Experimental study on the pathogenesis of heat stroke

CHUN-JEN SHIH, M.D., MAO-TSUN LIN, PH.D., AND SHIN-HAN TSAI, M.D.

Department of Surgery, and Department of Physiology and Biophysics, National Defense Medical Center and Tri-Service General Hospital, Taipei, Taiwan, Republic of China

A heat-balance study was carried out on conscious rabbits exposed to ambient temperatures (Ta) from 8°C to 40°C. At Ta = 40°C, heat gain exceeded heat loss and led to hyperthermia and heat stroke, and the latency for the onset of heat stroke was found to be around 87 minutes. At the onset of heat stroke, the comatose animals showed higher levels of rectal temperature, ear skin blood flow, respiratory evaporative heat loss, metabolic rate, intracranial pressure (ICP), and cerebral water content as compared to those of control animals (kept at an ambient temperature of 24°C). Before the start of heat stress, the animals had an average mean arterial blood pressure (MABP) of 94 mm Hg and cerebral perfusion pressure (CPP) of 80 mm Hg. However, at the onset of heat stroke, the average MABP and CPP decreased to 67 and 19 mm Hg, respectively. The reduction in CPP at the onset of heat stroke was due to both a decrease in MABP and an increase in ICP. In addition, the comatose animals which received an intravenous infusion of 10% glycerol (3 ml/min) had a survival time (interval between onset of heat stroke and death) longer than that of the comatose animals which received the control-vehicle solution. The prolongation of survival time in the glycerol-treated animals may be due to lower rectal temperature, lower cerebral water content, or lower ICP during the development of heat stroke. The present data indicate that not only hyperthermia but also cerebral edema, intracranial hypertension, decreased MABP, and decreased CPP are the main causes of heat stroke. The therapeutic values of glycerol on heat stroke may be related to the depressant action on cerebral edema, intracranial hypertension, and body temperature.

KEY WORDS: heat stroke • cerebral edema • cerebral ischemia • intracranial hypertension • hyperthermia • cerebral perfusion pressure

HEAT stroke is a complex clinical picture characterized by hyperthermia, coma, delirium, and other symptoms; it is especially prevalent in hot climates.9,26 The pathogenesis of heat stroke has been extensively investigated by researchers of different disciplines.9,26 In general, pathological investigations show cerebral edema, cerebroventricular petechiae, and degenerative neuronal change in the central nervous system.6,17 The cerebrospinal fluid is generally crystal clear and its pressure is normal or elevated.3,4,19,25 However, it must be stressed that most of the experiments or observations performed in studying the pathogenesis of heat stroke have been conducted during the hours or days after the onset of heat stroke. Relatively little information is available relating to the pathophysiological changes that occur at the onset of heat stroke.26

In this study conscious rabbits were exposed to a high ambient temperature (Ta = 40°C) to induce heat stroke and to observe alterations in several physiological parameters (including metabolism, respiration, cardiovascular functions, cerebral water content, and intracranial pressure, ICP) and changes in cerebral structures at the onset of heat stroke. By identifying the functional or anatomical alterations occurring at the onset of heat stroke, a clearer picture of the pathogenesis of heat stroke emerges.

Materials and Methods

Experiments were performed on male New Zealand rabbits, initially weighing between 3.0 and 3.5 kg each. The weight range was specified by the stereotaxic atlas of Sawyer, et al.22 Each animal was implanted with an indwelling ventricular guide tube. All animal experiments were conducted on conscious animals trained to sit quietly under minimal restraint in rabbit stocks.* The measurements were made at the same time (0900 hour). This animal study was conducted according to the guiding principles in the care and use of animals of the American Physiological Society, and meets with approval of the Committee on Animal Experimentation of the National Defense Medical Center, Taiwan.
Pathogenesis of heat stroke

to 1700 hours) for all experimental groups. Between experiments, the animals were individually caged and kept in an ambient temperature of 22°C to 25°C with natural light-dark cycles, and were maintained on laboratory rabbit chow with tap water available ad libitum.

Surgical Techniques

Ventricular cannulas were implanted under general anesthesia (pentobarbital sodium, 30 mg/kg intravenously). The stereotaxic coordinates used were from the atlas of Sawyer, et al.22 The cannulas were placed in the third ventricle; the stereotaxic coordinates were: A +1.0 mm; L 0.0 mm; and H +0.5 mm. A period of 2 weeks was permitted to allow the animals to recover before the experimentation.

Experimental Design

Three series of experiments were performed: 1) the responses (including body temperatures, ear skin blood flow (EBF), respiratory evaporative heat loss (Em), metabolic rate, ICP, and tissue water content) of the rabbits to a variety of ambient temperatures (8°C, 16°C, 24°C, 32°C, and 40°C) were observed; 2) the responses (including body temperatures, EBF, metabolic rate, ICP, cerebral water content, and mean arterial blood pressure, MABP) of the rabbits were measured at the time of onset of heat stroke; and 3) the survival time, as well as the peak values of either body temperature, ICP, and cerebral water content, of the two groups of saline-treated and glycerol-treated rabbits with heat stroke was measured immediately following the death of the rabbits. Heat stroke was induced by exposing the animals to a high ambient temperature of 40°C. The occurrence of loss of sensation, decreased muscle tone, and unconsciousness was taken as the onset of heat stroke.

Drug Solutions

All drug solutions were prepared in pyrogen-free glassware that was baked at 180°C for 4 hours before use. Glycerol was made up as a stock solution (10%) by diluting 99.9% of glycerol in 0.9% saline. Either the drug solution or the normal saline was injected into the marginal vein of the ear at a rate of 3 ml/min.

Measurements of Physiological Parameters

Metabolic rate, Em, vasomotor activities, and body temperatures were measured in a small-animal partitional calorimeter.14-16 Metabolic rate was calculated from the animal’s oxygen consumption in watts assuming a respiration quotient (RQ) of 0.83, so that 1 liter of oxygen consumed per hour was equivalent to a heat production of 5.6 W/kg. Respiratory evaporative heat loss (Em) was calculated by measuring the increase in water vapor content in the helmet effluent air over that of the ambient air. Evaporative heat loss expressed as watts was calculated from evaporative water loss, assuming the latent heat of the evaporation of water to be 0.7 W·hr/gm·°C. Estimated EBF was used as a sensitive index of ear vasomotor activity in terms of milliliters per minute. It was calculated from the equation:

\[ EBF = A_e \times h_{res} \times (T_e - T_a)/s \times (T_r - T_r) \]

where \( A_e \) is ear surface area (the ear skin surface was calculated by the equation \( A_e (sq \ m) = 0.0084 \times body wt (kg) \)), \( h_{res} \) is the combined coefficient of radiant and convective heat transfer of the ear, \( s \) is the specific heat of blood, \( T_r \) is the ear skin temperature, \( T_a \) is the ambient temperature, and \( T_r \) is the rectal temperature.

Rectal, ear, and back-skin temperatures were measured using copper-constantan thermocouples. All measurements were taken once every minute throughout the experiments; each variable was measured as a DC potential on a Hewlett-Packard digital voltmeter interfaced to an on-line 9825 computer. Each minute all temperatures, metabolic rate, EBF, and \( E_{res} \) were calculated instantaneously by the computer and relayed immediately back to the laboratory where they were displayed on an on-line Hewlett-Packard 9871 printer.† The ICP was monitored with a Statham P23AC transducer via a cannula insert which was introduced into the ventricular cannula at the time of measurement. All recordings were made on a four-channel Grass 7C polygraph.§ Cerebral edema was assessed by measuring brain water content. Water content (gm H2O/100 gm fresh weight) was determined by difference after drying at 95°C for 4 hours.

Histological Evaluation

Immediately following the onset of heat stroke, the animals were killed with an overdose of pentobarbital sodium. The cerebral circulation was perfused with 0.9% saline, followed by a 10% formalin solution. The fixed brain was then cut in 4-μm sections and stained with hematoxylin and eosin. Sections were studied to evaluate the pathology that occurred during the onset of heat stroke.

Data Collection and Analysis

Animals were permitted at each ambient temperature to attain thermal balance before data were collected. The responses (including body temperatures, EBF, Em, metabolic rate, and ICP) to each ambient temperature (8°C, 16°C, 24°C, and 32°C) were calculated by averaging consecutive determinations of each parameter, taken 1 minute apart during the 30-minute period after reaching thermal balance. For the induction of heat stroke, animals were exposed to an ambient temperature of 40°C. The occurrence of coma was taken as an indica-

† Model 9825 computer and Model 9871 on-line printer manufactured by Hewlett-Packard, 1501 Page Mill Road, Palo Alto, California.

‡ Transducer, Model P23AC, manufactured by Statham Instruments, Inc., 2230 Statham Boulevard, Oxnard, California.

§ Four-channel 7C polygraph manufactured by Grass Instrument Co., 101 Old Colony Avenue, Quincy, Massachusetts.
Physiological, Intracranial Pressure (ICP), and Cerebral Water Content (CWC) Responses of 17 Normal Rabbits to Various Ambient Temperatures ($T_a$)*

<table>
<thead>
<tr>
<th>$T_a$ (°C)</th>
<th>No. of Rabbits</th>
<th>$T_r$ (°C)</th>
<th>EBF (ml/min)</th>
<th>$E_{ev}$ (W/kg)</th>
<th>M (W/kg)</th>
<th>ICP (mm Hg)</th>
<th>CWC (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>8</td>
<td>5</td>
<td>39.4 ± 0.10</td>
<td>0.2 ± 0.08</td>
<td>0.24 ± 0.02</td>
<td>4.31 ± 0.07</td>
<td>12.3 ± 1.60</td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>5</td>
<td>39.2 ± 0.09</td>
<td>0.4 ± 0.07</td>
<td>0.34 ± 0.02</td>
<td>3.41 ± 0.05</td>
<td>12.8 ± 1.28</td>
<td></td>
</tr>
<tr>
<td>24</td>
<td>5</td>
<td>39.3 ± 0.11</td>
<td>0.7 ± 0.08</td>
<td>0.36 ± 0.03</td>
<td>3.02 ± 0.06</td>
<td>14.2 ± 1.12</td>
<td>78.2 ± 0.31</td>
</tr>
<tr>
<td>32</td>
<td>5</td>
<td>39.8 ± 0.12‡</td>
<td>10.9 ± 1.23‡</td>
<td>0.74 ± 0.07‡</td>
<td>2.84 ± 0.08</td>
<td>26.6 ± 2.01‡</td>
<td></td>
</tr>
<tr>
<td>40</td>
<td>12</td>
<td>43.5 ± 0.13‡</td>
<td>11.6 ± 1.56‡</td>
<td>0.79 ± 0.09‡</td>
<td>5.88 ± 0.23‡</td>
<td>48.6 ± 2.01‡</td>
<td>82.8 ± 0.27‡</td>
</tr>
</tbody>
</table>

* Rectal temperature ($T_r$), ear skin blood flow (EBF), respiratory evaporative heat loss ($E_{ev}$), and metabolic rate (M) were measured when the animals were in thermal balance at each $T_a$. The values are expressed as the mean ± standard error of the mean.

† Significantly different from corresponding control values (collected at $T_a = 24°$C), at $p < 0.05$ (one-way analysis of variance).

Results

Physiological Responses to Various Ambient Temperatures

A heat-balance study was carried out on five rabbits exposed once each to ambient temperatures from 8° to 32°C. Table 1 contains a summary of the mean and standard error values for each of the measured and calculated parameters collected at each of the four ambient temperatures used. Both $T_r$ and ICP were relatively constant from $T_a = 8°$ to 24°C, whereas above 32°C, both $T_r$ and ICP increased rapidly. Below $T_a = 32°C$, both EBF and $E_{ev}$ were minimal and almost constant; but above 32°C, both vasomotor and respiratory evaporative heat loss increased rapidly, associated with an increase in both body temperature and ICP. Metabolic rate was relatively constant (2.84 to 3.41 W/kg) from $T_a = 16°$ to 32°C; below 16°C, metabolic rate increased progressively. In the second series of experiments, heat stroke was induced by exposing 12 animals to an ambient temperature of 40°C (Table 1). The latency of the onset of heat stroke was found to be 87 ± 5.12 minutes for 12 animals. During the onset of heat stroke, the comatose animals showed higher values of $T_r$, EBF, $E_{ev}$, metabolic rate, ICP, and cerebral water content as compared to those of the control animals (kept at a heat balance of $T_a = 24°$C).

Changes in Brain Tissues at Onset of Heat Stroke

At the onset of heat stroke, the comatose animals were sacrificed for histological verification of brain tissues. The major anatomicopathological findings of heat stroke were as follows: 1) Congestion is common...
Pathogenesis of heat stroke

in both the leptomeningeal vessels (Fig. 1) and the choroid plexus of the lateral ventricles (Fig. 2); perivascular brain hemorrhages are not observed. 2) Cerebral cortex is edematous, with no petechial hemorrhages (Fig. 1). 3) Degeneration of neurons, chromatolysis, pyknosis, and swelling of the dendrites, with replacement by proliferating microglia are noted in the cerebral cortex (Fig. 1), hippocampus (Fig. 3), and pons (Fig. 4), but are very rare in the hypothalamus, cerebellum, and other brain regions.

**Therapeutic Effects of Glycerol on Heat Stroke**

In a series of experiments to determine the effects of glycerol, heat stroke was induced by exposing 16 animals (eight animals in a control group and eight animals in the experimental group) to an ambient temperature of 40°C. At the time of onset of heat stroke, the comatose animals were immediately removed to a room maintained at 24°C and separated into two groups for the following studies. The control group received an intravenous infusion of 0.9% saline, whereas the experimental group received an intravenous infusion of 10% glycerol at a rate of 3 ml/min. The interval between the onset of heat stroke and the incidence of death was recorded as the survival time. It was found that the comatose animals which received glycerol had a longer survival time than the comatose animals which received control-vesicle solution. The prolongation of the survival time in the glycerol-treated animals may be due to a lower level of either rectal temperature, cerebral water content, or ICP during the development of heat stroke. The results are summarized in Table 3.

**Discussion**

In the present study conscious rabbits were exposed to an environmental temperature of 40°C to induce...
heat stroke. Immediately before the onset of heat stroke, the rabbits displayed higher levels of rectal temperature, ear skin blood flow, respiratory evaporative heat loss, metabolic heat production, ICP, and cerebral water content as compared to those of the control animals that were kept at a heat balance of $T_a = 24^\circ C$. In contrast, both MABP and CPP were greatly reduced just before the onset of heat stroke. The reduction in CPP was due both to a decrease in MABP and to an increase in ICP. The present results also show that damage to the brain tissue is very mild at the onset of heat stroke. Although both leptomeninges and the choroid plexus of the ventricles exhibited many congested vessels, there were no cerebral or ventricular hemorrhages. In addition, degeneration of neurons, as well as pyknosis and swelling of the dendrites with replacement by proliferating microglia, was noted in the cerebral cortex, hippocampus, and pons, but was absent in the hypothalamus, cerebellum, and other brain regions.

This is not consistent with the findings of Stefanini and Malamud, et al. These investigators reported severe subarachnoid hemorrhages and cerebellar lesions in cases of heat stroke. The discrepancy between the results can be explained by the difference in the duration of symptoms. Our study reflects the histological changes occurring in rabbits at the onset of heat stroke, while the latter findings are postmortem changes that occurred several days after the onset of heat stroke.

A schematic representation of the pathological cycle for the development of heat stroke is suggested in Fig. 5. In this scheme, at environmental temperatures higher than those of the body, heat gain exceeds heat loss and leads to hyperthermia. Direct thermal injury to the brain tissues results in congestion of cerebral vessels, cerebral edema, and other neurological damage. Both cerebral edema and cerebral vascular congestion can induce intracranial hypertension. In response to heat stress, increased venous pressure and peripheral vaso-
Pathogenesis of heat stroke

### TABLE 3

Response of rabbits with heat stroke to glycerol treatment*

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>Peak T, (°C)</th>
<th>Peak CWC (%)</th>
<th>Peak ICP (mm Hg)</th>
<th>Survival Time (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (0.9% saline)</td>
<td>43.5 ± 0.31</td>
<td>82.5 ± 0.28</td>
<td>51.0 ± 3.38</td>
<td>12.0 ± 2.67</td>
</tr>
<tr>
<td>2 (10% glycerol)</td>
<td>42.6 ± 0.22†</td>
<td>80.0 ± 0.23†</td>
<td>38.0 ± 1.14†</td>
<td>76.0 ± 2.18†</td>
</tr>
</tbody>
</table>

* Peak values of rectal temperature (T<sub>r</sub>), cerebral water content (CWC), intracranial pressure (ICP), and survival time of two groups of eight rabbits receiving an intravenous injection of 3 ml/min of saline (control group) or 10% glycerol after heat stroke. Measurements were made immediately following death. The values are expressed as the mean ± standard error.
† Significantly different from corresponding control values, at p < 0.05 (one-way analysis of variance).

dilation would induce a decrease in MABP. Accordingly, both intracranial hypertension and decreased MABP eventually lead to a local or generalized reduction in CPP. Reduction of CPP to below the autoregulatory level causes cerebral ischemia, which leads to neurological damage and the onset of heat stroke. The accumulation of acidic metabolites resulting from cerebral ischemia initiates "cerebrovascular paralysis." In this situation both the ICP and cerebral blood flow progressively become more passively related to blood pressure. Small reductions in blood pressure can now cause regional or generalized cerebral ischemia, whereas a marked elevation in blood pressure not only increases cerebral flow, but also increases in cerebral blood volume, enhances cerebral edema formation, and elevates ICP. Eventually, an initially increased cerebral blood volume due to blood pressure elevation may lead to a progressively decreasing CPP. In fact, it has been proposed that anoxia alone is responsible for the cellular damage in hyperthermia and heat stroke. Thus, it appears that cerebral ischemia or anoxia is the main cause of the onset of heat stroke. The scheme proposed in Fig. 5 is further supported by the findings of Hirsch and Schneider. Their heat experiments on an isolated cat brain indicated that a complete disruption of nerve function would occur between 43° and 44°C. In the present experiments, hyperthermia of 43.5°C in response to an ambient temperature of 40°C induces a disruption of neuronal function and produces coma, delirium, and other symptoms.

Traditionally, treatments suggested for the relief of heat stroke are based on the hypothesis that hyperthermia is the main cause of heat stroke. The standard therapy of heat stroke is to lower body temperature. In general, reduction of hyperthermia is achieved by placing patients with heat stroke in a tub of ice water. On the other hand, the application of antipyretic drugs, phenothiazines, and steroids in heat stroke in man does not seem to be justified because of the possible side effects, the lack of experimental support, or an aggravation of the heat stroke. The present results point out that not only hyperthermia, but also intracranial hypertension and brain edema are the main causes of heat stroke. This strongly indicates that any agent acting against intracranial hypertension, edema, or hyperthermia would be potentially beneficial for the control of heat stroke. Therefore, in the present study, glycerol, a therapeutic preparation now being introduced to medical practice mainly for the treatment of intracranial hypertension or cerebral edema, was tested for its possible effect on the control of heat stroke induced experimentally in rabbits. We did observe that the survival time of comatose animals with heat stroke was greatly prolonged following the administration of glycerol. The potential benefit of glycerol on heat stroke may be related to the depressant action on brain edema, intracranial hypertension, and hyperthermia as demonstrated in the present results (Fig. 5).

In summary, the present results demonstrate that reduction of hyperthermia, intracranial hypertension, and brain edema is essential for the relief of heat stroke.

### References


---

**Fig. 5.** A schematic representation of the possible sequence of the pathological cycle for the development of heat stroke. For an explanation see text.