Alkalization of blood pH is responsible for survival of cancer patients by mild hyperthermia

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ABSTRACT

The effect of mild hyperthermia on venous blood pH was examined in 6 cancer patients. Mild hyperthermia was induced by continuation of a rectal temperature of 39.5°C for 30 min. All 6 patients were diagnosed as suffering from advanced cancer with or without surgery and chemotherapy pretreatments. In Cases 1 to 5, but not Case 6, venous blood pH was alkalized up to pH 7.7 by this mild hyperthermia and the effect was reproduced depending on the application of hyperthermia. At this time, alkalized pH was accompanied by increased PO₂ and decreased PCO₂ in the blood. These patients showed good physical conditions and improved clinical data. On the other hand, hyperthermia could not be continued in Case 6 due to his worsened physical condition. The present data suggest that mild hyperthermia is a useful method to improve circulation failure, physical condition and clinical data.

Many cancer patients are suffering from hypothermia and circulation failure (8, 11, 12, 18) due to vessel constriction induced by sympathetic nerve activation (1, 19). As a result, immunosuppression is often accompanied with these patients, showing lymphocytopenia. Restoration from this circulation failure seems to be important for the treatment of cancer. In this regard, there have been many trials of hyperthermia for the treatment of malignancy (6, 9, 17, 20). Hyperthermia indeed ameliorates not only immune functions but also other physical conditions.

In the course of these studies, we have noticed that hyperthermia (i.e., > 40°C) sometimes induced rather immunosuppression as a thermal stress (14). At this time, persons who experienced with hyperthermia showed granulocytosis and lymphocytopenia after the treatment. This might be due to the fact that overexposure of hyperthermia induced stress-associated sympathetic nerve activation and that granulocytes bear surface adrenergic receptors but lymphocytes bear surface cholinergic receptors (13, 15). A similar response was also reported in animal studies (16). Dogs and cats which experienced with severe hyperthermia showed immunosuppression, showing granulocytosis and lymphocytopenia.

In an earlier study, we showed that hyperthermia at the level up to 39.5°C (rectal temperature) for 30 min did not induce granulocytosis but rather induced immunopotentiation (14). In the present study, we applied this condition of hyperthermia for 6 cancer patients. As shown previously and in this study, an appropriate condition of hyperthermia is well correlated with the alkalization of blood pH with increased PO₂ and decreased PCO₂ after the application of hyperthermia.

MATERIAL AND METHODS

Subjects. Diagnosis of all cancer patients, including
sex, age and the number of application of hyperthermia, is listed in Table 1. Cases 1, 2 and 4 were operated with hyperthermia, without the history of surgical operation and chemotherapy. By PET and CT examinations, tumor size became small in these cases and therefore hyperthermia was continued. In Case 3, surgical operation and irradiation were conducted. However, tumor size was not changed but physical conditions were worsened. Thereafter, hyperthermia was started in this case.

In Case 5, he was suffering from type C chronic hepatitis and was thereafter diagnosed as hepatocellular carcinoma. Chemotherapy was conducted but size of tumors (three spots of tumors in the liver) was enlarged. Thereafter, hyperthermia was started. Case 6 was the end stage of lung cancer and chemotherapy was conducted. However, he was suffered from bad physical conditions and therefore chemotherapy was ceased and was changed into hyperthermia.

In all cases, applications of hyperthermia were conducted in 2006 and 2007. Except Case 6, all cases could be continued with hyperthermia and they kept good life in Spring, 2008. All cases accepted the informed consent.

Temperature control equipment. The “Thercura System” is a big hot water bath equipped with a temperature control system (ThermoVision, Osaka, Japan) (14). This device is able to maintain the rectal temperature up to the range of 0.1°C. In this study, the rectum temperature of subjects was controlled at 39.5 (± 0.2)°C for 30 min. To reach this level, approximately 40 to 50 min was required in each patient. In general, the hyperthermia application was done twice a week.

Parameters tested. Thermal exposure influenced various parameters in the circulation and immune system. To test a change of the circulation, pH, PO$_2$ and PCO$_2$ were measured in the venous blood. The parameters of the immune system included the number of leukocytes and their subsets in the venous blood. Tumor markers and virus titers were also examined in the clinic.

RESULTS

Relationships between hyperthermia and blood pH

Kinetics of rectal temperature after exposure of the hyperthermia equipment was shown in Cases 1 to 3 (Fig. 1). Within 60 min, rectal temperature in all

![Fig. 1](image-url)

**Table 1  Cancer patients treated with hyperthermia**

<table>
<thead>
<tr>
<th>Case No</th>
<th>Type of cancer</th>
<th>Sex</th>
<th>Age</th>
<th>Number of application</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case 1</td>
<td>Neuroblastoma</td>
<td>M</td>
<td>26</td>
<td>18</td>
</tr>
<tr>
<td>Case 2</td>
<td>Papillary thyroid carcinoma</td>
<td>F</td>
<td>59</td>
<td>20</td>
</tr>
<tr>
<td>Case 3</td>
<td>Tongue carcinoma</td>
<td>M</td>
<td>63</td>
<td>14</td>
</tr>
<tr>
<td>Case 4</td>
<td>Breast carcinoma</td>
<td>F</td>
<td>40</td>
<td>16</td>
</tr>
<tr>
<td>Case 5</td>
<td>Hepatocellular carcinoma</td>
<td>M</td>
<td>64</td>
<td>38</td>
</tr>
<tr>
<td>Case 6</td>
<td>Lung carcinoma</td>
<td>M</td>
<td>72</td>
<td>25</td>
</tr>
</tbody>
</table>

Application means the treatment of hyperthermia.
Blood pH and hyperthermia

The most prominent sign was a change of venous blood pH before and after the application of hyperthermia (Fig. 2). Before the application, blood pH was low showing less than pH 7.4 in Cases 1 to 6. However, this level was changed up to pH 7.4 to 7.7, irrespective of the repeated number of application, especially Cases 1 to 5. In Case 6, such the change after the application was not seen. The application in Case 6 was not able to be continued due to his bad physical conditions.

A relationship between rectal temperature and blood pH was then examined in Cases 1 to 6 (Fig. 3). The data included those before and after the application of hyperthermia. It was clearly demonstrated that rectal temperature and blood pH were well correlated in Cases 1 to 5. In Case 6, the alkalization of blood pH was not induced even by hyperthermia.

**Fig. 2** Venous blood pH before and after hyperthermia. Just after hyperthermia, blood pH was increased up to 7.7. In Cases 3 to 5, the reached level of pH was increased as a function of the application. In Case 6, alkalization of pH was not induced even by hyperthermia.

**Fig. 3** Relationship between rectal temperature and blood pH. Alkalized pH was obtained by the increased rectal temperature in Cases 1 to 5.

High blood pH accompanied high PO₂ and low PCO₂

Venous blood was examined on the levels of PO₂ and PCO₂ before and after the application in Cases 1 to 6 (Figs. 4 and 5). In Cases 1 to 5, alkalized blood pH was correlated with high PO₂ and low PCO₂. However, these correlations were not seen in Case 6. More precisely, the phenomenon of alkalized blood pH, high PO₂ and low PCO₂ by hyperthermia was not induced in Case 6.

Variation of the number of white blood cells, lymphocytes and red blood cells during hyperthermia

The number of blood cells was examined during the application of hyperthermia (Fig. 6). In Cases 1 to 4 (and Case 6), the levels of the number of white blood cells were around 5,000/μL even before the application. However, that was very low (approximately 2,000/μL) in Case 5. After the application, the level was increased in Case 5 and 6 but that was stationary in other cases.

The number of lymphocytes was high in Case 4
DISCUSSION

For a long time, many clinicians and investigators have considered that the onset of cancer is induced by external carcinogens such as over-exposure to ultraviolet rays from sun, some food-derived carcinogens, habits of heavy smokers, etc (2–5, 7, 10). There are such cases in some patients. However, we propose another possibility that hard works or mental stresses which stimulate sympathetic nerves induce the onset of cancer via circulation failure and granulocytosis (and lymphocytopenia) (1). Circulation failure which is accompanied with hypothermia and granulocytosis may then induce tissue-destruction (19). Under these conditions, such tissues have to continue cell division to restore the damage under bad conditions of circulation failure. In addition to immunosuppression of lymphocytopenia, these conditions finally induce the onset of malignancy, namely, the external causes of cancer.

In the course of these studies, we have applied hyperthermia and noticed that high temperature of hyperthermia (i.e., > 40°C) induced thermal stress rather than immunopotentiation (14). The maximum condition might be 39.5°C of rectal temperature for

but that was low in Case 3 and 5. Those in other cases were almost a normal level (i.e., around 2,000/μL). In Case 3, the number of lymphocytes was increased by hyperthermia but not in the others. In Case 6, the number of lymphocytes were rather decreased by hyperthermia, suggesting that the number of granulocytes was inversely increased.

The number of red blood cells tended to be slightly increased in all cases.

Improvement of tumor makers and other factors

Clinically, Cases 1 to 5 kept good conditions during and after hyperthermia, showing even tumor regression by CT examination. In Case 6, hyperthermia could not be continued by his worsen physical conditions. In this figure (Fig. 7), time kinetics of tumor markers and others were shown. In Cases 1, 3 and 5, an improvement of tumor makers was observed, whereas it was not the case in Case 6. In Case 2 the level of thyroglobulins was almost normal and in Case 5, the level of HCV-RNA was decreased as a function of the application of hyperthermia.

Fig. 4 Relationship between blood pH and PO₂

Fig. 5 Relationship between blood pH and PCO₂
Blood pH and hyperthermia

30 min. If we selected more strong conditions of hyperthermia, it was experienced that such hyperthermia induced granulocytosis and lymphocytopenia. Therefore, in this study, we conducted a mild hyperthermia which did not induce granulocytosis.

We experienced that many cancer patients with good results showed alkalized level of venous blood pH. This change of pH was due to the increase of PO\textsubscript{2} and the decrease of PCO\textsubscript{2}. Actually, all patients, except Case 6, changed their face color from pale to red. The color of venous blood was also changed from black to fresh red in a syringe. In other words, these patients could escape from circulation failure by the operation of mild hyperthermia.

In Cases 3 and 5, alkalization level of blood pH was increased as a function of the number of application. This might be due to the adaptation response of hyperthermia. Such a response was lacked in Case 6. At a short period after the thermal therapy, this patient finally died of the lung cancer. In Case 3 and 5, the number of lymphocytes was also prominently increased depending on the number of application and their physical conditions were good after a final treatment of hyperthermia. These two cases showed good results even from clinical data shown in Figure 7.

Since hyperthermia increases the metabolism of patients, this treatment is considered to increase somewhat respiration rates in patients. However, we

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**Fig. 6** Variation of the number of blood cells during hyperthermia

**Fig. 7** Variation of tumor markers and other factors during hyperthermia. NSE: neuron-specific enolase, Tg: thyroglobulin, SCC: squamous cell carcinoma-related antigen, PIVKA-II: protein induced by vitamin K absence-2, HCV-RNA: hepatitis C virus-RNA (ribonucleic acid)
could not observe hyperventilation in our patients during the hyperthermia treatment. Therefore, the alkalization of blood pH was not due to hyperventilation. It is conceivable that the improvement of circulation itself in patients might be important for induction of the present phenomenon.

If clinicians think about direct heat effects on cancer cells (i.e., >40°C), thermal applications directly surfer such patients and induce immunosuppression (16). We think that thus far thermal treatments have not achieved good results for cancer therapy. On the other hand, the mild hyperthermia applied here showed good results for many cancer patients even with advanced malignancy. The improvement of circulation failure is a key word in the present study and the alkalization of pH seems to be a good indicator for the treatment. However, if such the alkalization of pH is not able to be induced, the result may not be good.

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