

## Time-Course of Body Temperature and Postoperative Complication in Whole Body Hyperthermotherapy

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### SUMMARY

Whole body hyperthermotherapy was applied to 15 cases of 12 patients as treatment for malignant tumor, by means of extracorporeal circulation with 12 cases, including 7 cases of the V-A bypass and 5 cases of the A-V bypass, as well as surface warming with 3 cases. The therapeutic temperature of 41 °C or above was maintained on all of them for 2 hours and 57 minutes on an average. The longer time was required for body temperature elevation by extracorporeal circulation, while no difference was noted in both ways for lowering body temperature. In addition to 5 cases of paralysis on the femoral area for the extracorporeal circuit, each one case of herpes zoster, renal failure, heart failure and posttransfusion hepatitis was noted as postoperative complication by the extracorporeal circulation. As to the renal function more than a half of them showed increase of serum BUN and serum creatinine. Referring to blood examination, thrombocytopenia and leukocytopenia were noted on nearly all of those with extracorporeal circulation. The therapeutic effect was determined positively with 4 patients.

### INTRODUCTION

Recently, besides surgical, radiological and chemical therapies for malignant tumor,

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the hyperthermotherapy has been closed up. Thus, together with the local hyperthermotherapy for bladder tumor and uterine tumor (3), the whole body hyperthermotherapy by extracorporeal circulation (11, 14) and surface warming (1, 9) have been applied commonly. In this study, the authors employed the hyperthermotherapy by means of both extracorporeal circulation and surface warming for the patients with malignant tumor and as a supplemental step before the radical operation. It was applied to 15 cases of 12 patients accordingly. The time-course of body temperatures and postoperative complications are reported below.

## MATERIALS AND METHODS

The patients with malignant tumor treated in the our medical college Hospital, to whom the radical operation was inapplicable, or those treated for the purpose of preventing metastasis before the radical operation, underwent this therapy. Extracorporeal circulation was conducted as follows: A bypass was made between femoral artery and femoral vein, and blood was warmed up using the Console 5000 (Sarns) artificial heart, lung and heat exchanger set at the highest water temperature of 44°C to maintain the circulate blood temperature of about 42°C. Perfusion flow out of the artificial heart was adjusted to be about 1/2 to 1/3 of the optimal flow. Thus, in this hyperthermotherapy, extracorporeal circulation was conducted in 2 ways, namely, the arteriovenous bypass (A-V Bypass) and the venoarterial bypass (V-A Bypass). Surface warming was conducted as follows: A patient was covered with vinyl sheet and dipped in the hypothermia unit of Iwate Medical College System controlled by the thermounit (Taiyu 201) to have a water temperature at about 3°C higher than the patient's temperature. Thus, having the water temperature set at 45°C, whenever the patient's temperature arrived at 42°C, the water temperature was adjusted to keep the same level.

In both ways, the patients were induced with 5mg/kg of thiamylal, and maintained with nitrous oxide and infusion of thiamylal at 5-10mg/kg/hour. Meanwhile, fentanyl was dosed appropriately upon surgery for extracorporeal circulation. As the monitors, chest lead ECG, arterial pressure at left radial artery, cardiac output and PA pressure by Swan-Ganz catheter inserted from internal jugular vein, etc., were used. Body temperature were measured at 5 spots, namely, at esophagus and rectum by ETC-21A (Top), at forehead and planta by a thermometer (Terumo), and at pulmonary artery by the Swan-Ganz catheter.

For two weeks after the therapy, the course was observed according to the blood examination and biochemical tests.

## RESULTS

As shown in Table 1, the hyperthermotherapy was applied to 12 patients of their age ranged from 14 to 74 years (47.1 years on an average), including 3 patients who were treated twice with this therapy. Sarcoma was noted more in the younger age, while carcinoma was noted more in the older age. Mostly Adriamicin was used concomitantly as antitumor drug, except one. V-A Bypass was applied to 7 cases and A-V Bypass was applied to 5 cases, while surface warming was applied to the remaining 3 cases.

Referring to the report of NOGUCHI *et al.* (12), changes of body temperature were all compared with pulmonary artery temperature. Fig. 1 showed 3 cases each of surface warming and extracorporeal circulation, while Table 2 shows the time course and the highest temperature of the surface warming and extracorporeal circulation respectively. In comparison with those over 41°C as therapeutic temperature, it required a little longer time to arrive at the therapeutic level with extracorporeal circulation, while maintenance of the temperature was shorter with surface warming being 2 hours compared with that of extracorporeal circulation being longer than 3 hours. The highest temperature was 41.3°C to 42.1°C, 42.79°C on an average of the total cases. There was no difference in time needed for lowering of body temperature, being 30 minutes on an average.

As to changes in the circulatory system according to a elevation of body temperature, (Fig. 2 shows each one case of examples), either extracorporeal circulation or surface warming showed nearly no difference, increasing both heart rate and cardiac output as body temperature elevation, and decreasing mean arterial pressure. Although it is not shown in the figure, total vascular resistance also decreased as body temperature increased.

As postoperative complications, leukocytopenia was noted on almost all of the patients with extracorporeal circulation 10 to 14 days after the therapy, with white blood cells reduced to 2000-3000 per  $\text{mm}^3$ , including one case showing the lowest of 400-600 per  $\text{mm}^3$ , in addition to one case of postoperative hemorrhage noted upon the hematological examination. At the same time thrombocytopenia was observed 2 to 4 days after the therapy with platelet reduced to 30,000-70,000 even upon platelet transfusion, which was not found at all in those with surface warming. As to electrolytes, remarkable change was not noted

Table 1. Patients of hyperthermotherapy

name	sex	age	wt	diagnosis	method	antitumor drugs	complication
O. R.	M	17	50	synovial cell sarcoma	V-A Bypass	ADM	hypesthesia right leg
O. R.	M	17	48	synovial cell sarcoma	Surface	(-)	
W. S.	F	74	49	lung cancer	V-A Bypass	ADM	leucopenia (400)
O. H.	F	61	47	bladder cancer	V-A Bypass	ADM	
N. Y.	M	57	53	bladder Cancer	V-A Bypass	ADM	herpes zoster, hypesthesia
T. S.	M	50	54	pancreas cancer	V-A Bypass	MMC	hepatitis, hypesthesia
O. Y.	M	61	63	lung cancer	V-A Bypass	C-DDP, VCR	renal failure, hypesthesia
T. M.	F	48	47	synovial cell sarcoma	A-V Bypass : pre op.	ADM	post operative bleeding, pulmonary edema
K. F.	M	43	52	malignant melanoma	Surface	PEP	
T. S.	M	51	54	pancreas cancer	A-V Bypass	MMC	
O. K.	F	35	49	synovial cell sarcoma	A-V Bypass	ADM	ICU synd.
O. K.	F	36	49	synovial cell sarcoma	A-V Bypass	ADM, C-DDP	
S. H.	F	53	47	rectal cancer	A-V Bypass	MMC	hypesthesia leg
T. R.	F	53	56	renal cancer	Surface	ADM	
M. T.	F	14	40	osteosaroma	V-A Bypass : pre op.	ADM	

ADM : adriamycin, MMC : mitomycin, VSR : vincristine, PEP : pepleomycin, CDDP : cisplatin

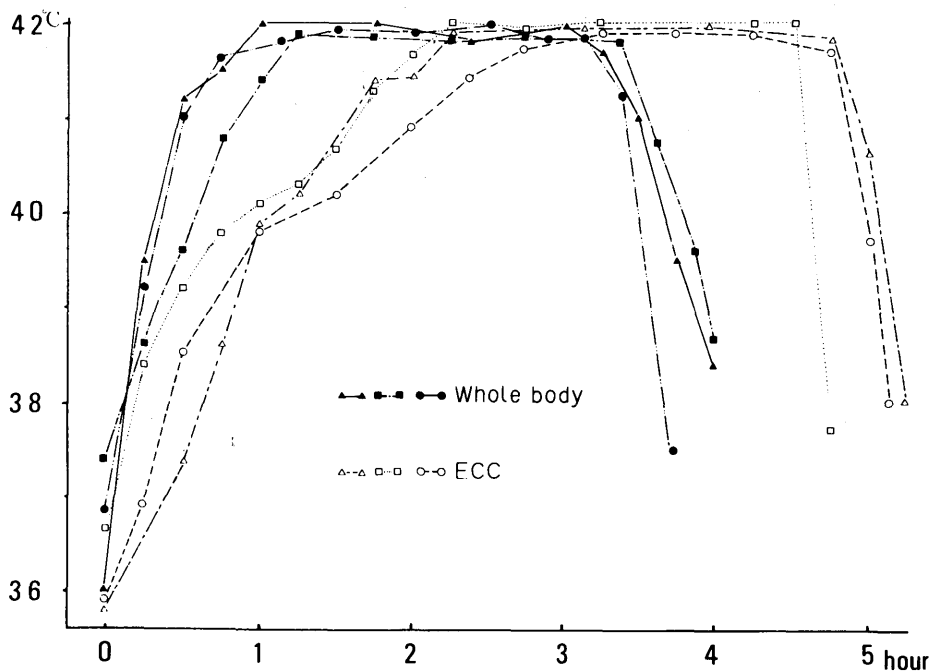
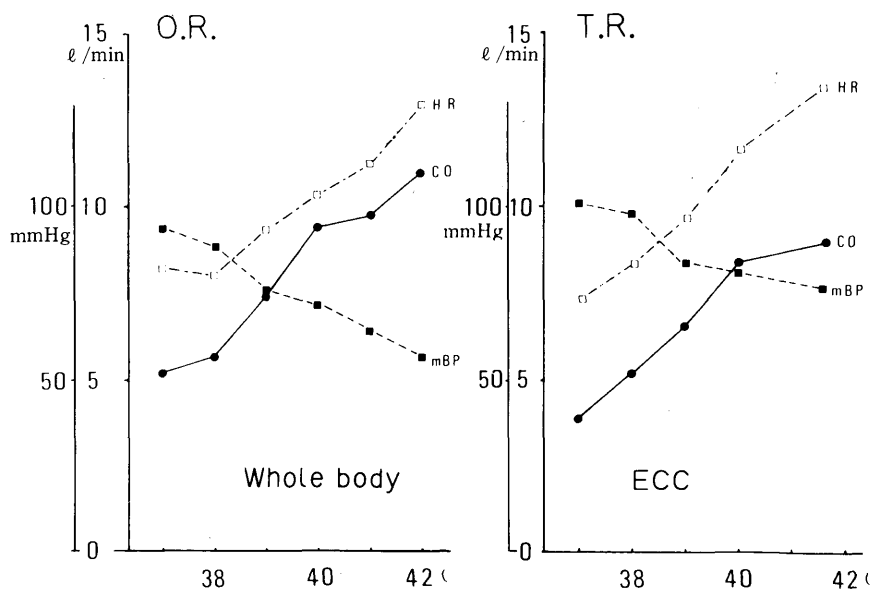


Fig. 1. Pulmonary artery temperature during hyperthermotherapy of each 3 cases of surface warming and extracorporeal circulation method.

**Table 2.** Time course and highest temperature during hyperthermotherapy.

name	elvatig time	maximum temp(°C)	holding time	lowering time	total time
<b>V-A Bypass</b>					
O. R.	0 : 50	41.4	2 : 40	0 : 45	4 : 15
W. R.	1 : 45	41.9	3 : 00	0 : 45	5 : 30
O. H.	1 : 00	41.5	3 : 05	0 : 15	4 : 20
N. M.	1 : 00	41.5	3 : 30	0 : 30	5 : 00
T. S.	1 : 40	41.3	2 : 30	0 : 15	4 : 25
O. Y.	1 : 00	42.0	3 : 15	0 : 20	4 : 35
M. T.	0 : 50	41.9	3 : 45	0 : 15	5 : 00
<b>A-V Bypass</b>					
T. M.	1 : 05	41.8	3 : 20	0 : 15	4 : 40
T. S.	1 : 00	41.8	3 : 15	0 : 30	4 : 45
O. K.	2 : 00	41.9	2 : 10	0 : 45	4 : 55
O. K.	0 : 55	42.0	4 : 00	0 : 25	5 : 20
S. H.	1 : 30	42.1	3 : 20	0 : 45	5 : 35
<b>Surface Warming</b>					
O. R.	1 : 10	41.8	2 : 00	0 : 30	3 : 40
R. F.	1 : 00	41.8	2 : 10	0 : 26	3 : 36
T. R.	0 : 45	42.1	2 : 15	0 : 45	3 : 45
average	1 : 10	41.79	2 : 57	0 : 30	3 : 37

**Fig. 2.** Cardiovascular responses during hyperthermotherapy

O. R.: patient's name: Surface warming method

T. R.: patient's name: Extrcorporeal circulation method

with Na and K ions but P and Ca ions. P ion was reduced 2-4 days after the therapy to 1.1-3.6mg/dl, 2.52mg/dl on an average, which occurred markedly on those with extracorporeal circulation. Next, upon serum biochemical tests, GOT and GPT rose temporarily, but reduced to the normal range in 3 or 4 days. Increase of LDH, however, was notable with 8 cases exceeding 1,000 unit, with the maximum value of 45,841 unit. On the contrary, cholesterol showed reduction postoperatively, which however returned to the preoperative level within a week. As to serum BUN and creatinine reflecting the renal function, firstly 9 patients exceeded the normal range of serum BUN, 20mg/dl, and 4 patients did that of 1.5mg/dl, out of which one patient died of renal failure 3 weeks after the therapy.

As other notable complications, 5 patients complained of muscle weakness and hypesthesia of femur used for perfusion, while each one case of herpes zoster and heart failure respectively was observed.

Lastly, the hyperthermotherapy was markedly effective on 2 cases, effective on 2 cases, ineffective on 6 cases and unknown on 2 cases.

## DISCUSSION

Concerning the hyperthermotherapy, already at the end of the last century COLEY *et al.* (2) reported that high body temperature was efficacious as treatment of cancer. However since 1971 when PETTIGREW *et al.* (4) employed the transtracheal warming in addition to surface warming, the hyperthermotherapy was watched again. Thus, whole body hyperthermotherapy has been applied in many ways, being considered to be more effective on tumors compared with local hyperthermia (15) using microwave for prevention of metastasis.

In this study 15 cases in 12 patients were treated in two ways by means of extracorporeal circulation and surface warming by hot bath. Extracorporeal circulation was conducted also in two ways of bringing out and sending in the blood. On account of tumor located in femur specially the V-A Bypass was employed for the first case followed by the same way for the case 4 and 5, and after that A-V Bypass was employed. It seems that when tumor is located in the lower limbs, V-A Bypass is used and A-V Bypass shall be used for other cases, which gives less effect on femoral nerves.

As to a rise of body temperature, extracorporeal circulation indicates a little delayed trend. Since it is largely influenced by the highest temperature of the heat exchanger, we tried to maintain temperature of the heat exchanger in contact with blood not exceeding

43 to 44°C, which required the longer time to raise body temperature of the patients compared with those in the other reports. (11, 14) However, in consideration of the effect on the circulatory system by rapidly raising body temperature, it might be in danger of circulatory collapse according to rapid vasodilatation. Therefore, further studies need to be done on an elevating rate of body temperature. Furthermore, the time required to elevate at the highest temperature was shorter with surface warming, which is considered to be due to about 2 degrees higher temperature given from the outside. Difference of maintenance time was caused because surface warming was suspended earlier than expected as ST depression was noted on ECG over 2 hours. It is considered to be not so meaningful to compare the time needed for lowering body temperature, because it differs much by temperature of cooling water, however, the less effect on the circulatory system seemed to be expected by lowering body temperature not so fast.

In the circulatory system, cardiac output and heart rate increased as body temperature elevation and mean arterial pressure is somewhat reduced as stated in other reports (8, 13, 16) but changes are not so particular. Peripheral resistance reduced rapidly showing the same trend as reported on other hyperthermotherapies as well as changes in the circulatory system while body temperature is rising as reported by Honda *et al.*<sup>5,6)</sup>

As the hematological findings, leukocytopenia was noted after the therapy, on which effect of high body temperature is undeniable, but it is assumed to be influenced by the function of bone marrow, as abundant antitumor drug was used during the therapy. However, thrombocytopenia is considered to be occurred due to the effect of extracorporeal circuit, since it was not noted with surface warming. As treatment, MAEDA *et al.* (11) obtained a favorable result by administration of prostaglandin. In this study, however, platelet had to be dosed after the therapy as prostaglandin was nearly ineffective, probably on account of the smaller dose.

TANAKA *et al.* (16) reported that there was no notable postoperative complications, no remarkable change on the important organs either. In this study, only one case of postoperative serum hepatitis was noted as an effect on the liver. However, the effect on the kidney was remarkable, losing a patient 3 weeks after the therapy, and upon postoperative biochemical examinations, more than a half of the patients showed serum BUN and creatinine exceeding the normal level. KIM *et al.* (7) reported that upon autopsy of heatstroke, tubulorrhesis was found on the kidney, and LEE *et al.* (10) stated too that effect of hyperthermia on the kidney is not negligible. In this study, use of an antitumor drug with strong renal toxicity is supposed to be one of major reasons why renal failure was caused. As a treatment it seems to be necessary at least to maintain the kidney output in

addition to keep the blood pressure on a certain level.

Out of 15 cases treated with hyperthermotherapy in this study, 4 cases were effective but 1 case was lost by renal failure. There are still much of unknown points in the hyperthermotherapy, therefore, it is considered to be necessary to further accumulate the basic study with more experiences.

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