Effect of Extracorporeally Induced Total Body Hyperthermia for Cancer on Cardiovascular Function

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SUMMARY

Total body hyperthermia (TBHT) was induced in patients with terminal cancer, using a femoral arterio-venous shunt as an extracorporeal circuit incorporating a heat exchanger. A total of 31 systemic hyperthermic treatments lasting 3 to 4 hours at 41.5°C to 42°C (rectal temperature) were performed on 11 patients; chemotherapy had previously been unsuccessful in all of these cases. The effect of TBHT on cardiovascular function was explored in these patients. The heart rate and cardiac output were always markedly increased during hyperthermia, however, the peripheral arterial, central venous, pulmonary arterial and pulmonary wedge pressures were little affected and no progressive metabolic acidosis occurred. TBHT was generally well tolerated and there was no instance in which this treatment had to be terminated because of severe cardiovascular failure during hyperthermia.

Additional Indexing Words:
Hyperthermic treatment  Systemic hyperthermia  Extracorporeal circuit  Terminal cancer  Hemodynamic changes

ALTHOUGH the mechanism underlying the anticancer effect of hyperthermia in heat-sensitive malignant cells remains obscure, it is now generally accepted that the fever induced must be at least 41.5°C to achieve cancer regression. Although clinically applied hyperthermic treatment can be divided into local and total body hyperthermia (TBHT). Although local hyperthermia involves no or minor invasion to patients, it is difficult to apply the optimal temperature to extensive or deep tumors using this technique. We have performed TBHT using an extracorporeal circuit (ECC) modified

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from the original of Parks et al\(^3\) in terminal cancer patients whose tumors were too extensive to be treated with local hyperthermia. We have reported the antitumor effects\(^4\)\(^{-}\)\(^6\) and the effect on host immunocompetence\(^7\) of TBHT in the multimodal treatment of cancer. In this treatment, not only cancerous tissues but also normal organs are heated to a non-physiological level for a long time, raising concerns that damage to the normal organs may ensue, although it appears that the damaging effects of hyperthermia are relatively greater on malignant than normal cells.\(^8\) The effect on cardiovascular function is of particular importance clinically. This aspect, however, has not been widely studied.\(^3\) We now report on the effect of extracorporeally induced TBHT on the cardiovascular function of cancer patients.

**PATIENTS AND METHODS**

*Patients*

Thirty-one hyperthermic treatments were performed on 11 cancer patients ranging in age from 33 to 57 years. All of them were selected for the absence of overt cardiac failure. All patients had recurrent or metastatic cancers after resection of the primary tumor and all of them had undergone

<table>
<thead>
<tr>
<th>Case age</th>
<th>Primary disease</th>
<th>Organ affected by recurrence or metastasis</th>
<th>Pre-treatment cardiac condition</th>
<th>No. of treatments</th>
<th>Antitumor effect</th>
<th>Complication</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. 48 M</td>
<td>Gastric cancer</td>
<td>Liver, Lung</td>
<td>Good</td>
<td>3(2)</td>
<td>NC</td>
<td>NE</td>
</tr>
<tr>
<td>2. 47 F</td>
<td>Gastric cancer</td>
<td>Peritoneum</td>
<td>Good</td>
<td>1(1)</td>
<td>NE</td>
<td>PR</td>
</tr>
<tr>
<td>3. 43 M</td>
<td>Gastric cancer</td>
<td>Lymph nodes</td>
<td>Good</td>
<td>2(2)</td>
<td>NC</td>
<td>NE</td>
</tr>
<tr>
<td>4. 39 M</td>
<td>Gastric cancer</td>
<td>Liver</td>
<td>Good</td>
<td>4(3)</td>
<td>PR</td>
<td>NE</td>
</tr>
<tr>
<td>5. 52 M</td>
<td>Gastric cancer</td>
<td>Liver, Peritoneum</td>
<td>Good</td>
<td>2(2)</td>
<td>PR</td>
<td>NE</td>
</tr>
<tr>
<td>6. 57 M</td>
<td>Gastric cancer</td>
<td>Liver</td>
<td>Good</td>
<td>1(1)</td>
<td>NE</td>
<td>Intraabdominal hemorrhage</td>
</tr>
<tr>
<td>7. 56 M</td>
<td>Rectal cancer</td>
<td>Lung</td>
<td>Good</td>
<td>3(3)</td>
<td>PR</td>
<td>Intrafraftal thrombosis</td>
</tr>
<tr>
<td>8. 51 F</td>
<td>Rectal cancer</td>
<td>Lung, Pelvis</td>
<td>Tachycardia (80–90/min)</td>
<td>1(1)</td>
<td>NE</td>
<td>PR</td>
</tr>
<tr>
<td>9. 57 M</td>
<td>Rectal cancer</td>
<td>Lung</td>
<td>Good</td>
<td>4(2)</td>
<td>NC</td>
<td>NE</td>
</tr>
<tr>
<td>10. 33 M</td>
<td>Malignant melanoma</td>
<td>Subcutaneous tissue</td>
<td>Good</td>
<td>6(3)</td>
<td>PR</td>
<td>NE</td>
</tr>
<tr>
<td>11. 54 F</td>
<td>Osteosarcoma</td>
<td>Pelvis</td>
<td>Tachycardia (80–90/min)</td>
<td>4(3)</td>
<td>NC</td>
<td>NE</td>
</tr>
</tbody>
</table>

Number in parenthesis indicates the number of treatments during which effect of hyperthermia on cardiovascular function was explored.

Abbreviations: NC = no change; NE = not evaluable; PR = partial response.
unsuccessful chemotherapy. The cardiovascular function of these 11 patients was studied during 23 of the 31 treatments they received (Table I).

_ECC induced TBHT_

The inguinal region was incised and a 15 cm loop of a 6 mm vascular graft (Gore-Tex) was anastomosed end-to-side to the common femoral artery and vein as an arteriovenous shunt. The shunt flow volume was 1,350 to 1,900 ml/min (average 1,740 ml/min). The shunt was placed under the skin and the shunt wound was allowed to heal for several days.

On the day of hyperthermic treatment, under general endotrachial anesthesia, a 3 to 5 cm incision was made and the graft was brought through the opening. Heparin (100 units/Kg) was administered and the graft was clamped and divided. Both ends of the graft were connected to the ECC primed with 800 ml Hespander solution (a 6% solution of hydroxyethyl starch with a degree of substitution of 0.55 in lactated Ringer's solution). Heparin (100 units/Kg) was infused intravenously every hour during the hyperthermic treatment. The arterial limb of the ECC was led through a roller pump set to maintain the ECC flow at 1,000 to 1,500 ml/min. The body temperature was checked by thermister probes placed in the esophagus and rectum. The initial temperature of the heat exchanger was set at 48°C; the temperature of the blood from the heat exchanger was approximately 45°C.

When the patient's rectal temperature reached 41.5°C, the temperature of the heat exchanger was reduced to 44–45°C, the flow was decreased to 500–600 ml/min, and the rectal temperature was maintained at 41.5–42°C for 3 to 4 hours (average 3 hrs 32 min). Anti-cancer agents, mainly mitomycin-C (0.3–0.4 mg/Kg) and 5-fluorouracil (10–20 mg/Kg) were administered during hyperthermia.

Upon completion of the hyperthermic treatment the patient's temperature was rapidly lowered by decreasing the temperature of the heat exchanger. When the patient's rectal temperature reached 38°C the ECC was separated from the graft. The ends of the graft were anastomosed end-to-end and the skin incision was closed. This treatment was performed 1–6 times at 7–14 day intervals.

The cardiovascular changes during hyperthermia were monitored continuously by electrocardiography, peripheral arterial and central venous pressures and checked periodically by blood gas determinations and Swan-Ganz thermodilution catheters inserted percutaneously. The blood gas analyses were corrected for the effect of high temperature on the solubility of the gases and on the pKa of carbonic acid for pH determinations. This was done with a preprogrammed hand-held calculator.
Results were expressed as mean±SD, and Student's t-test was used for statistical analysis. A p-value of less than 0.05 was considered to be significant.

RESULTS

There were no instances of severe cardiovascular failure (based on heart rate, peripheral arterial pressure, blood gas, electrocardiographic change, chest roentgenographic cardiothoracic ratio and subjective complaints) following the shunting operation. One patient (Case No. 7) developed thrombosis in the graft 2 days after shunt placement; the thrombi were removed before connecting the graft to the ECC on the day of hyperthermic treatment.

A typical time course of the temperature is shown in Fig. 1. The ECC was efficient enough to elevate the rectal temperature to 41.5°C within 35 to 45 min.

The heart rate and cardiac output were always increased during hyperthermia. The heart rate was 73±13/min and cardiac output was 5.3±0.7 l/min before the shunt was connected to the ECC; when the rectal temperature reached 41.5°C, these values increased to 118±15/min (p<0.001) and 10.3±2.5 l/min (p<0.001), respectively. Neither value returned to the pretreatment level within 1 hour after termination of hyperthermia. Peripheral arterial and central venous pressures were little affected during hyper-

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![Fig. 1. Typical time course and temperature changes during hyperthermic treatment. HE=heat exchanger; EB=extracorporeal blood; R=rectum; E=esophagus.](image-url)
Fig. 2. Effects of hyperthermia on cardiovascular function (Part 1). Values are mean±SD. The heart rate (HR) is shown by solid circles and straight lines and the cardiac output (CO) by solid circles and broken lines. The systolic arterial pressure (SAP) is shown by open circles and straight lines and the central venous pressure (CVP) by open circles and broken lines. HR and CO were increased during hyperthermia, SAP and CVP were little affected. * p<0.01, ** p<0.05 vs pretreatment values.

Hyperthermia (Fig. 2). The systolic pulmonary pressure was elevated (p<0.01) only when the rectal temperature reached 41.5°C; it declined gradually thereafter. The diastolic pulmonary and pulmonary wedge pressures were not affected (Fig. 3). PaO₂ was little affected. While the base excess and pH declined gradually, no progressive metabolic acidosis occurred (Table II).

Hyperthermic treatment was generally well tolerated and there was no instance in which this treatment had to be terminated because of severe arrhythmia, sinus tachycardia or other electrocardiographic changes.

DISCUSSION

Hyperthermia as a new modality in cancer treatment has become a topic of broad interest and many clinical and experimental studies are in progress. In our series, partial regression (tumor regression exceeding 50%) was observed in 4 of 8 evaluable patients. This suggests that TBHT may be useful in the treatment of terminal cancer.

Recurrent or metastatic cancer is not a local but a systemic disease at the
Fig. 3. Effects of hyperthermia on cardiovascular function (Part 2). Values are mean ± SD. The systolic pulmonary pressure (SPP) is shown by solid circles and straight lines, the diastolic pulmonary pressure (DPP) by solid circles and straight lines and the pulmonary wedge pressure (PWP) by open circles and straight lines. SPP was elevated during the initial phase of hyperthermia, DPP and PWP were not affected. * p<0.01 vs pretreatment values.

Table II. Effects of Hyperthermia on Arterial Blood Gases
(n=11, 23 treatments)

<table>
<thead>
<tr>
<th>Analysis</th>
<th>Before</th>
<th>Rectal temp. (41.5-42°C)</th>
<th>1 h after hyperthermia</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>0</td>
<td>1 h</td>
</tr>
<tr>
<td>PaO₂ (mmHg)</td>
<td>158.9 ± 40.8</td>
<td>158.9</td>
<td>164.2</td>
</tr>
<tr>
<td>PaCO₂ (mmHg)</td>
<td>33.7 ± 6.2</td>
<td>39.8 ± 5.2*</td>
<td>38.7</td>
</tr>
<tr>
<td>Base excess</td>
<td>0.055 ± 1.769</td>
<td>-0.525</td>
<td>-1.667</td>
</tr>
<tr>
<td>pH</td>
<td>7.499 ± 0.058</td>
<td>7.403</td>
<td>7.381</td>
</tr>
</tbody>
</table>

* p<0.05, ** p<0.01 vs pretreatment values.
Values are mean ± SD.

time of its diagnosis. Therefore, hyperthermic treatment should be applied to the total body. Various approaches for TBHT have been tested, e.g., the heated gas inhalation method accompanied by the molten paraffin method,9) the heat-blanket method,10,11) the hyperthermic chamber method,12) the
water perfusion suit method\textsuperscript{13)} and the extracorporeal circulation method.\textsuperscript{3,4,5)} Irrespective of the heating method used, it is indispensable to control the body temperature and to monitor bodily reactions during treatment. The extracorporeal method facilitates the precise control of body temperature.

As severe cardiovascular disorders were not observed following the shunting operation, the use of a large-flow arterio-venous shunt most probably does not excessively overload the heart.

Regarding the effects of TBHT on cardiovascular function, the heart rate and cardiac output were always increased, however, peripheral arterial, pulmonary arterial, pulmonary wedge and central venous pressures were little affected. No progressive metabolic acidosis occurred. These findings suggest that the increase of tissue oxygen consumption and the dilation of peripheral blood vessels induced by hyperthermia were compensated for by an increase in both the heart rate and the cardiac output. All of our patients tolerated both shunting and hyperthermia well. The observed cardiovascular changes were not markedly different from those reported for the water perfusion suit method\textsuperscript{13)} and the heat-blanket method.\textsuperscript{11)}

Our results showed that the cardiovascular changes induced by hyperthermic treatment were well tolerated in patients with terminal cancer, excluding those with severe dysfunction of the cardiovascular system. However, we strongly suggest that patients undergoing TBHT treatment should be monitored closely. Careful attention must be given to the cardiovascular changes and the potential development of progressive acidosis.

\textbf{REFERENCES}

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