neovascularization, in diseases associated with choroidal subretinal neovascularization.

To summarize, vascular repair of the choroid after laser treatment is characterized by recanalization of damaged pre-existing vessels and the bidirectional growth of new ones, as well as by capillary regression.

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1 Ferris, F. L., Fine, S. L., and Hyman, L., Archs Ophthal. *102* (1984) 1640.
2 Green, W. R., and Wilson, D. J., Ophthalmology *93* (1986) 1169.
3 Ryan, S. J., Trans. Am. Ophthal. Soc. *77* (1979) 707.
4 Perry, D. D., Reddick, R. L., and Risco, J. M., Invest. Ophthal. Vis. Sci. *25* (1984) 1019.
5 Miller, H., Miller, B., and Ryan, S. J., Am. J. Ophthal. *99* (1985) 263.
6 Dobi, E. T., Puliafito, A., and Destro, M., Archs Ophthal. *107* (1989) 264.
7 Pollack, A., Heriot, W. J., and Henkind, P., Ophthalmology *93* (1986) 1113.
8 Burger, P. C., Chandler, D., and Klintworth, G., J. Electron Microsc. Techn. *1* (1984) 341.
9 Gerszberg, T., Roa, N., and Korte, G. E., Bull. Electron Microsc. Soc. Am. *15* (1985) 106.
10 Pollack, A., Korte, G. E., and Henkind, P., Documenta Ophthalmologica, Ocular Circulation and Neovascularization, p. 475 (1987).
11 Tano, Y., Chandler, D., and Machemer, R., Am. J. Ophthal. *92* (1981) 110.
12 Korte, G. E., and Pua, F., Acta anat. *133* (1988) 224.
13 Burger, P., Chandler, D., and Klintworth, G., Lab. Invest. *48* (1983) 169.
14 Fryczkowski, A., Peiffer, R., Merritt, J., Kraybill, E., and Eifrig, D., Archs Ophthal. *103* (1985) 224.
15 Perry, D. D., and Risco, J. M., Am. J. Ophthal. *93* (1982) 787.
16 Kalebic, T., Garbisa, S., Glaser, B., and Liotta, L. A., Science *221* (1983) 281.
17 Ohkuma, H., and Ryan, S. J., Invest. Ophthal. Vis. Sci. *24* (1983) 481.
18 Korte, G. E., Invest. Ophthal. Vis. Sci. *30* (1989) 1938.
19 Bellhorn, R. W., Burns, M. S., and Benjamin, J. V., Invest. Ophthal. Vis. Sci. *19* (1980) 584.
20 Korte, G. E., Bellhorn, R. W., and Burns, M. S., Invest. Ophthal. Vis. Sci. *24* (1983) 962.
21 Korte, G. E., Bellhorn, R. W., and Burns, M. S., Invest. Ophthal. Vis. Sci. *25* (1984) 1027.
22 Glaser, B. M., Campochiaro, P. A., and David, J. L. Jr., Archs Ophthal. *103* (1985) 1870.
23 Connor, T., and Glaser, B., Invest. Ophthal. Vis. Sci. *28* (1987) 203.
24 Mancini, M. A., Frank, R. N., and Keirn, R. J., Invest. Ophthal. Vis. Sci. *27* (1986) 336.
25 Pollack, A., and Korte, G. E., Invest. Ophthal. Vis. Sci. *31* (1990) 890.

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Cerebral ischemia is the main cause for the onset of heat stroke syndrome in rabbits [1]

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Abstract. During the onset of heat stroke, rabbits displayed hyperthermia (42.8 °C), and decreased cerebral perfusion pressure and decreased cerebral blood flow (as reflected by a prolonged cerebral circulation time) compared to those of normothermic rabbits. On the other hand febrile rabbits, during the fever plateau did not show the above responses, although they had a similar level of hyperthermia (42.4 °C). The data support the concept that cerebral ischemia is the main cause for the onset of the heat stroke syndrome.
Key words. Heat stroke; fever; cerebral blood flow; cerebral perfusion pressure.

It has frequently been stated that the tissue damage and the multiple systemic effects associated with heat stroke are caused by a combination of elevated body temperature and exposure duration [2]. The question of whether cerebral blood flow could be an operative factor in heat stroke was raised by Wyndham [3]. The possibility was rejected by Shibolet et al. [4] on the basis of experiments on anesthetized dogs, in which there was no evidence of changes in cerebral blood flow at rectal temperatures up to 42 °C. However, our previous results [5] showed that in unanesthetized rabbits, at the onset of heat stroke both a decrease in mean arterial blood pressure and an increase in intracranial pressure occurred, resulting in a reduction in cerebral perfusion pressure. This indicated that cerebral ischemia is indeed a factor which determines the severity of heat stroke. Therefore, in the present study, we sought to ascertain whether the main cause for the onset of heat stroke is thermal injury, cerebral ischemia, or both. Experiments were carried out to assess alterations in rectal temperature, arterial blood pressure, intracranial pressure, cerebral perfusion pressure and cerebral circulation time parameters in nor-

mothermic rabbits, in hyperthermic rabbits during the onset of heat stroke, and in febrile rabbits during the fever plateau.

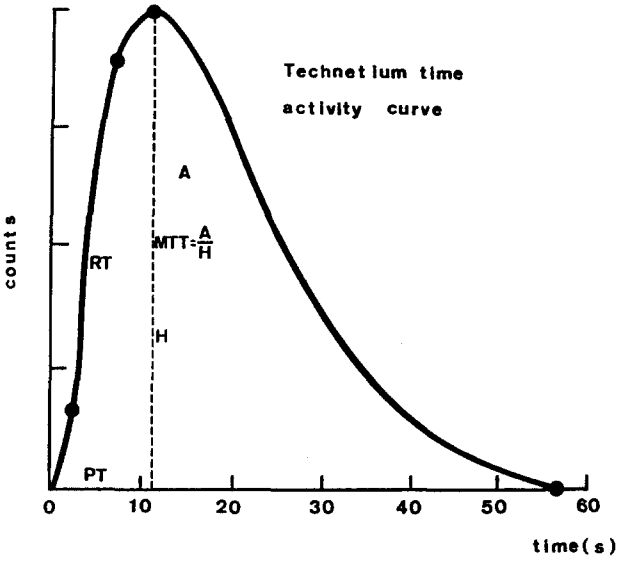
Materials and methods

Experiments were performed on male New Zealand rabbits, weighing between 3.0 and 3.5 kg each. Each animal was implanted with an indwelling ventricular guide tube. All animals were trained to sit quietly under minimal restraint in rabbit stocks. Between experiments, the animals were individually caged and kept at an ambient temperature (T_a) of 22–24 °C with natural light-dark cycles, and were maintained on laboratory rabbit chow with tap water available ad libitum.

Ventricular cannulas were implanted under general anesthesia (pentobarbital sodium, 30 mg/kg, i.v.). The stereotaxic coordinates used were from the atlas of Sawyer et al.[6]. 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 two weeks was permitted to allow the animals to recover before the experimentation.

Three groups of animals were studied. (1) Heat stroke rabbits: heat stroke was induced by exposing the rabbits, under pentobarbital sodium anesthesia, to a T_a of 40 °C; the occurrence of hyperthermia (rectal temperature up to 42.8 °C) was taken as the onset of heat stroke. (2) Febrile rabbits: The rabbits were given an i.v. dose of 50 µg/kg of polyriboinosinic acid: polyribocytidylic acid (Poly I:C; Pharmacia Molecular Biologicals, Uppsala, Sweden) to induce fever (42.4 °C) at a T_a of 24 °C. (3) Control rabbits: The rabbits, under pentobarbital sodium anesthesia, were given an i.v. dose of normal saline (ml/kg) at a T_a of 24 °C. The following were measured in these three groups of animals: (1) rectal temperature, mean arterial blood pressure, intracranial pressure and cerebral perfusion pressure; and (2) cerebral circulation time parameters. The rectal temperatures of the control rabbits were continuously recorded for 3 h.

Rectal temperature was measured using a copper-contantan thermocouple. The arterial blood pressure and the intracranial pressure were monitored with a Statham P23 AC transducer via a cannula insert introduced into the central artery of the ear or the cerebral ventricle. All recordings were made on a 4-channel Grass 7C polygraph. Measurement of cerebral circulation time parameters were carried out using an Elscint Apex 410 gamma camera connected to an Informatek Simis-VI computer. The examination was started with the rapid injection of 5 mCi of ^{99m}Tc pertechneate into the ear marginal vein, followed by flushing with 1 ml of normal saline. Data were collected for 1 min at 0.5-s intervals. The activity curves were then analyzed by the modified gamma function fitting method [7]. As shown in the figure, the following cerebral circulation time parameters were calculated: (1) rise time (RT): the time interval between 10 and 80 percent of the peak height; (2) peak time (PT): the duration of the peak value; (3) mean transit time (MTT): area/height; and (4) transfer time (TT): the parameter corresponds to the time required for the bolus to go through the cerebral hemisphere. It is calculated from the mean transit time by correcting for the dispersion of the bolus.



Schema of the technetium time activity curve and parameters. (1) Rise time (RT): The time interval between 10 and 80% of the peak height. (2) Peak time (PT): The duration of the peak value. (3) Mean transit time (MTT): area (A)/height (H). (4) Transfer time (TT): The parameter corresponds to the time required for the bolus to go through the cerebral hemisphere. It was calculated from the mean transit time by correcting for the dispersion of the bolus [7].

Results and discussion

Table 1 contains a summary of the mean and standard error values for each of the measured and calculated parameters collected from three groups of animals. Hyperthermia (42.8 °C rectal temperature) or heat stroke was induced by exposing 8 rabbits to a T_a of 40 °C. The latency of the onset of hyperthermia or heat stroke was found to be 65 ± 3 min for all these animals. Pyrogenic fever was induced by administering 50 µg/kg of Poly I:C into the ear marginal vein of 10 rabbits at a T_a of 24 °C. The rectal temperature reached its fever plateau (42.4 °C) about 160 min after the injection. It can be seen from the table 1 that the heat-stroke rabbits had lower values for mean arterial blood pressure (65.2 mmHg) and cerebral perfusion pressure (18.1 mmHg), but a higher value for intracranial pressure (47.1 mmHg), than the control animals (acclimatized to a T_a of 24 °C) or the febrile rabbits during the fever plateau. The reduction in the cerebral perfusion pressure that occurred at the onset of heat stroke was brought about by both a decrease in mean arterial blood pressure and an increase in intracranial pressure.

Table 2 contains a summary of the means and the standard error values for each of the cerebral circulation time

Table 1. Rectal temperature and pressure values of 8 normal rabbits, 8 rabbits with heat stroke, and 10 rabbits with pyrogen-induced fever

Group of animals	Rectal temperature, °C	Mean arterial pressure, mm Hg	Intracranial pressure, mm Hg	Cerebral perfusion pressure, mm Hg
Control	38.6 ± 0.1	94.4 ± 4.8	14.8 ± 1.5	79.6 ± 3.2
Heat-stroke	42.8 ± 0.4*	65.2 ± 1.8*	47.1 ± 1.7*	18.1 ± 1.6*
Pyrogen fever	42.4 ± 0.3*	101.3 ± 5.6	17.7 ± 1.8	83.6 ± 3.5

The values are expressed as mean ± SEM. * Significantly different from the corresponding control values, at $p < 0.01$ (one-way analysis of variance).

Table 2. The values of cerebral circulation time parameters were collected from 8 normal rabbits, 8 rabbits during the onset of heat stroke, and 10 rabbits during the fever plateau

Groups of animals	Left hemisphere MTT (seconds)	PT	TT	RT	Right hemisphere MTT	PT	TT	RT
Control	14.1 ± 0.2	8.7 ± 0.5	44 ± 5	3.5 ± 0.4	13.7 ± 0.3	8.5 ± 0.4	42 ± 4	3.4 ± 0.3
Heat stroke	20.4 ± 0.5*	12.5 ± 0.4*	68 ± 4*	3.8 ± 0.2	19.7 ± 1.0*	13.8 ± 0.6*	64 ± 2*	4.0 ± 0.4
Pyrogen fever	13.2 ± 0.3	9.2 ± 0.2	42 ± 3	3.3 ± 0.4	12.4 ± 0.6	8.2 ± 0.5	39 ± 4	2.9 ± 0.2

The values are expressed as mean ± SEM. * Significantly different from the corresponding control values, at $p < 0.05$ (one-way analysis of variance). Abbreviations: MTT, mean transit time; PT, peak time; TT, transfer time; RT, rise time.

parameters collected from the control animals, the heat-stroke animals and the febrile animals. Again, compared with the control animals, or the febrile animals, the heat-stroke animals showed a lower value of cerebral blood flow (as reflected by a higher value of mean transit time, peak time or transfer time). In the current study, the heat-stroke rabbits and control rabbits were under pentobarbital anesthesia whereas the febrile rabbits were awake. In order to determine the influence of the anesthesia on the parameters measured, experiments were carried out to assess the values of these parameters in unanesthetized rabbits. It was found that the values of these parameters in unanesthetized rabbits were not distinguishable from those of the anesthetized rabbits.

According to the findings of Rowell[8], in humans in a warm environment the rate of skin perfusion rises, the tone of the capacitance vessels in the skin is reduced, heart rate and cardiac output increase, and the arterial blood pressure decreases. Both our present and previous[5] results showed that at the onset of heat stroke, peripheral vasodilation and decreased arterial blood pressure are also observed in rabbits. The reduction in the arterial blood pressure at the onset of heat stroke may be due to decreased tone of the capacitance vessels, and peripheral vasodilation[9]. On the other hand, intravenous administration of Poly I:C produced fever in rabbits[10]. The Poly I:C-induced fever was due to peripheral vasoconstriction and increased metabolism in rabbits at room temperature (24 °C). The current results also showed that the febrile rabbits still maintained a normal value for arterial blood pressure during the fever plateau.

In addition, the results showed that both increased intracranial pressure and decreased arterial blood pressure resulted in a reduction in cerebral perfusion pressure in hyperthermic rabbits during the onset of heat stroke. The induced intracranial hypertension could be due to cerebral edema and cerebral vascular congestion[5]. Reduction of cerebral perfusion pressure to below the auto-regulatory level would induce cerebral ischemia[11]. This concept is fully supported by the present results. In the present study, it was found that there was a reduction in cerebral blood flow (as reflected by an increase in cerebral circulation time parameters) in rabbits during the onset of heat stroke. However, febrile rabbits during the fever plateau had values for cerebral circulation time parameters which were not different from those of the control animals. Thus, it appears that cerebral hypoxia (due to cerebral ischemia or decreased cerebral blood flow), rather than thermal injury (due to hyperthermia), is the main cause for the onset of heat stroke syndrome in rabbits.

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2 Baynum, G. P., Pandolf, K. B., Schuette, W. H., Goldman, R. F., Lees, D. E., Whang-Peng, T., Atlienson, E. R., and Bull, J. M., Am. J. Physiol. *235* (1978) R 228.
3 Wyndham, C. H., A. Rev. Physiol. *35* (1973) 193.
4 Shibolet, S., Lancaster, M. C., and Danan, Y., Aviat. space envir. Med. *47* (1976) 280.
5 Shih, C. J., Lin, M. T., and Tsai, S. H., J. Neurosurg. *60* (1984) 1246.
6 Sawyer, C. H., Everett, J. W., and Green, J. D., J. comp. Neurol. *101* (1954) 801.
7 Kuikka, J., Ahonen, A., Koivula, A., Kallanranta, T., and Laitinen, J., Phys. Med. Biol. *22* (1977) 958.
8 Rowell, L. B., Physiol. Rev. *54* (1974) 75.
9 Gold, J., JAMA *173* (1960) 1175.
10 Won, S. J., and Lin, M. T., in: Thermal Physiology, p. 421. Ed. J. B. Mercer. Elsevier Science Publishers B.V., Amsterdam 1989.
11 Reis, D. J., and Doba, N., Prog. cardiovasc. Dis. *17* (1974) 51.

0014-4754/92/030225-03$1.50 + 0.20/0