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Platelet Survival Studies in Stroke-Prone Spontaneously Hypertensive Rats (SHRSP)

MINORU OKUMA, M.D., PH.D.,* AND YUKIO YAMORI, M.D., PH.D.†

SUMMARY Platelet survival was studied by using ⁵¹Cr-labeled platelets in stroke-prone spontaneously hypertensive rats (SHRSP), stroke-resistant SHR (SHRSR) and normotensive control rats of the Wistar-Kyoto (WK) strain. Relatively young animals of the same age prior to the development of cerebrovascular lesions (cerebral infarction and/or hemorrhage) were used.

Platelet half-life time in SHRSP was slightly but significantly shorter than in any other groups of rats, irrespective of the type of platelet donors. Mean platelet consumption was also significantly in-

creased in SHRSP only. Platelets of SHRSP injected into SHRSR showed normal survival. These data support the concept that the shortened platelet survival in SHRSP is brought about by some extracorporeal abnormalities. Although the vascular changes in SHRSP could be the most likely explanation for the shortened platelet survival, its mechanism remains to be solved. This investigation suggests that studies of the platelet survival in hypertension may be useful in predicting the development of stroke before its clinical recognition.

Introduction

THE STROKE-PRONE spontaneously hypertensive rats (SHRSP) in which cerebrovascular lesions (cerebral infarction and/or hemorrhage, or stroke) would spontaneously develop were established by a proper successive selective breeding of the SHR in which stroke developed spontaneously.¹ The involvement of genetic factors in the development of stroke in the rat was postulated from observations on its familial occurrence.² SHRSP thus selected at the Department of Pathology, Faculty of Medicine, Kyoto University, were the offspring of one or both parents who had died from stroke for the past eight or ten generations, and their spontaneous incidence of stroke was more than 80%. Studies on the mechanisms of stroke up to the present indicated that hypertension was an important systemic factor for stroke,^{1,2} while local factors such as recurrent branching and boundary zone were similar to those of stroke in man.³ Therefore, SHRSP were expected to be useful as the best animal model for human stroke.

Attempts to develop hematological methods which can anticipate the development of thrombosis or detect occult thrombotic disease before it is recognized clinically have been mostly fruitless. Tests for detecting alterations in platelet function and blood coagulation cannot reliably indicate a prethrombotic state and may reveal abnormalities following the development of thrombosis.⁴ It has been well known that the platelet is not only related to blood coagulation but plays an important role in the maintenance of vascular integrity and in disease processes.⁵⁻⁸ Importance and primary role of the platelet in the production of arterial thrombi are well established.⁹ Studies of platelet survival and turnover are virtually the only available measures of the activity of the platelet in vivo, and may provide some information on vascular disease and thrombosis as well as on the fate of the platelets in circulation. Therefore, the present investigation was undertaken to evaluate platelet survival and consumption in the relatively young SHRSP, which were thought to be in the prethrombotic state and were destined to have a stroke spontaneously in the future, and stroke-resistant SHR (SHRSR), in which the incidence of stroke was less than 10%; normotensive rats of Wistar-Kyoto (WK) strain were used as the control.

*From the First Division, Departments of *Internal Medicine and †Pathology, Faculty of Medicine, Kyoto University, Sakyo-ku, Kyoto 606, Japan.

Methods

ANIMALS

The SHRSP, weighing 250 to 320 gm, at F_{32} to F_{34} generations of SHR substrains (A_3 and A_4)^{1,2} and the SHRSR, weighing 250 to 380 gm of F_{34} generations of SHR substrain (C)^{1,2} were used in these studies. Rats, weighing 250 to 310 gm, from the WK colony from which the ancestors of SHR were separated¹ were also employed as normotensive controls. Rats were maintained at the Department of Pathology, Faculty of Medicine, Kyoto University, as reported previously,^{1,2} and only age-matched male animals between 14 and 16 weeks of age at the beginning of experiments were utilized. No signs of stroke were observed throughout the experiment in any rats. Blood cells were counted¹⁰ for samples obtained from the tail, and blood pressure was measured by a plethysmographic or pulse-pickup method as described previously.^{1,2}

PLATELET SURVIVAL

Aster's¹¹ method for the study of platelet life span in the rat with cells labeled with ^{51}Cr was modified as follows. Blood was collected from the rats in ACD-A anticoagulant as described previously.¹⁰ About 5 ml of platelet-poor plasma (PPP) prepared from the same substrain of rats were added to decrease the relative packed-cell volume and the mixture was centrifuged at $190 \times g$ for 15 minutes. After separation of the platelet-rich plasma (PRP), both PRP and the remainder of blood were centrifuged at $1,100 \times g$ for 30 minutes to obtain platelets and PPP separately. The resulting platelet button derived from each donor rat was gently resuspended in 1 ml of PPP, and 100 μCi of ^{51}Cr (as sodium chromate in isotonic saline, Daiichi Radioisotope Laboratory, Tokyo, Japan) were added to it. After incubation at room temperature for 30 minutes, the platelets prepared from one to three rats were pooled and were washed once with 5 ml and once with 3 ml of PPP. The ^{51}Cr -labeled platelets thus obtained were then resuspended in a suitable volume of PPP. To determine the relative amounts of radioactivity present in the solution, attached to platelets, or incorporated into contaminated red blood cells, 0.1-ml aliquots of the labeled platelet suspension were added to 1.9 ml of isotonic saline and 1.9 ml of 1% ammonium oxalate, respectively, and centrifuged at $1,100 \times g$ for 30 minutes. Three percent to 5% and less than 5% of the total radioactivity were found in the isotonic saline supernatant and in contaminated red blood cells, respectively, and the remainder was adherent to the platelets themselves. After preparation of a standard, 0.5 to 1 ml of the labeled washed platelet suspension was quantitatively injected into a tail vein of each of the recipient rats through a 25-gauge needle with a 1-ml plastic syringe. Platelets from one donor rat contained sufficient radioactivity to inject two or three recipient rats. Samples of tail blood (0.1 ml) were obtained with disposable 100 μl pipettes and added to counting tubes containing 1.9 ml of 1% ammonium oxalate at 2, 24, 48, 72, and 96 hours after injection. The tube containing the 2-ml mixture of blood and oxalate was centrifuged at $1,100 \times g$ for 30 minutes. One milliliter of the supernatant was separated and counted for radioactivity, which was subtracted from

the radioactivity of the tube containing the platelet button. Radioactivity was counted in a well-type scintillation counter (automatic gamma counting system, 1185 series, Nuclear-Chicago). The coefficient of variation for the determination of circulating radioactivity was $\pm 3\%$. Total platelet ^{51}Cr circulating in the recipient rat was calculated by multiplying counts per minute per milliliter of blood by blood volume which was estimated from the body weight.¹² Platelet recovery was defined as the percent of transfused cells which remained in the general circulation two hours after injection. Platelet survival curve was drawn by plotting the radioactivity in samples obtained after injection of the labeled platelets on an arithmetic graph scale using radioactivity two hours after injection as 100% value. Platelet half-life time ($T_{1/2}$) was the time spent from two hours after injection, when the first sample was taken, until platelet radioactivity reached 50% of the first sample. Mean platelet consumption was calculated from mean platelet count and the half-life time of labeled platelets according to the following formula:¹³

mean platelet consumption (number/ μl /day) =

$$\frac{\text{mean platelet count}}{T_{1/2} \times 2}$$

Statistical significance was assessed by the *t*-test.

After study of platelet survival, all rats were autopsied for routine pathological examination and, especially, brains were cautiously removed and cut into sections for macroscopical observations and for preparation of histological specimens as described previously.¹

Results

Blood cell counts of the three groups of animals are shown in table 1. Platelet counts per microliter of the peripheral blood of the SHRSP, SHRSR and WK were $1,028,000 \pm 39,000$ (mean \pm SE), $1,039,000 \pm 47,000$ and $972,000 \pm 27,000$, respectively, and no significant difference was observed among them. Throughout this experiment, no significant anemia developed in any group of rats. Tail blood pressures of SHRSP, SHRSR and WK rats at 15 weeks of age were 202 ± 3 mm Hg (mean \pm SE), 184 ± 2 mm Hg and 128 ± 1 mm Hg, respectively, and rapid increase in blood pressure at a young age was characteristically observed in the SHRSP.

The mean values in normotensive WK were used as the normal reference standard with which studies of other groups of rats were compared.

TABLE 1 Peripheral Blood Cell Count*

Rat	No. of studies	Erythrocyte per μl	Leukocyte per μl	Platelet per μl
WK	8	9,590,000 $\pm 182,000$	14,100 ± 500	972,000 $\pm 27,000$
SHRSR	13	9,910,000 $\pm 159,000$	23,000 $\pm 1,200$	1,039,000 $\pm 47,000$
SHRSP	14	10,030,000 $\pm 110,000$	17,900 $\pm 1,000$	1,028,000 $\pm 39,000$

*Variance about mean given as \pm SE.

TABLE 2 Recovery, Survival and Consumption of ^{51}Cr -Labeled Platelets*

Donor rat	Recipient rat	No. of studies	Platelet recovery (%)	Platelet half-life time (days)	Platelet consumption (no./ μl /day)
WK	WK	5	79 ± 2.2	1.97 ± 0.06	246,000 $\pm 3,000$
SR	SR	6	78 ± 2.5	1.96 ± 0.06	260,000 $\pm 11,000$
SP	SP	8	81 ± 1.8	1.74 ± 0.06	295,000 $\pm 8,000$
SP	SR	5	80 ± 2.0	2.10 ± 0.02	251,000 $\pm 10,000$
SR	SP	5	80 ± 2.3	1.71 ± 0.03	310,000 $\pm 9,000$

*Variance about mean given as \pm SE.
SP = stroke-prone SHR (SHRSP), SR = stroke-resistant SHR (SHRSR), WK = normotensive rats of Wistar-Kyoto.

Recovery of ^{51}Cr -labeled platelets in SHRSP, SHRSR and WK is summarized in table 2. In all groups of recipient rats, averages of approximately 80% of injected platelets were recovered in the general circulation irrespective of the type of platelet donor, and no significant difference in platelet recovery was observed.

Platelet survivals in WK, SHRSR and SHRSP are shown in figures 1 and 2. Results of studies in which each group of rats was transfused with platelets obtained from the same

group of animals are summarized in figure 1, and those in which each group of rats was transfused with platelets from a different group of animals are summarized in figure 2. Survival curves of platelets in normotensive control WK were almost straight lines during the four days following injection and those in SHRSR were similar, whereas those in SHRSP were slightly exponential, irrespective of the type of donor (figs. 1 and 2). In normotensive control WK, platelet half-life time was 1.97 ± 0.06 days (mean \pm SE) when platelets from the same group of rats were used (table 2). SHRSP had platelet survivals ($T_{1/2}$) ranging from 1.42 to 2.08 days, irrespective of the type of donor, and their means, approximately 1.7 days, were slightly but significantly shorter than normal values (tables 2 and 3). When ^{51}Cr -labeled platelets of SHRSR and those of SHRSP were injected into SHRSR, platelet survivals ($T_{1/2}$) were normal and averaged 1.96 days and 2.10 days, respectively (tables 2 and 3). Further statistical analysis of platelet survival is given in table 3. Thus, shortened platelet survival was observed only in SHRSP, irrespective of the type of donor.

Platelet consumption in normotensive control rats averaged $246,000/\mu\text{l}$ per day $\pm 3,000$ (SE) and that in the SHRSR was normal, ranging from 222,000 to 292,000/ μl per day, whereas this consumption in SHRSP slightly but significantly increased to between 264,000 and 355,000/ μl per day, irrespective of the type of donor (tables 2 and 3).

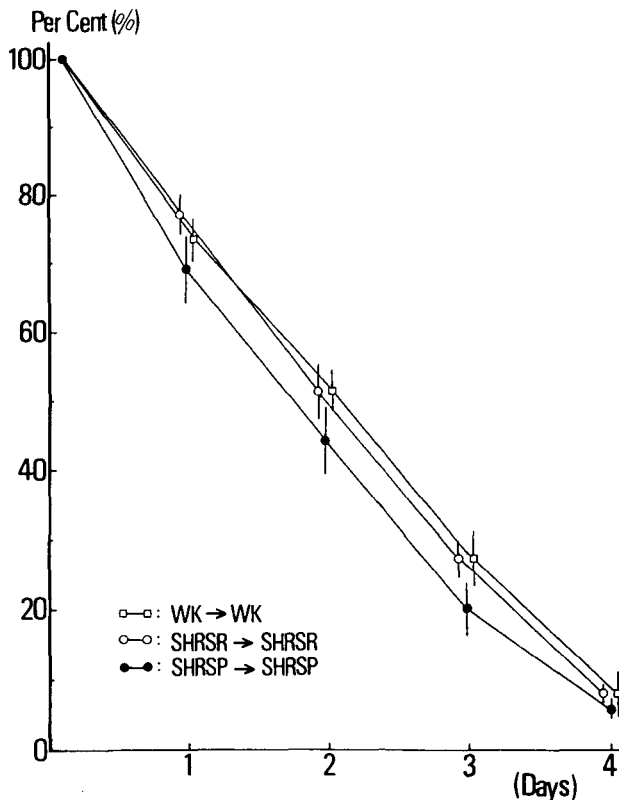


FIGURE 1 Survival of ^{51}Cr -labeled platelets in rats during the four days following injection of platelets obtained from the same groups of animals. Open squares: Wistar-Kyoto (WK) donor, WK recipient. Open circles: stroke-resistant (SHRSR) donor, SHRSR recipient. Closed circles: stroke-prone (SHRSP) donor, SHRSP recipient. The symbols denote the mean values \pm SD.

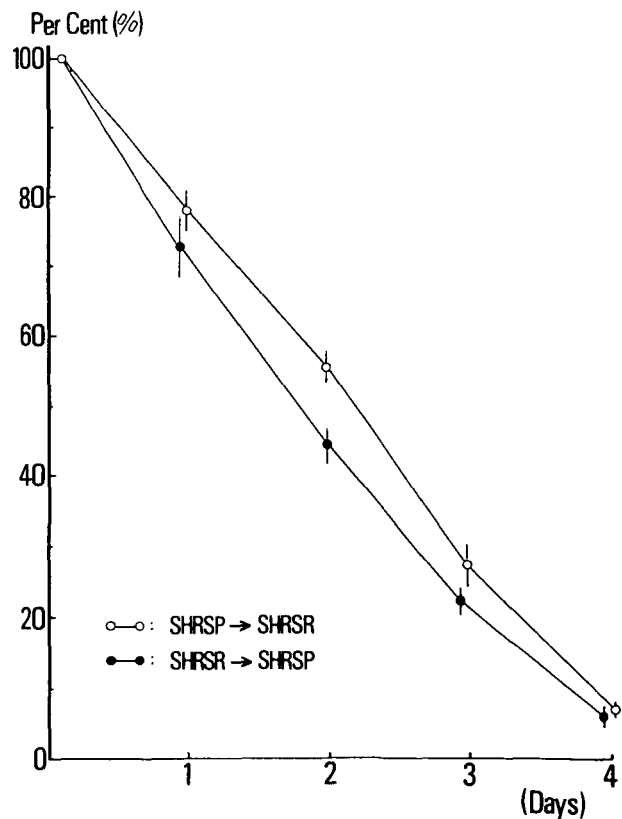


FIGURE 2 Survival of ^{51}Cr -labeled platelets in rats during the four days following injection of platelets obtained from the different groups of animals. Open circles: SHRSP donor, SHRSR recipient. Closed circles: SHRSR donor, SHRSP recipient. The symbols denote the mean values \pm SD.

Macroscopical observation of these experimental groups of SHRSP, SHRSR and WK at the age of 16 weeks revealed no cerebrovascular lesions. The brain, kidney, testes and adrenal glands, which were predilection sites of hypertensive vascular lesions, were further observed microscopically especially in SHRSP and SHRSR. Neither cerebral hemorrhage nor softening was observed in SHRSP. Thickening of arterial or arteriolar walls was noted in the kidney of these hypertensive groups, but angionecrosis, which was frequently observed in SHRSP over the age of 25 weeks, was not noted in any organs of young SHRSP used in this experiment. There seemed to be no obvious qualitative differences in vascular lesions between SHRSP and SHRSR at the age of 16 weeks.

Discussion

A slight reduction in platelet life span has been reported in association with atherosclerosis,^{13, 14} arterial hypertension,¹³ and thromboembolic diseases.¹³⁻¹⁶ In patients with acute disease, such as venous thrombosis, myocardial infarction and cerebrovascular attack, shortening of platelet survival was temporary, whereas in those with chronic diseases, such as peripheral occlusive arteriosclerosis and severe arterial hypertension with vascular complications, the shortening of platelet survival continued longer.¹³ In these studies, such findings were mainly obtained after the disease had been recognized clinically. In the present investigation, the platelet survival could be studied before the stroke developed by using relatively young SHRSP in the "prethrombotic" state as an animal model for human disease.

The incidence of spontaneous cerebral lesions in SHRSP (F_{29}) in males more than 100 days of age was more than 80% and that in SHRSR about 5%.¹ The incidence of spontaneous stroke in SHRSP more than 150 days of age of the same generations as used in this experiment was 88% and average life span 39 weeks. Therefore, more than 80% of SHRSP used in the present studies (F_{32} to F_{34}) were thought to be destined to have a stroke spontaneously in the future, although they showed neither signs of stroke throughout the experiment nor remarkable pathological findings at autopsy because of their young age of 100 days at the beginning of the experiment. However, even at this age, marked hypertension was already observed in SHRSP and SHRSR, especially in the former rats.

The results of the present investigation demonstrate that

shortened platelet survival and increased platelet consumption are present in a high proportion of SHRSP and that platelet survival and consumption in SHRSR are not significantly different from those in normotensive control rats. However, in SHRSP a quantitative platelet abnormality was not observed and it was assumed that their platelets might be maintained at the normal level by a compensatory increase in production. It was reported that thrombopoiesis of the rat appeared to be regulated by the demand for circulating platelets.¹⁷ It seemed highly unlikely that a qualitative abnormality in the platelet of SHRSP was responsible for shortened platelet survival and for increased platelet consumption, since platelets of SHRSP injected into the SHRSR showed normal platelet survival and no increase in consumption of transfused platelets was observed in the recipient. On the other hand, platelets of SHRSR transfused into SHRSP survived a shorter time and their consumption was more than those transfused into SHRSR. These data can be interpreted as evidence that the shortened platelet survival in SHRSP is caused by abnormal extracorporeal factors. The fate of the circulating platelet is probably determined by the following factors: the character of the platelets (e.g., the age of the platelet, metabolic or congenital defect in the platelet), the reaction of the platelet to the vessel wall, the consumption of platelets in coagulation and sequestration or phagocytosis of platelets by the spleen, the liver, reticuloendothelial cells or other cells. Vascular changes in SHRSP¹ seem to be the most likely explanation for the slightly reduced platelet survival in SHRSP, although the lesions are slight and not clearly observed by light microscopy except for medial hypertrophy or hyperplasia at the age of 16 weeks. Further detailed clarification of the mechanism of shortened platelet survival in SHRSP was not completed in the present investigation and remains to be solved in the future. In a study of platelet survival and turnover in atherosclerotic and control subjects, a relationship between platelet survival or turnover and the complications of atherosclerosis was reported.¹³ The subjects with no clinical complications of atherosclerosis but a positive family history for such disorders had shorter platelet survival and greater platelet turnover values, comparable to the group with complications of atherosclerosis, than the control group with a negative family history that had the longest mean platelet survival and the smallest mean platelet turnover values.¹⁴ This study demonstrated the importance of family history of complications of atherosclerosis in such in-

TABLE 3 Statistical Analysis for Platelet Half-Life Time and Mean Platelet Consumption in Rats

Comparison Donor→ Recipient : Donor→ Recipient	Platelet half-life time		Platelet consumption	
	t	P	t	P
SP → SP : SR → SP	0.456	NS	1.056	NS
SP → SP : SR → SR	2.226	<0.05	2.304	<0.05
SP → SP : SP → SR	4.846	<0.001	2.575	<0.05
SP → SP : WK → WK	2.452	<0.05	5.107	<0.001
SR → SR : SR → SP	3.285	<0.01	2.956	<0.02
SR → SR : SP → SR	1.912	NS	0.451	NS
SR → SR : WK → WK	0.167	NS	1.029	NS
SR → SP : SP → SR	9.234	<0.001	3.168	<0.02
WK → WK : SR → SP	3.646	<0.01	5.307	<0.001
WK → WK : SP → SR	1.782	NS	0.318	NS

NS: not significant; others are same as described in table 2.

vestigation. Our present experimental study indicated the possibility that the examination of platelet survival or turnover might be useful as one of the measures to detect minute alterations of hypertensive vascular damages in the subclinical state and to predict the development of severe vascular lesions such as stroke. Such detection of minute vascular damages or prediction of stroke is obviously indispensable for the prevention of stroke, one of the three commonest causes of death in most civilized societies.

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Temporal Profile (Clinical Course) of Acute Carotid System Cerebral Infarction

H. ROYDEN JONES, M.D.,* AND CLARK H. MILLIKAN, M.D.†

SUMMARY The records of 179 consecutive patients with acute carotid system cerebral infarction were studied to describe the temporal profile of the clinical events during the first week of the illness. Only those patients admitted to the cerebrovascular hospital service within 36 hours of the onset of the first symptom were included.

The neurological status of 39% was stable (unchanged) at the end of seven days; 35% of the patients gradually improved. Nineteen percent had a progressing neurological deficit from the onset which

stabilized within 48 hours of onset. Six patients (3%) had a remitting-relapsing course during the first 36 hours. Eight patients (4%) had a significant late worsening, after 48 hours of stable or improving course.

Mortality was 11% for the entire group. However, a high risk of death group was identified — the mortality was 41% for those patients who had any degree of decreased level of consciousness and hemiplegia at the time of admission.

WHAT is the temporal profile of acute progressing carotid system cerebral infarction? How often does the progressing course halt (apparently becoming a completed stroke) only to have serious additional progression take place a few hours later? Another way of saying this: if 100 consecutive patients are observed within the first few hours of beginning carotid system cerebral infarction, what is the expected natural

history — progression, stasis, regression, etc? An obvious secondary question is: does any particular type of treatment make any difference in this natural history or expected condition of the patient at the conclusion of a relatively short period of time (one or two weeks)?

Lack of clarity of definition or use of the term "progressing stroke" (stroke-in-evolution) may partially explain the lack of definite answers in the literature to these important questions. Care in defining the categories making up the temporal profile of stroke is primary to the issue of studying the natural history of each category.

Definitions

It is now customary to divide the temporal profile of stroke into three principal categories:¹⁻³ transient ischemic

*Instructor of Neurology, Harvard Medical School, Beth Israel Hospital, Boston, Massachusetts 02215.

†Professor of Neurology, Mayo Medical School; Director, Mayo Clinical Cerebrovascular Research Center, Mayo Clinic, Rochester, Minnesota 55901.

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Reprint requests to Dr. Millikan.