Special Topics from Japan
Thrombotic and Hematostatic Reactions to Bathing in Very Hot Hot-Spring

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Abstract
Very hot hot-spring is loved by the Japanese, although it might cause thrombotic events. It causes addiction to hyperthermia possibly because of an increase in the production of morphine-like substance. Increases in platelet activation, adhesion molecules on the platelet surface, platelet-derived microparticles, and blood viscosity as well as decreases in fibrinolytic capacity and blood pressure were observed after bathing in very hot hot-spring. Bathing in very hot hot-spring is not recommended for the elderly in view of age-related changes in endothelial function, fibrinolytic capacity, dehydration, and dysregulation of blood pressure. Instead, hydrotherapy or bathing in hot-spring in temperatures under 42℃ is beneficial with little risk regarding hemostasis and thrombosis.

Keywords: very hot hot-spring, Jikan-yu, Kusatsu, thrombosis, stroke

INTRODUCTION
The Japanese love to bathe in hot water around 42℃ up to the shoulder level. No other nationality can understand this bathing habit and some refers to this temperature as excessively hot. However, the Japanese think of it as a comfortable temperature. This difference may partly be derived from heat shock proteins gradually induced in the Japanese because of such bathing habits. This type of Japanese bathing is characterized by immersion in hot water with the head out and no exercise. In contrast, in Europe, hydrotherapy is performed by using water at 25–38℃ for the sake of exercise under water.1) The difference between both bathing habits might explain the difference in hot-spring therapies between Europe and Japan. On the other hand, the number of diseases associated with hot water bathing in Japan is reported to be higher than that in other countries.2) Why do the Japanese prefer bathing in very hot hot-spring? We studied the clinical reactions to bathing in very hot hot-spring water at 47℃. This article summarizes a study series performed at Kusatsu Branch Hospital, Gunma University Hospital
(Figure 1) in the Kusatsu hot-spring resort (Figure 2), Japan, with special reference to thrombotic diseases and very hot hot-spring water immersion.

I  TIMED BATHING “JIKAN-YU”

The Japanese have a traditional bathing method known as timed bathing, Jikan-yu in Japanese, which has been performed since the 18th century in a hot-spring resort, Kusatsu, Japan. People bathe in very hot (47℃) hot-spring water 4 times a day at certain times, which is the reason why it is called timed bathing. First, the bather mixes very hot hot-spring water of 50℃ or higher using a long board in order to lower the temperature to 47℃ (Figure 3). Next, the hot-spring water is poured onto the head to adapt to the high temperature. Last, the bather bathes in the very hot hot-spring water of 47℃ up to shoulder level. A 3-min bath in this manner is taken 4 times a day. The bathers enter in and out of the bathing pool in a group following a bathing captain’s command. This bathing method has been historically used in treating dermatologic diseases such as leprosy and syphilis before the introduction of modern therapy; its therapeutic effects are attributed to hyperthermia and acidity. The precise study of this practice was reported by Elwin von Baelz in 1893 at Wiesbaden, Germany. Today, this bathing method is rarely used as medical treatment, though it is still used by some Japanese. As a daily habit, the Japanese usually take a bath at 40-42℃.

The components dissolved in Kusatsu hot-spring were H⁺ 10.1, Na⁺ 53.7, K⁺ 16.0, Mg²⁺ 39.0, Ca²⁺ 72.0, Fe²⁺ 14.5, Mn²⁺ 1.4, Al³⁺ 39.0, F⁻ 12.0, Cl⁻ 343.0, SO₄²⁻ 611.0, HSO₄⁻ 206.0, HiSO₃⁻ 250.0, and HBO₂ 8.2 mg/kg water, and the pH was 2.0.

II  ADDICTION TO VERY HOT HOT-SPRING

We studied the reason why some people prefer bathing in such very hot hot-spring water...
using a single immersion by the timed bathing method. We found that the serum levels of the endogenous morphine-like substance, \(\beta\)-endorphin were markedly elevated for a brief period immediately after bathing in very hot hot-spring at 47\(^\circ\)C.\(^5\) In contrast, the serum levels of \(\beta\)-endorphin was unchanged after bathing at 42\(^\circ\)C. Bathing in very hot hot-spring is found to cause an addiction to endogenous morphine-like substance and possible dependence on it, which is not a medical effect. The Japanese preference for bathing in very hot hot-spring is suggested to be a kind of addiction to endogenous brain opioids. Today, it is generally accepted that the optimal effect of bathing in hot water is obtained at 41–42\(^\circ\)C. Many patients must have relied on this drastic and extreme remedy in ancient times when no effective medical therapy existed for specific complaints.

### III BODY TEMPERATURE AND BLOOD PRESSURE

After 3-min bathing in 47\(^\circ\)C water, the sublingual temperature increased by 1.8\(^\circ\)C.\(^6\) On the other hand, after 10-min bathing in 42\(^\circ\)C water, the sublingual temperature increased by 1.1\(^\circ\)C. The blood pressure increased from 124 to 158 mmHg at the beginning of bathing in 47\(^\circ\)C, decreased to 108 mmHg just after the end of bathing, and thereafter remained around 110 mmHg for hours (Figure 4). The difference between the maximum and minimum blood pressures associated with bathing in 47\(^\circ\)C water was bigger than that associated with bathing in 42\(^\circ\)C or 37\(^\circ\)C water. Bathing in 42\(^\circ\)C and 47\(^\circ\)C hot-springs resulted in hypotension for hours.

### IV PLATELET ACTIVATION

1. Platelet ultrastructure

Figure 5 demonstrates the ultrastructure of platelets before and after bathing in 47\(^\circ\)C water. The surface membrane changed drastically to present many extrusions (pseudopods) and platelet granules were destroyed to release the various substances that activate platelets and coagulation.\(^7\),\(^8\) The adhesion molecule, P-selectin (CD62) appears on the surface of platelet and adheres to other platelets, leukocytes, erythrocytes, and endothelial cells.\(^9\),\(^10\) In \textit{in vivo} conditions, aggregation or microthrombi could be dissolved by fibrinolytic substances secreted from endothelial cells. In this \textit{in vitro} study, where endothelial cells were absent, the aggregation could not be dissolved due to lack of fibrinolysis caused by endothelial cells. Granules, folds, and pseudopods were reduced in number while the number of vacuoles increased. After platelet activation by hyperthermia, a decrease was observed in the content of various substances.
contained within the granules such as β-thromboglobulin (β-TG), platelet factor-4 (PF-4), fibrinogen, and von Willebrand factor. The platelet granules were destroyed and decreased in number and vacuoles were formed in place of the destroyed granules. Microtubules exist at the periphery of resting platelets and these microtubules encircle organelles. After platelet activation by a mechanical or chemical stimulus, microtubules contract and squeeze organelles into the center of the platelet (centralization). Table 1 shows the frequencies of platelet shape changes before and after 3-min bathing in 47°C water. The frequency of the occurrence of folds, pseudopods, vacuoles, and centralization increased after the bathing. This result suggests that bathing in very hot hot-spring causes morphological activation of circulating platelets.

2. Platelet peroxidase

Platelet peroxidase (PPO) is the enzyme that promotes production of prostaglandins and

Fig. 4  Systolic blood pressure and bathing in hot-spring.
Both the increase just after the beginning of bathing in 47°C and the decrease after the end of it in systolic blood pressure were greater than those associated with bathing in 42°C water.

Fig. 5  The platelet shape changes before and after bathing in 47°C hot-spring.
A transmission electron microscope demonstrated that pseudopods (p), folds (f), and vacuoles (v) increased and α-granules (αG) decreased after bathing. a: before bathing in 47°C water. b: after bathing in 47°C water.
thromboxane from arachidonic acid in cooperation with cyclooxygenase. Peroxidase exists in the dark tubular system of platelets. Figure 6 demonstrates platelet peroxidase staining by electron microscope. The amount of peroxidase was decreased after bathing in 47℃ water, which suggests that platelet peroxidase was consumed by platelet activation.

3. Fibrinogen

Fibrinogen exists exclusively in α-granules and is released to the exterior of platelet by means of degranulation after platelet activation. Immunogold marking for fibrinogen (Fbg) by electron microscope is shown in Figure 7. After bathing in 47℃ water, the fibrinogen labeled with gold particles was decreased within the platelets, which suggests that it was released outside the platelet. Some gold particles coupled to fibrinogen were seen in the cytoplasm, which means that fibrinogen moved from α-granules to the exterior via the cytoplasm. Thus, after bathing in 47℃ water, fibrinogen is released from platelet granules to promote further platelet aggregation.

4. P-selectin

P-selectin is a transmembrane protein present in α-granules of platelets, and it appeared on platelet surface after bathing in 37℃, 42℃, and 47℃ water. Following platelet activation, P-selectin rapidly migrates to the cell surface and interacts with platelets, leukocytes, and...
endothelial cells. It is also suggested that platelets become adhesive after bathing in hot water. 5

5. β-TG and PF-4

In addition to these platelet changes, the plasma concentrations of substances released from platelet granules were examined before and after bathing. The plasma levels of β-TG and PF-4 increased after bathing in 47℃ water and gradually returned to the previous values. This result is compatible with the changes in ultrastructure. β-TG and PF-4 are released from a-granules to the exterior of the platelet after bathing in 47℃ water and might further promote coagulation and aggregation.

V PLATELET ACTIVATION AND AGING

Platelet activation increases with atherosclerosis rather than with aging. In addition, platelet activation is increased by hyperthermia, which might elevate the risk of a thrombotic event after bathing in hot water in the elderly patients with endothelial dysfunction. In contrast, thrombotic events would rarely be induced after bathing in hot water in young people since they generally do not have disorders of endothelial function, fibrinolytic capacity, and autoregulation of blood pressure.

VI COAGULATION AND FIBRINOLYSIS

After hyperthermal stress, the amount of platelet-derived microparticles (PDMPs) increases in the plasma. The platelet derived microparticles containing a small amount of cytoplasm and membrane are separated from the platelet surface. They include various reactive substances derived from platelet granules and membrane such as P-selectin and glycoprotein IIbIIIa, which promote activation, aggregation, and coagulation. The fact that platelet-derived microparticles increase after bathing in hot water might be associated with thrombotic events.

The plasma level of tissue plasminogen activator (tPA) was decreased slightly and plasminogen activator inhibitor-1 (PAI-1) was increased markedly after bathing in very hot hot-spring water. Both tPA and PAI-1 are secreted from endothelial cells. Moreover, tPA dissolves thrombi, although PAI-1 inhibits tPA to accelerate thrombus formation. Bathing in 47℃ might
decrease fibrinolytic capacity and increase antifibrinolytic capacity, the combination of which could lead to a thrombotic state.

In addition to the in vivo study of bathing in hot-spring, we studied in vitro reactions of endothelial cell lines by heating culture media. The in vitro study used human umbilical venous endothelial cell line (HUVE) and demonstrated that the concentration of PAI-1 in the culture media was increased by heating at 47°C. On the other hand, P-selectin on the surface of the platelets collected from healthy subjects was increased by heating the culture medium at 47°C. Thus, both in vivo and in vitro studies suggest that fibrinolytic capacity is decreased and thrombogenic function is increased by hyperthermal stress.

VII  BLOOD VISCOSITY

We reported some cases of stroke after bathing in very hot hot-spring and suggested that increased blood viscosity is associated with thrombotic events. Elderly patients with previous experience of stroke exhibit a circadian rhythm-dependent change in blood viscosity, with a rapid increase early in the morning. Bathing often leads to diuresis because of increased secretion of human atrial natriuretic peptide due to cardiac enlargement from hydraulic pressure after immersing the body in water with the head out. In addition, sleeping without drinking water over night causes dehydration, bathing in hot water causes sweating, and thereafter hemoconcentration occurs at midnight or dawn. Taken together, bathing in hot water increases blood viscosity, decreases blood pressure, and might contribute to thrombotic events. Hyperthermia itself does not directly increase blood viscosity or hematocrit values but indirectly increases viscosity by sweating and diuresis. In contrast, bathing in under 42°C water causes little increase in blood viscosity and is of use in physical therapy and exercise. Bathing in very hot hot-spring which is over 42°C, therefore, would not be recommended for the elderly, or those with endothelial dysfunction or disordered autoregulation of blood pressure.

VIII  ALCOHOL DRINKING AND THROMBOTIC EVENT

The association between alcohol drinking and the onset of stroke is still controversial. The number of stroke patients referred to our hospital after drinking alcohol and bathing in hot water was higher than that of patients who had not drink alcohol, though this was a retrospective observation. Bathing in hot water resulted in diuresis and vasodilation. Furthermore, alcohol drinking also leads to diuresis and vasodilation. Alcohol drinking and bathing in hot water, if combined, would promote hemostasis or brain ischemia and might increase the risk of thrombotic events. Drinking a glass of water after bathing in hot water would be recommended to avoid thrombotic events from the view point of blood viscosity.

CONCLUSION

Bathing in very hot (47°C) hot-spring increased the following:
changes in platelet shape (pseudopods, folds, vacuoles, and centralization),
adhesion molecules (P-selectin or CD62) on the platelet surface,
plasma levels of β-TG and PF-4,
antifibrinolytic capacity (PAI-1)
blood viscosity,
and endogenous morphine-like substance (β-endorphin)
and decreased the following:
peroxidase in dark tubular system,
fibrinogen in α-granule,
fibrinolytic capacity (tPA),
and blood pressure.

It is recommended that bathing in very hot hot-spring should be avoided especially in case of
atherosclerosis or endothelial dysfunction (Figure 8). The Japanese preference for very hot hot-
spring could be derived not from medical effect but from endogenous brain opioid addiction.
The medical effect of hydrotherapy or hot-spring therapy is optimal at 41–42°C in temperature.

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Fig. 8  A possible mechanism of thrombosis after bathing in very hot water.
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Conflict of Interest

No potential conflicts of interest were disclosed.

References


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