoflurane-induced vasodilation during hyperthermia.

Data Acquisition

The data acquisition system used in this study was the cDAQ9172 (National Instruments, Austin, TX) with a temperature module (NI-9219), a pressure module (NI 9237), and a flow module (NI 9215). The temperature module was connected to temperature probes placed in the bladder, right/left nasopharynx, and blood in/out tubing for constant temperature measurement. The core temperature was defined as the average of the bladder and right/left nasopharynx temperatures. The pulmonary artery temperature measured via the Swan-Ganz catheter was not included in the core temperature calculation due to its close proximity to the site where the heated blood enters the right atrium via the double lumen cannula (DLC). The pressure module was connected to the pressure sensors for PAP, ABP and CVP monitoring. The flow module was connected to the flow meter (T110, Transonic Systems Inc.) for circuit blood flow monitoring. Data acquisition software (DAQ, Labview 8.6, National Instruments, Austin, TX) was used to record temperature, blood pressure, and pump flow rates simultaneously at 5Hz.

VV-PISH Groups

The first three sheep were used to establish a standard vv-PISH sheep model without preheating the priming solution. In the following seven sheep, we preheated priming solution for complete deairing to mitigate pulmonary embolism and associated pulmonary hypertension. The vv-PISH system consisted of: 1) a DLC (Avalon Elite™, Avalon Laboratories, LLC, Rancho Dominguez, CA)¹⁸, 2) centrifugal pump (Bio-Pump 560), 3) heat exchanger (BIOtherm™), and 4) heater/cooler (modified Blanketrol III™, Cincinnati Subzero). A pump and heat exchanger were integrated into one piece and tested in one sheep.

Priming Solution Preheating and Complete De-airing of VV-PISH Circuit

The steps for preheating the priming solution and complete deairing of the vv-PISH circuit were: 1) flushing the vv-PISH circuit with CO₂ to replace air, since CO₂ has significantly higher water solubility and less likely to generate bubbles; 2) preheating the priming

solution (lactated Ringers or Plasmalyte) to 42–46°C with a warming cabinet to decrease air solubility, allowing the air in the solution to be released before priming the circuit, 3) priming the system with preheated lactated Ringers or Plasmalyte (1 U heparin/ml); 4) tapping the tubing and manipulating flow for further circuit deairing. As soon as the vv-PISH blood circuit was primed, the heat exchanger was connected with the water circulated heater to maintain circuit temperature.

Installation and Maintenance of VV-PISH

Systemic anticoagulation was initiated with a bolus of intravenous heparin (150 U/kg) and maintained at an activated clotting time of 180–250 seconds throughout the experiment. The DLC was inserted through a small incision on the right jugular vein into the superior vena cava (SVC), traversing the right atrium (RA), with the tip positioned in the inferior vena cava (IVC). This DLC was connected to the prime dvv-PISH circuit. When the pump was started, the venous blood was drained from the DLC drainage lumens (IVC and SVC) and sent to the heat exchanger for heating. The heated blood was pumped back through the DLC infusion lumen into RA-pulmonary circulation. The circuit blood flow was set at 1.5–2.0 L/min to heat the sheep, targeting a 42°C core temperature. The core temperature was maintained at 42–42.5 °C for 2 hrs for the cancer therapeutic window.

Experiment Termination and Animal Euthanasia

The cooling phase was started by circulating cool water through the heat exchanger until the core temperature returned to 39 °C. The sheep were then taken off perfusion and decannulated. Two sheep experiments were terminated after decannulation, and the remaining 5 were terminated after successful completion of five day survival study. All sheep were euthanized with Beuthanasia-D (1 mL/10 lb body weight, Schering-Plough Animal Health, Union, NJ) upon completion of the hyperthermia experiment.

Animal monitoring and Blood Analysis

Blood chemistries, complete blood counts, free hemoglobin, cardiac output, and pulmonary artery wedge pressure (PAWP) were measured at the following time-points: 1) baseline, 2) therapeutic start, 3) therapeutic middle (1 hour of 42 °C hyperthermia), 4) therapeutic end (2 hours of 42 °C hyperthermia), and 5) the end of cooling (when 39 °C was achieved). Arterial blood gases and electrolytes were measured every 15 minutes using a blood gas analyzer (Cobas b221 Roche Diagnostics, Indianapolis, IN). Hemodynamic parameters were continuously monitored, and urine output was measured hourly. Continuous intravenous infusion of lactated Ringer's (700–999 ml/hr) was used to maintain the blood volume for stable hemodynamics. Supplemental intravenous calcium chloride (100 mg/ml) or potassium chloride (10–40 mEq) was used as necessary to correct hypocalcemia or hypokalemia, respectively. An intravenous bolus of furosemide (5–20 mg) was given if hourly urine output was less than 50 ml.

Data Analysis

All data are expressed as mean $\pm$ standard deviation (SD). A p-value of < 0.05 was considered statistically significant. Differences between the baseline and subsequent time-points were evaluated using analysis of variance with a Dunnett post test.

RESULTS

All ten sheep survived the experiment and achieved 2 hrs of 42 °C therapeutic hyperthermia. All of the first three sheep developed significant pulmonary hypertension during the heating phase (Figure 1A). Their mean PAP reached up to 44, 41 and 35 mmHg, respectively. By contrast, in the subsequent 7 sheep with priming solution preheating/complete circuit de-airing, mean PAPs stayed very stable without any increase during the heating phase (Figure 1B). The simplified vv-PISH system also maintained blood electrolytes/volume in physiological range.

vv-PISH Circuit Performance

A 33 ± 14 min heating time was required to achieve the therapeutic core temperature. After the two hour therapeutic window was completed, 43 ± 11 min was required to cool the sheep to 39°C. The sheep temperature did not exceed 42.5°C at any measured site (Figure 2A). The vv-PISH circuit blood flow rate was 1.75 ± 0.21 L/min. During the heating phase, the circuit blood infusion temperature reached a maximum of 43.0 ± 0.7 °C (Figure 2B). Once the target core temperature (42 °C) was achieved, it was maintained at 42–42.5 °C for 2 hours. During the cooling phase, there was up to a 3.5 °C difference between the blood infusion and core temperatures.

Hemodynamics

Mean PAPs were stable and unchanged throughout the hyperthermia experiment (Table 1). Mean arterial pressure (MAP), CVP, and PAWP were also maintained in the physiological range throughout the experimental period (Table 1). Heart rate and cardiac output were significantly increased during the therapeutic phases and were also elevated during the cooling phase.

Fluid and Electrolyte Balance

Lactated Ringer's infusion ($3,330 \pm 353$ mL) was used to maintain the blood volume (CVP) for stable hemodynamics. Urine output was 201 ± 113 mL/hr. Arterial sodium levels were significantly reduced at the end therapeutic and end cooling time-points, but these values were still within normal physiological range (Table 2). Blood potassium, calcium, chloride, bicarbonate, and pH were stable throughout the hyperthermia experiment (Table 2).

Blood Parameters and Liver/Kidney Function

Hemoglobin, hematocrit, and red blood cell counts were unaffected by hyperthermia (Table 3). Free hemoglobin levels reached a maximum of 10.7 ± 2.1 mg/dl when the target temperature was met, suggesting an absence of hemolysis. Total white blood cell counts

along with the percentage of granulocytes, lymphocytes, and monocytes were unchanged (Table 3). Platelet counts were within normal range.

Blood glucose was significantly elevated at the end of the therapeutic and cooling phases (Table 3). Alkaline phosphatase and alanine aminotransferase levels remained stable, suggesting the absence of hepatocellular injury. Blood urea nitrogen and creatinine were in normal range, indicating normal kidney function. Albumin and total protein were significantly reduced by hyperthermia.

DISCUSSION

In this study, we developed a technique to prevent the occurrence of severe pulmonary hypertension during vv-PISH application. In this paper, pulmonary artery pressure was maintained at normal levels throughout the entire systemic hyperthermia experiment in all seven sheep, demonstrating complete resolution of the pulmonary hypertension problem. Therefore, the vv-PISH system safely delivered a reliable therapeutic hyperthermia dose to adult healthy sheep.

Systemic hyperthermia is a promising therapy for advanced cancer because most cancer cells are thermo-sensitive with significantly reduced heat shock protein expression.^{1,4} Rapid heating prevents cancer cells from recruiting limited thermo-protective mechanisms, promoting apoptosis and selectively killing cancer cells.^{19–20} Hyperthermia also increases the cytotoxicity of chemotherapy.^{2–5}

A safe and effective hyperthermia temperature range for cancer therapy is narrow (core temperature 41.5 to 42°C),^{1,21} requiring precise regulation of systemic hyperthermia. Temperatures below this range do not kill cancer cells, whereas temperatures above it may cause serious cardiovascular and/or neurological complications.^{22–23}

Hyperthermia has been successfully achieved either through external heating by infrared radiation or through internal heating by venovenous blood perfusion. Infrared radiation-induced whole body hyperthermia is non-invasive, but a long heating time (2–3 hours) is required,^{7–9,24–25} which decreases the efficacy of cancer treatment. Heterogeneous heating also occurs, causing insufficient heat delivery to metastases which compromises therapeutic efficacy.^{10–12}

Venovenous perfusion-induced systemic hyperthermia (vv-PISH) utilizes an extracorporeal pump-heat exchanger circuit to withdraw a portion of venous blood for heating, which is then pumped back into the venous system. The heated blood is well mixed with unheated venous blood through the pulmonary circulation and is distributed to the systemic circulation by the heart, which results in homogenous delivery of systemic hyperthermia.^{14–15} Fast heating can also be achieved with the vv-PISH system, which enhances cancer cell kill.¹⁹ Thus, vv-PISH rapidly and homogeneously delivers a therapeutic dose, meeting the requirements needed for efficacious hyperthermic cancer therapy. Furthermore, the core temperature can be precisely controlled in the desired narrow therapeutic window for safety and effectiveness.

The original vv-PISH system was complicated, causing circulatory and electrolyte instability. We then simplified the vv-PISH circuit to improve the performance and ease of operation by: 1) using a double lumen cannula for vascular access, 2) removing the dialysis unit, and 3) using a centrifugal blood pump. Despite these improvements in the vv-PISH circuit, significant pulmonary hypertension developed during the heating phase, resulting in circulatory instability.¹⁵

Significant elevations in pulmonary artery pressure in the application of systemic hyperthermia can be severe, causing the death of one pig from circulatory collapse.¹⁵ Our goal, in this study, was to develop a protocol to prevent pulmonary hypertension for safe application of our simplified vv-PISH system. We hypothesized that fast heating of the priming solution in the heat exchanger circuit from room temperature (20 °C) to 45 °C at the beginning of the heating phase would decrease priming solution air solubility, generating numerous micro air bubbles and causing global pulmonary air embolism with subsequent pulmonary hypertension.^{16–17} In this study, the priming solution was preheated to decrease air solubility, releasing air before priming. Since the circuit priming solution temperature (42–46°C) was equal to or higher than the highest circuit blood temperature (43.0 ± 0.7 °C), it did not rise further during heating, eliminating heat-induced micro air bubble generation and subsequent global pulmonary air embolism. Atmospheric air is composed of 78% N₂, 21% O₂ and 0.04% CO₂. Since the CO₂ water solubility at 45 °C is much higher than N₂ (60 times) and O₂ (25 times),²⁶ we used CO₂ to replace air in the vv-PISH circuit. When priming the vv-PISH circuit, CO₂ bubbles instead of air bubbles were generated. This CO₂ can easily be dissolved into the priming solution, eliminating micro bubble formation and associated global pulmonary embolism. This paper proves that our simple strategy to prevent pulmonary hypertension is fully effective.

In this paper, we indirectly proved that heat induced-air embolism caused pulmonary hypertension. Further investigation is required to clarify the direct relationship between heat-induced air bubble generation and pulmonary hypertension.

Conclusion

Our simple strategy completely resolved the problem of pulmonary hypertension during the heating phase of vv-PISH application. We have made a milestone toward developing a safe, simple, and easy to use vv-PISH system for effective cancer treatment.

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Figure 1.
Pulmonary Artery Pressure During the Heating Phase. 1A: Mean pulmonary artery pressure was elevated in the Control Group sheep. 1B: Mean pulmonary artery pressure was stable

during the heating phase in all seven Experimental Group sheep. Each line represents mean pulmonary artery pressure data from one sheep.

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Figure 2. Hyperthermia Temperature Profile. **2A:** Bladder right/left nasopharynx temperatures measured during the heating, therapeutic, and cooling phases. Homogeneous heat distribution was observed with no temperature readings above 42.5°C. **2B:** The relationship

between core temperature and circuit infusion (blood in)/drainage (blood out) blood temperatures. Maximal circuit blood infusion temperature was 43°C.

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Table 1

Hemodynamics

Parameter	Baseline	Therapeutic Start	Therapeutic Middle	Therapeutic End	Cooling End
MAP	102±10	96±10	98±11	92±10	94±11
HR	114±15	161±12 *	156±22 *	152±21 *	151±27 *
CVP	5±2.3	5±3.0	6±2.4	7±2.5	7±2.1
mPAP	15±3.0	15±3.5	16±2.0	16±2.0	17±1.4
CO	4.8±1.7	9.4±3.5 *	10.6±3.8 *	10.4±2.5 *	9.9±2.5 *
PAWP	7±2.9	6±2.4	6±2.2	7±2.4	6±2.5

Hemodynamics were recorded at Baseline, Therapeutic Start (when 42°C target was met), Therapeutic Middle (1 hr at 42°C), Therapeutic End (2 hrs at 42°C), and Cooling End (baseline temperature restored) time-points.

MAP=mean arterial pressure, HR=heart rate, CVP=central venous pressure, mPAP=mean pulmonary artery pressure, CO=cardiac output, PAWP=pulmonary artery wedge pressure.

N= 7 sheep.

* = p<0.05 vs baseline.

Table 2

Electrolytes

Parameter	Baseline	Therapeutic Start	Therapeutic Middle	Therapeutic End	Cooling End
Sodium (Na ⁺)	143±2	142±2	140±3	139±2 *	139±2 *
Potassium (K ⁺)	3.30±0.35	3.76±0.35	3.73±0.35	3.71±0.40	3.06±0.26
Calcium (Ca ²⁺)	1.05±0.08	1.05±0.18	1.04±0.10	1.06±0.07	1.08±0.13
Chloride (Cl ⁻)	104±2	105±2	104±4	103±4	103±3
Bicarbonate (HCO ₃ ⁻)	27.1±4.2	25.5±3.2	26.0±4.4	24.9±4.9	23.6±5.0
pH	7.40±0.07	7.40±0.04	7.38±0.02	7.39±0.05	7.41±0.07

Arterial blood electrolytes were measured at Baseline, Therapeutic Start (when 42°C target was met), Therapeutic Middle (1 hr at 42°C), Therapeutic End (2 hrs at 42°C), and Cooling End (baseline temperature restored) time-points.

N= 7 sheep.

* = p<0.05 vs baseline.

Table 3**Blood Parameters**

Parameter	Baseline	Therapeutic Start	Therapeutic Middle	Therapeutic End	Cooling End
Hematocrit (%)	27±2.9	28±2.7	27±1.8	27±2.3	26±3.5
Hemoglobin (g/dL)	9.5±0.84	9.3±0.39	9.6±0.74	9.2±0.72	9.0±0.91
RBC ($\times 10^6/\mu\text{L}$)	9.6±1.5	9.6±1.1	9.3±0.60	9.2±1.1	9.0±1.4
WBC ($\times 10^3/\mu\text{L}$)	6.1±1.5	6.3±2.3	7.3±2.7	6.5±2.1	6.1±2.5
Granulocytes (%)	47±19	45±17	41±7	44±18	34±9
Lymphocytes (%)	49±18	51±19	55±7	53±17	61±8
Monocytes (%)	3±0.9	4±2.9	4±2.1	3±0.6	4±2.5
Platelets ($\times 10^3/\mu\text{L}$)	433±135	474±95	462±99	460±114	391±100
Glucose (mg/dL)	85±9	91±17	105±20	129±34 *	142±56 *
ALP (IU/L)	163±41	170±35	174±35	175±36	174±38
ALT (IU/L)	17±6	15±4	14±3	14±3	14±3
BUN (mg/dL)	23±5.6	24±6.0	24±6.1	24±6.4	24±6.9
Creatinine (mg/dL)	0.9±0.3	0.9±0.3	1.0±0.4	1.0±0.4	1.1±0.5
Albumin (g/dL)	2.9±0.3	2.5±0.1 *	2.4±0.2 *	2.3±0.1 *	2.3±0.2 *
Total Protein (g/dL)	5.5±0.5	4.7 ±0.4 *	4.2 ±0.5 *	4.1±0.4 *	4.1±0.5 *

Complete blood counts and blood chemistry were measured at Baseline, Therapeutic Start (when 42°C target was met), Therapeutic Middle (1 hr at 42°C), Therapeutic End (2 hrs at 42°C), and Cooling End (baseline temperature restored).

RBC=red blood cells, WBC=white blood cells, ALP=alkaline phosphatase, ALT=alanine aminotransferase, and BUN=blood urea nitrogen.

N= 7 sheep.

*
=p<0.05 vs baseline.