

## A Simplified Technique For Hyperthermic Limb Perfusion

---

Charles W. Dyson,\* Robert C. Emerson,\* and F. Kristian Storm +

\*Division of Thoracic Surgery, Extracorporeal Technicians, and the +Division of Surgical Oncology

John Wayne Clinic

The Jonsson Comprehensive Cancer Center

UCLA School of Medicine

Los Angeles, CA

and

Surgical Service, Veterans Administration Medical Center

Sepulveda, CA

### Introduction

---

Regional hyperthermic chemotherapeutic perfusion for in-transit metastatic malignant melanoma of the lower extremity has been an integral part of the Surgical Oncology program at the UCLA School of Medicine for the past two decades. The UCLA program reserves perfusion for those patients whose metastatic lesions are unresponsive to intralesional injections of Bacille Calmette Guerin,<sup>1</sup> whereas other investigators employ perfusion as initial adjuvant therapy.<sup>2,3</sup>

Hyperthermic chemotherapeutic perfusion has been shown to be effective for control of extremity melanoma and is currently available in many major cancer centers. Whereas early perfusion with L-phenylalanine mustard (L-PAM) (Melphalan<sup>TM</sup>)<sup>a</sup> based on a pharmacokinetic rationale<sup>4</sup> at normothermic (37°C) temperatures induced a 30 percent tumor response, the response rate increased to 80 percent when heat of 41-42°C was applied.<sup>3</sup>

The original method for limb perfusion was first practiced 25 years ago.<sup>3,4,5</sup> The technique was not without risk and required substantial technical expertise and sophisticated instrumentation. Our extensive experience with these early methods suggested that certain readily available modifications might not only reduce the operative time and technical difficulties associated with the procedure, but could increase safety. Historically, adequate limb temperature was provided by a single heat

exchanger and temperature was maintained by "heating blankets" connected to commercially available hyperthermia equipment that circulated water at a maximum temperature of 40.5°C.

A single heat exchanger is an extremely inefficient method for heat transfer, and its use for rapid heat deposition can cause red-cell damage. Moreover, the many problems associated with the heating blanket include 1) time-consuming preparation and sterilization, 2) the need to maintain sterile techniques during handling, 3) the possibility of a block of effective water flow by kinking or twisting of the water conduits, causing heterogeneity of heating, 4) a maximum temperature limit of 40.5°C with commercial heating-cooling machines, which automatically induces a cooling phase that extracts heat from the treated limb as it approaches this temperature, and 5), most importantly, blanket leakage, which can bathe the surgical site with non-sterile fluid.

Our dissatisfaction with these historic methods led to the present study. We theorized, first, that arterial blood temperatures could be safely raised to 42°C with two active heat exchangers in series that would reduce temperatures enough to lessen the potential for denaturation of blood protein, and, second, that two layers of insulated blankets could maintain skin and muscle temperatures of the extremity at a consistent 41-42°C without using heating blankets, because these blankets are known to reflect  $\geq 80$  percent of the incident heat.<sup>6</sup>

### Methods

---

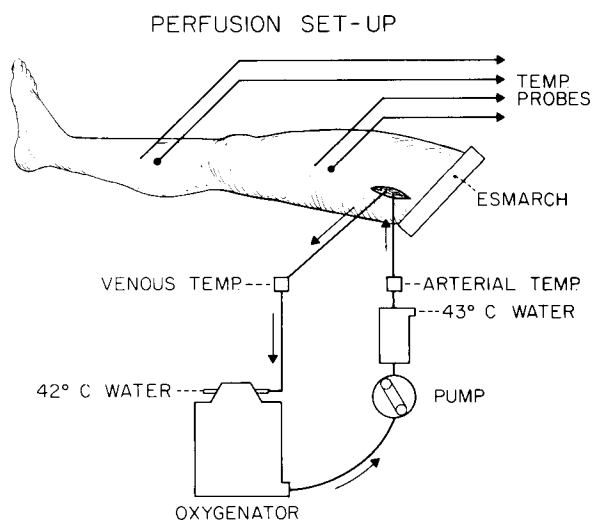
Ten adult patients with metastatic melanoma of the lower extremity underwent chemotherapeutic perfusion with L-PAM at doses of 1.0 mg/kg of body weight. Five received heat by the single-heat-exchanger and hot-water blanket method described above.<sup>1,3</sup> A second

---

Direct communications to: F. Kristian Storm, M.D., Clinical Fellow, American Cancer Society, Division of Surgical Oncology, 9th Floor Louis Factor Building, UCLA School of Medicine, Los Angeles, CA 90024

Presented at AmSECT's 18th International Conference, Philadelphia, PA, March 15, 1980.

a Burrows Welcome Company, London, England.



**Figure 1:** Isolated limb with position of the temperature probes shown. Water at 42 °C is shown going to the heat exchanger built into the oxygenator. 43 °C water is shown going to the heat exchanger in the arterial line.

group received modified perfusion with two in-series heat exchangers and two passive external insulators.

In both groups of patients, the venous-arterial temperature gradient was held to less than 10 °C to prevent oxygen embolism. Neither group had blood gas samples drawn from the pump circuit because oxygen delivery was always in excess of tissue needs (as evidenced by the arterIALIZATION of the venous blood on all patients). Finally, in both groups, the pump was primed with 500 ml of 5 percent albumin and 25 ml of lactated ringers solution.

#### Modified Technique

For the perfusion, the entire leg was surgically prepped before Yellow Springs thermistor probes<sup>b</sup> were placed on the skin and in the deep muscle of both the calf and thigh.<sup>1</sup> The leg was loosely wrapped in a single layer of gauze, and the femoral or iliac artery and vein were cannulated with the largest feasible USCI (Type 1855) cannula.<sup>c</sup> The arterial and venous lines were connected to a Shiley model S-70 Oxygenator<sup>d</sup> with a Travenol 5M0337 Miniprime<sup>e</sup> heat exchanger placed in the arterial line distal to the pump head. Two Sarns<sup>f</sup> 1/4-inch temperature probes, one in the arterial line distal to the

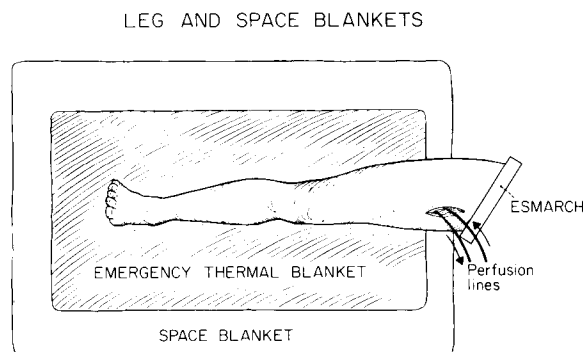
b Yellow Springs Instrument Co., Inc. Yellow Springs, OH 45387

c Bard Surgery Div., Bellerica, MA 01821

d Shiley Laboratories Inc. Irvine, CA 92714

e Omnis Surgical Laboratories Inc. Deerfield, IL 60015

f Sarns, Inc. Ann Arbor, MI 48106



**Figure 2:** Isolated limb on the double layer of Emergency Thermal Blanket™ and Space Blanket™ ready for enclosure.

Travenol heat exchanger and another in the venous line just proximal to the oxygenator (Fig. 1), were used to monitor blood temperatures. With *two* temperature probes in the arterial line, we were able to regulate the water temperature so that the arterial blood was always between 42 °C and 40 °C. (For safety, the maximum water temperature used in this series was 46 °C.) With the venous line temperature probe, we were able to check for blood leaks to the oxygenator circuit (as evidenced by a failure of the venous blood temperature to rise because of the presence of “cool” body blood). The leg was isolated by an Esmark tourniquet around the proximal thigh and held by four to six Steinman Pins placed superficially through the skin in a circumferential manner, as previously described.<sup>1</sup> Perfusion was started and, if pump blood flow was adequate (at least 400 cc per minute) and there were no blood leaks to or from the body of the patient (as evidenced by large volume shifts in the oxygenator), the leg was enclosed with an inner layer of an Emergency Thermal Blanket™<sup>g</sup> and then covered by a Space Blanket™<sup>g</sup> (Fig. 2).

Systemic anticoagulation was performed in both groups of patients with 3 mg/kg heparin. Pump flow ranged from 400 ml to 700 ml per minute for both groups. The cannula and tourniquet were readjusted until a stable state was achieved in each patient. Once one or more of the skin or muscle thermistors reached 40.5 °C, L-PAM was injected into the venous extracorporeal line, and simultaneously, the anesthesiologist administered 20 mg of Furosemide intravenously. The temperature of the arterial blood was adjusted to maintain skin and muscle temperatures between 41 °C and 41.5 °C, with 42 °C as the maximum acceptable temper-

g King Seeley Co., Norwich, CT

ature.<sup>1</sup> Temperatures were recorded every 5 minutes. The thermal perfusion continued for 60 minutes, after which the limb was washed out with two liters of Dextran-40 (10% W/V) in normal saline. One unit of heparinized and recalcified autologous blood was administered before the cannulae and tourniquet were removed and the vessels repaired.

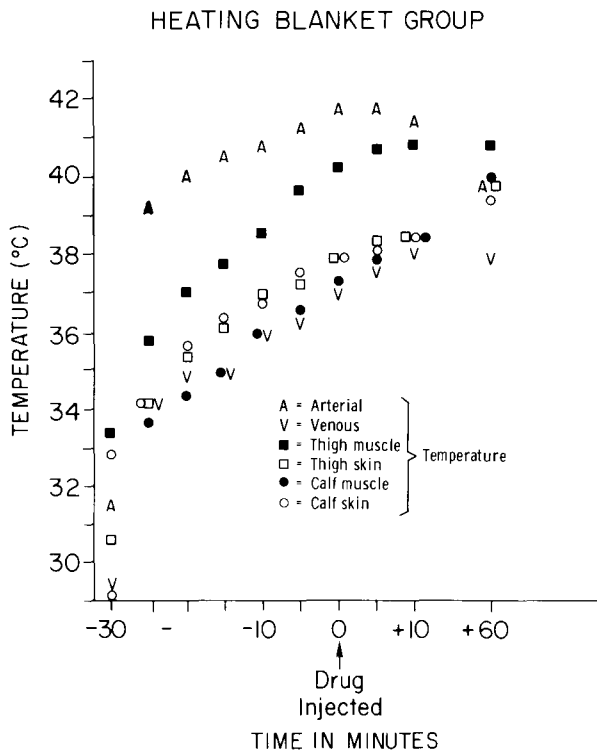
## Results

The mean temperature profiles of the group perfused by historic methods (controls) and for the study group are shown in Figures 3 and 4. Perfusion times for both groups were similar (Table 1), with the historical heating blanket group ranging from 80-100 minutes (a mean of 92.5 minutes) and an average time to drug injection of 29 minutes. The Space Blanket™ and dual heat-exchanger group had perfusion times that ranged from 75 to 95 minutes (a mean of 88 minutes) and an average time to injection of the drug of 28 minutes.

Table 1

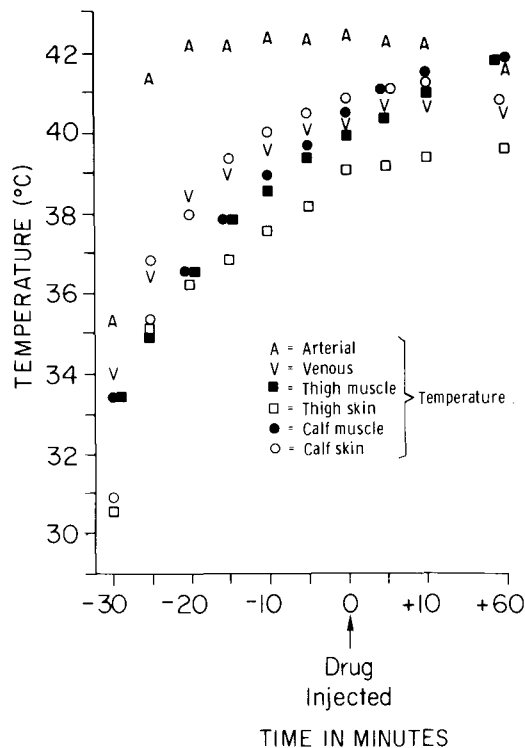
### PERFUSION TIMES (in minutes)

	Group	
	Space Blanket	Heating Blanket
Range of perfusion time	75-95	80-100
Mean perfusion time	88	92.5
Mean time drug given	28	29



**Figure 3:** The mean temperature curves of the five patients warmed with historic heating blankets. The minus times represent the warming period prior to perfusion. The zero time represents the beginning of perfusion with L-phenylalanine mustard (1 mg/kg); +60 minutes is the end of the perfusion.

### SPACE BLANKET GROUP



**Figure 4:** The mean temperature curves of the five patients warmed with the Emergency Thermal™ and Space Blanket™. The minus times represent the warming period prior to perfusion. The zero time represents the beginning of perfusion with L-phenylalanine mustard (1 mg/kg); +60 minutes is the end of the perfusion.

## Discussion

---

While L-PAM perfusion may be a useful tool for the control of metastatic melanoma in the extremity when combined with regional hyperthermia, we believe it should be reserved for a select population of patients.<sup>1</sup> All patients in this series had complete or long-term local response to perfusion, as we had previously observed.<sup>1</sup>

In theory, the use of two heat exchangers in series and passive insulation of a limb with Space Blankets™ could not only simplify the perfusion procedure by providing clinically acceptable heating but could reduce the possibility of a break in sterile technique.

The time required to prepare for the perfusion using Space Blankets™ seemed to be reduced when compared to available commercial hot-water-circulating blankets. Moreover, with Space Blankets™, the more proximal areas of the limb could be included in the therapeutic temperature range, and the heat was more uniformly distributed initially when compared with the bulky heating-blanket method. For example, in patients who were warmed with heating blankets, the thigh muscles reached 40 °C first, with the other areas of the leg lagging behind by 2-2.5 °C. Conversely, patients warmed with the Space Blanket™ had the thigh muscle, calf skin, and calf muscle reach 40 °C at approximately the same time (Fig. 4). Because of the limited number of patients in each group, we could not establish any difference in perfusion times, although there was a trend towards a

shorter time in the Space Blanket™ group. More importantly, those patients treated with in-series heat exchangers and passive insulation achieved temperatures equal to or greater than those treated by historic methods when compared at the same time interval.

Hyperthermic chemotherapeutic limb perfusion has been established as an important treatment modality for metastatic melanoma of the extremity. Our modifications of the original technique suggest that operative time and risk of infection may be reduced by passive insulation of the extremity and optimization of arterial inflow temperature by dual heat exchangers. Our technique provides reduced preoperative and intraoperative preparation and increased patient safety, all factors that encourage the use of this potentially therapeutic modality.

## References

---

1. Storm, F.K., Sparks, F.G., Morton, D.L.: Treatment of melanoma of the lower extremity with intralesional injection of bacille Calmette-Guerin and hyperthermic perfusion. *Surg. Gynecol. Obstet.* 149:17-21, 1979.
2. Rochlin, D.G., Smart, C.R.: Treatment of malignant melanoma by regional perfusion. *Cancer* 18:1544-1550, 1965.
3. Stehlin, J.S., Giovanella, B.C., Ipolyi, P.D., et al: Results of hyperthermic perfusion for melanoma of the extremities. *Surg. Gynecol. Obstet.* 140:339-348, 1975.
4. Berryessa, R., Smart, C.R.: Regional perfusion. *AmSECT Proc.* IV:72-74, 1976.
5. Kremenz, E.T., Ryan, R.F.: Chemotherapy of melanoma of the extremities by perfusion: Fourteen years clinical experience. *Ann. Surg.* 175:900-917, 1972.
6. Personal communication with company.