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# Effect of age on cerebral venous circulation disturbances in the rat

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*Object.* Mild cerebral venous circulation disturbances (CVCDs) in aged patients are frequently known to cause unexpectedly severe postoperative complications in neurosurgical practice. The object of the present study was to determine whether there are age-related differences involved in vulnerability to CVCDs.

*Methods.* Thirty-eight male Wistar rats were used. A single cortical vein with a 100-μm diameter was occluded photochemically by using rose bengal dye and fiberoptic illumination in young (Group Y, 19 animals aged 10–14 weeks) and aged (Group A, seven animals aged 80–100 weeks) rats. Five young and seven aged animals served as sham-operated controls. Regional cerebral blood flow (rCBF) was determined from local CBF, which was measured at 25 ($5 \times 5$) identical locations, with the occluded vein located central to the scanning field, by using a laser Doppler scanning technique every 15 minutes for 90 minutes after venous occlusion. The cerebral venous flow pattern was examined using fluorescence angiography until 90 minutes after occlusion. Histological specimens were examined 24 hours after occlusion. In Group Y, rCBF did not change significantly after venous occlusion. However, in Group A, rCBF decreased rapidly beginning 15 minutes after occlusion. Significant intergroup differences were observed 30, 60, and 90 minutes after occlusion. Venous flow arrest, which resulted in venous infarct, was observed on angiography 90 minutes after occlusion in two (10.5%) of 19 young and six (85.7%) of seven aged rats. The venous thrombus in Group A rats was significantly larger than that in Group Y rats 90 minutes after occlusion. Venous infarction was seen in all aged rats (100%) and in six young rats (31.6%); the infarct size, expressed as a percentage of the size of the ipsilateral hemisphere, was significantly larger in aged rats than in young rats.

*Conclusions.* This study demonstrated an age-related increase in the rate and size of venous infarct following vein occlusion, suggesting that the greater vulnerability to CVCDs in the aged brain might be attributed to early and extensive hypoperfusion of circumscribed brain areas drained by the occluded vein. The larger thrombus formation in aged animals indicates that a shift in the thrombogenetic/thrombolytic equilibrium is responsible for the observed effect.

**KEY WORDS • cerebral blood flow • vascular occlusion • laser Doppler scanning • rose bengal photothrombosis • rat**

COMPLICATIONS arising from venous obstruction are being observed more frequently because of the increasing number of neurosurgical operations performed in elderly patients and the development of skull base neurosurgery.[10,11,19,27–29,33,37,39] The frequency of postoperative venous infarction following CVCDs is reportedly higher in aged than in young patients.[7,46] However, this suspected difference between older and young patients or experimental animals remains unproven, and no study on venous infarction in elderly animals has been reported so far. Experiments with aged animals are difficult to perform because such experiments are costly and time consuming and, most important, because of the vulnerability of these animals.[43] Previous attempts to use aged animals in stroke research have been hampered by their fragility; for example, middle cerebral artery occlusion in mature adult (12-month-old) rats resulted in the deaths of these animals from cardiac dysfunction within 12 hours.[17] We have established a reliable CVCD model with photochemically induced cortical vein occlusion in the rat brain, in which endothelial alteration stimulates platelet activation resulting in a venous thrombus.[28] Occlusion of a single vein is an appropriate model for studies on the variable pathophysiological characteristics of venous occlusion observed experimentally and clinically. One of the distinct characteristics of this model is the absence of local and systemic invasiveness.[30] Therefore, this technique appears suitable for studies on weak older animals and is compatible with a major aim of the present study, which is to investigate the effect of age on the pathophysiological changes of CVCDs and venous infarction in this rat single-cortical-vein occlusion model.

*Abbreviations used in this paper:* CBF = cerebral blood flow; CVCD = cerebral venous circulation disturbance; lCBF = local CBF; LD = laser Doppler; LDU = LD unit; MABP = mean arterial blood pressure; rCBF = regional CBF; SD = standard deviation.

## Materials and Methods

This study was conducted according to the animal experiment guidelines approved by the 89th General Assembly of the Japan Science Council in 1980.

*Animal Preparation*

The experiments were conducted using 24 young male Wistar rats (260–340 g body weight, 10–14 weeks of age) and 14 aged male Wistar rats (520–700 g body weight, 80–100 weeks of age). The animals were housed at a constant temperature of 20°C, with a light/dark cycle of 12/12 hours, and allowed free access to food and water before surgery. The methods used have been previously described in detail.[28] Each animal was anesthetized by an initial intraperitoneal injection of chloral hydrate after having been premedicated with 0.5 mg atropine. Anesthesia was maintained by administration of chloral hydrate through a peritoneal catheter. In all animals, rectal temperature was kept at approximately 37°C throughout the experiment by using a feedback-controlled heating pad. Spontaneous ventilation was maintained during the experiment. Polyethylene catheters were inserted into the tail artery and the right femoral vein. The arterial line served for continuous registration of MABP and arterial blood gas sampling, and the venous lines were used for administration of fluid and drugs. Each animal's $PaO_2$, $PaCO_2$, and arterial pH were measured using a blood gas analyzer. Blood pressure and heart rate were continuously monitored via the intraarterial catheter, which was connected to a pressure transducer. Each rat was mounted on a stereotactic frame. After a 20-mm midline skin incision had been made, the parietal skull was thinned to translucency, by using a high-speed drill with the aid of an operating microscope, for photochemical occlusion, fluorescence angiography, and CBF monitoring, which was performed using LD flowmetry. During the craniectomy, the drill tip was cooled continuously with physiological saline to avoid thermal injury to the cortex.

*Cortical Vein Occlusion Induced by Photochemical Thrombosis*

Cortical vein occlusion was induced using rose bengal dye and fiberoptic illumination (6500–7500 lux, wavelength 540 nm) connected to a 100-μm fiber in 19 young (Group Y) and seven aged (Group A) rats. The diameter of the occluded vein was approximately 100 μm. Rose bengal dye was injected slowly without effect on systemic arterial pressure (young rats received 50 mg/kg body weight and aged rats received 25 mg/kg body weight); care was taken to avoid illumination of tissue and other vessels near the targeted vein. The fiber was pointed at the vein for 10 minutes. Complete or incomplete occlusion of the targeted cortical vein and the status of other undamaged intact vessels around the illumination point were confirmed using a second fluorescence angiography study. Subsequently, after the third fluorescence angiography study had been completed, the skin wounds were closed using No. 4-0 silk sutures. The rats were returned to individual cages and allowed free access to water and food. In addition, 12 (five young and seven aged) rats served as sham-operated controls; these rats underwent the same surgical treatment and intravenous injection of rose bengal dye without fiberoptic illumination.

*Fluorescence Angiography*

Fluorescence angiography was performed in all rats. Epicortical vessel structures were studied using an intravenous injection of 2% $Na^+$-fluorescein solution (0.5 ml) and an excitation source at the I2 filter (wavelength 450–490 nm). A photomacroscope equipped with a 50-W mercury lamp and a fluorescence filter was used for fluorescence angiography before and 15 and 90 minutes after induction of venous occlusion. The images were recorded on a supervideo home system. To minimize the damage caused by fluorescence excitation, illumination was restricted to angiography sessions. The degree of flow reversal in the occluded vein at the time the third angiography study was performed was compared with that recorded during the first angiography study. In addition, the size of the venous thrombus was measured 90 minutes after occlusion, during the third angiography session, by using a video image analyzer.

*Measurement of CBF by Using LD Scanning*

Local CBF was measured using LD flowmetry, which was performed with a 0.8-mm needle probe and expressed in LDUs. Using a motor-driven computer-controlled micromanipulator connected to a personal computer, the lCBF was measured at 25 (5 × 5) locations with the occluded vein located central to the scanning field. Thus, there was random registration of 25 individual measurements in one scanning procedure, with information provided from 25 different locations spaced 500 μm apart. To avoid artifacts caused by measurements recorded with a probe still in motion, a delay of 2 seconds was allowed before each measurement. Twenty values measured over the next 2 seconds were averaged to give a single lCBF value. This technique permits repeated scans for a given set of locations. Scanning was performed from the beginning to the end of the experiment at identical locations at 15-minute intervals. Regional CBF was determined by calculation of median values at the 25 locations. A recently performed series of experiments served to calibrate our LD system to absolute values of regional cortical blood flow.[40] Absolute values of CBF ($CBF_{ABS}$ in milliliters per 100 grams per minute) were calibrated from CBF measured by LD flowmetry ($CBF_{LD}$) in LDUs according to the formulas:

$CBF_{ABS} = 1.7 \times CBF_{LD} + 1.4$ (young rats) and
$CBF_{ABS} = 1.3 \times CBF_{LD} + 8.3$ (aged rats).

The coefficients of the formulas for aged and young rats were independently determined for both groups.

*Histological Preparations and Quantitative Analysis*

Twenty-four hours after the operation, the rats were subjected to perfusion fixation with 4% paraformaldehyde after general anesthesia had been induced using chloral hydrate. In each rat, the brain was removed from the skull carefully and embedded in paraffin to obtain coronal sections of the parietal region. The sections were stained with hematoxylin and eosin. The section demonstrating the largest infarct area and sections obtained from sites 0.4 mm anterior and posterior to it were used for quantitative assessment of brain injury. The infarct size was determined using a microcomputer imaging device image analyzer. Infarct sizes obtained from the three sections were averaged and expressed as a ratio of the size of the ipsilateral hemisphere.

*Statistical Analysis*

Data are expressed as the means ± SD for physiological variables, infarct size, and the median lCBF found in each rat. The Mann–Whitney U-test was used to analyze physiological variables such as blood gas levels ($PaO_2$ and $PaCO_2$), MABP, and infarct size. Differences in rCBF were evaluated using Dunnett's test for analysis of variance for repeated measures and by using an unpaired t-test. The chi-square test was used for discrete variables in the angiographic findings. A probability value less than 0.05 was considered significant. Statistical analysis was performed using statistical software, and illustrations were plotted using plotting software.

*Sources of Supplies and Equipment*

The feedback-controlled heating pad (model CMA 150) was obtained from Carnegie Medicine AB, Stockholm, Sweden. The blood gas analyzer (model ABL 330) was purchased from Radiometer, Copenhagen, Denmark. The pressure transducer (Polygraph System RM-600) was obtained from Nihon Koden, Tokyo, Japan. The stereotactic frame (model SR-6) was purchased from Narishige, Inc., Tokyo, Japan. Photochemical thrombosis was induced using rose bengal dye obtained from Katayama Chemicals, Osaka, Japan, and the L4887 fiberoptic illumination system was purchased from Hamamatsu Photonics, Hamamatsu, Japan. Fluorescence angiography was performed using a 2% $Na^+$-fluorescein solution obtained from Nacalai Tesque, Kyoto, Japan, and the I2 filter was obtained from Leitz, Wetzlar, Germany. Images were recorded using a supervideo home system (model SR-S600) from Victor, Tokyo, Japan, and were analyzed using a video image analyzer (model DVS-20) from Hamamatsu Photonics, Hamamatsu, Japan. Measurement of CBF was made using an LD flowmetry unit (model ALF-21) purchased from Advance, Tokyo, Japan, and a motor-driven computer-controlled micromanipulator (XYZ scanning stage) from Scholar Tec, Osaka, Japan, connected to a personal computer (98 Note SX) manufactured by NEC, Tokyo, Japan. The infarct size was determined using a microcomputer imaging device image analyzer ob-

TABLE 1

*Physiological variables in young and aged rats**

| Physiological Variable | Young Rats (24 animals) | Aged Rats (14 animals) |
|---|---|---|
| MABP (mm Hg) | 108.6 ± 6.8 | 117.6 ± 8.0 |
| $PO_2$ (mm Hg) | 125.1 ± 7.5 | 120.0 ± 31.9 |
| $PCO_2$ (mm Hg) | 42.9 ± 2.7 | 43.1 ± 2.8 |
| pH | 7.38 ± 0.04 | 7.40 ± 0.03 |
| hematocrit (%) | 47.8 ± 1.6 | 45.3 ± 3.3 |

* Values are expressed as the means ± SD. There is no statistically significant difference in any physiological variable between the two groups.

tained from Neuroscience, Inc., Tokyo, Japan. To aid data management and statistical analyses, Sigma-Stat and Sigma-Plot software were purchased from Jandel Scientific, Erkrath, Germany.

## Results

### *Physiological Variables*

There were no statistical differences in the physiological parameters of blood gases ($PaO_2$, $PaCO_2$ and pH), hematocrit, and MABP levels between aged and young groups (Table 1).

### *Fluorescence Angiography Findings*

Fluorescence angiography offered information about the direction of cerebral venous blood flow and the extent of thrombosis after vein occlusion. No changes were apparent in the sham-operated group when the three angiography studies were compared. The second angiography study indicated flow reversal, dilation of the distal portion of the occluded vein, or deceleration of flow. Moreover, the third angiography session revealed facts such as the degree of flow reversal, further extension of thrombosis, and extravasation of fluorescein into the parenchyma close to the occluded vein. In Group Y, good reverse flow was observed 90 minutes after occlusion in 14 (73.7%) of the 19 rats, slow reverse flow in three rats (15.8%), and an arrest of flow in two rats (10.5%). On the other hand, in Group A an arrest of flow was observed in six (85.7%) of the seven rats and slow reverse flow in only one rat (14.3%) ($p < 0.001$, chi-square test; Table 2). Furthermore, in all rats in which an arrest of flow was observed, extravasation of fluorescein into the parenchyma was demonstrated during the third angiography session, as well as development of cerebral infarction in both groups (Table 2). Furthermore, in Group A, the size of the thrombus (497 ± 399 μm) was larger than that found in Group Y (136 ± 41 μm) ($p < 0.05$, unpaired t-test).

TABLE 2

*Flow reversal and size of venous thrombus at 90 minutes after occlusion**

| Factor | Young Rats (19 animals) | Aged Rats (7 animals) |
|---|---|---|
| good reverse flow (no. of rats) | 14 (2) | 0 |
| slow reverse flow (no. of rats) | 3 (2) | 1 (1) |
| arrest of flow (no. of rats) | 2 (2) | 6 (6) |
| size of thrombus (μm)† | 136 ± 41 | 497 ± 399 |

* Numerals in parentheses indicate the number of rats that suffered from cerebral infarction. The degree of flow reversal is significantly different in both groups ($p < 0.001$, chi-square test). In aged rats, the size of the thrombus was larger than that in young rats ($p < 0.05$, unpaired t-test).
† Values are expressed as the means ± SD.

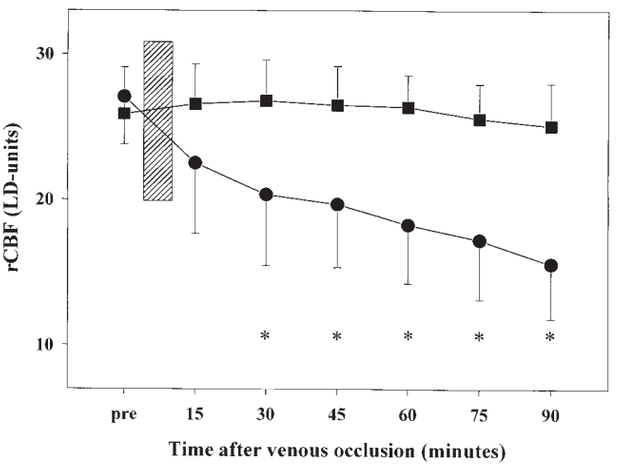


FIG. 1. Graph showing sequential changes in rCBF in the aged sham-operated group (seven animals) and in Group A (seven animals). The values are expressed in LDUs (mean ± SD of median lCBF from 25 locations in each animal). The shaded rectangle indicates the illumination of the vein. In the aged sham-operated group *(squares)*, there were no significant changes. In the venous occlusion group (Group A, *circles*), rCBF significantly decreased from 15 minutes after venous occlusion to the end of experiment, compared with preocclusion rCBF ($p < 0.05$) and from 30 minutes after venous occlusion to the end of the experiment, compared with rCBF in the aged sham-operated group. * $p < 0.05$.

### *Sequential Changes in rCBF*

The calculation of median rCBF values from the 25 locations in each animal demonstrated no change in rCBF during the experiment in either the young sham-operated group (29.6 ± 3.8 LDUs at the beginning and 24.7 ± 9.1 LDUs at the end of the experiment) or the aged sham-operated group (25.9 ± 3.2 LDUs at the beginning and 25.1 ± 2.9 LDUs at the end of the experiment). No significant differences between the sham-operated groups were found. In Group Y, rCBF did not change significantly, although it decreased from 31.4 ± 10.9 LDUs to 26.4 ± 13.2 LDUs. No significant differences were seen between Group Y and the young sham-operated group. On the other hand, rCBF in Group A decreased significantly (27.1 ± 3.3 LDUs at the beginning and 15.6 ± 3.8 LDUs at the end of the experiment) 15 minutes after vein occlusion compared with preocclusion rCBF values ($p < 0.05$, analysis of variance by using Dunnett's test), and had dropped significantly 30 minutes after occlusion, compared with the aged sham-operated group ($p < 0.05$; Fig. 1). Significant differences were observed between Groups Y and A at 30, 60, and 90 minutes after occlusion ($p < 0.05$, unpaired t-test; Fig. 2).

### *Histological Studies*

Histopathological investigation showed that the brains

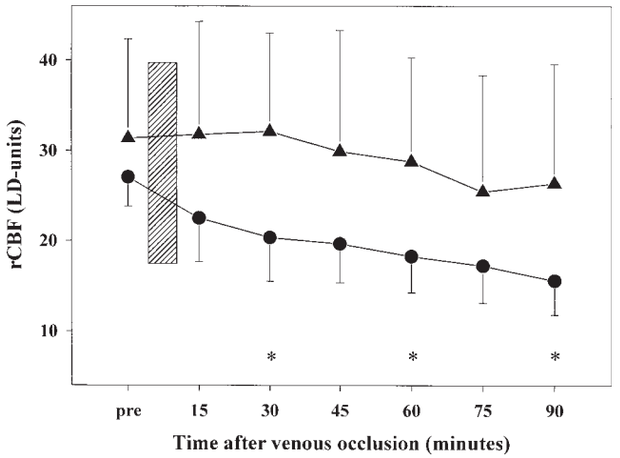


FIG. 2. Graph showing sequential changes in rCBF in Group Y (19 rats) and Group A (seven rats). The values are expressed in LDUs (mean ± SD of median lCBF from 25 locations in each animal). The shaded rectangle indicates the illumination of the vein. In the young rats in which venous occlusion was induced (Group Y, *triangles*), the rCBF did not change significantly, compared with the preocclusion rCBF. In the aged rats in which venous occlusion was induced (Group A, *circles*), the rCBF significantly decreased at 30, 60, and 90 minutes after venous occlusion, compared with rCBF in Group Y. * $p < 0.05$.

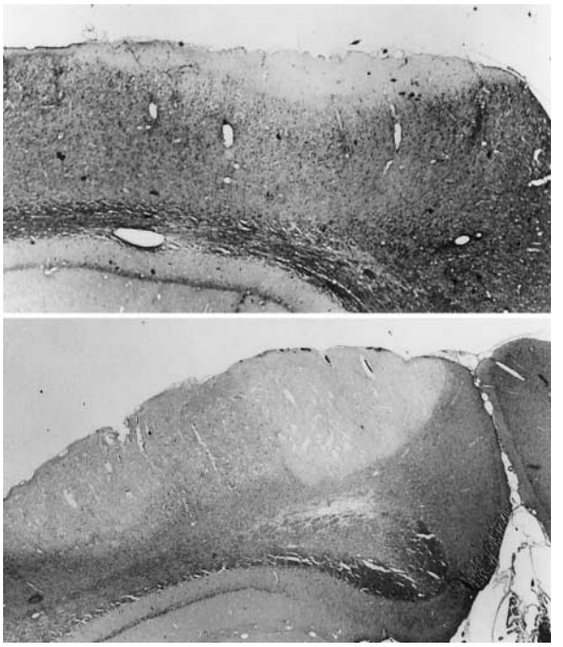

FIG. 3. *Upper:* Light micrograph of a coronal section obtained in an animal in Group Y, depicting a smaller infarct (2.2% of the contralateral hemisphere) than those found in Group A. H & E, original magnification × 25. *Lower:* Light micrograph of a coronal section obtained in an animal in Group A, demonstrating a large infarct (14% of the contralateral hemisphere). H & E, original magnification × 12.5.

of the sham-operated control animals had normal appearances. In Group Y, six (31.6%) of the 19 rats demonstrated parenchymal damage surrounding the dilated capillaries as well as edematous areas in both white and gray matter (Fig. 3 *upper*). All rats (100%) in Group A displayed extensive infarction (Fig. 3 *lower*). The infarction areas were clearly demarcated in hematoxylin and eosin staining. Quantitative assessment of brain injury, which was expressed as a percentage ratio of the ipsilateral hemisphere, showed a significantly larger infarct size in Group A (10.1 ± 5.2%, seven animals) than in Group Y (3.1 ± 1.3%, six animals) ($p < 0.05$; Fig. 4).

*Relationship Between Infarct Size and rCBF 90 Minutes After Occlusion*

After cortical vein occlusion, there was a negative correlation between the infarct size and the rCBF measured 90 minutes after occlusion in Group A: the correlation coefficient was 0.82 ($p = 0.024$; Fig. 5).

## Discussion

The majority of experimental studies on stroke have been conducted in young adult animals although stroke is a disorder associated with aging. Recently, several reports about experiments on focal cerebral ischemia in aged rats have appeared,[12,17,43] in which the authors have suggested the importance of such investigations and described the considerable difficulties encountered in establishing a reproducible model in animals of a relevant age. In the present experiment, we also encountered two major problems. First, the appropriate dosage of dye for the elderly animal differed from that for the adolescent. During the operation in our preliminary study some old rats died after administration of the same dosage of rose bengal dye given to the young rats. In a preliminary study, rose bengal dye at a dosage of 25 mg/kg was sufficient to induce thrombosis in 100% of aged rats, but only 70% of young rats, and the

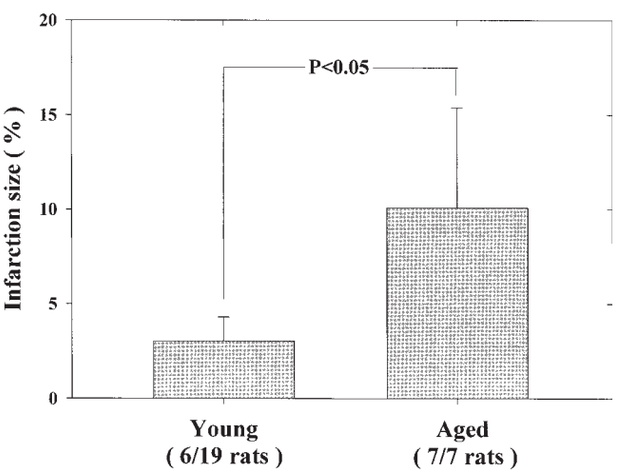


FIG. 4. Bar graph depicting the quantitative assessment of infarct size, expressed as a percentage of the size of the ipsilateral hemisphere, and error bars indicating SDs in Group Y (young rats) and Group A (aged rats). Infarct size was significantly larger in Group A than in Group Y. * $p < 0.05$.

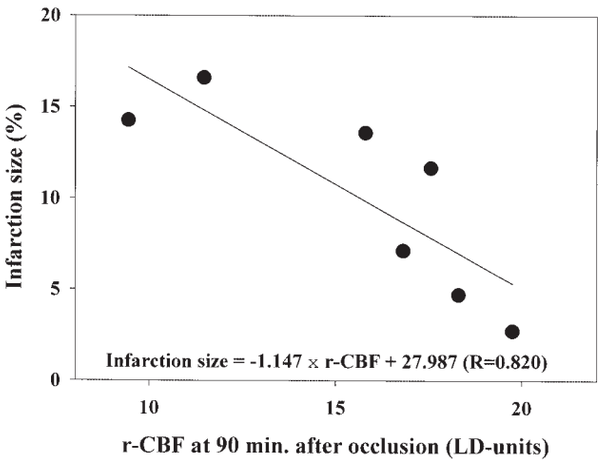


FIG. 5. Correlation between rCBF measured 90 minutes after venous occlusion and infarct volume determined 24 hours later in Group A. Note the increased infarct volumes in animals with rCBF reduction.

success rate of vein occlusion decreased in the younger animals. Therefore, in the current experiment, old animals received half the dose of rose bengal dye (50 mg/kg in young and 25 mg/kg in old rats). One might argue that this study should be performed using identical dosages of dye. However, the dye exerts no protective effect that might interfere with the ensuing venous infarction. In addition, we have already verified that the dye does not affect cerebral parameters such as CBF, cerebral blood volume fraction, and histological structure, or global physiological parameters such as systemic blood pressure, heart rate, arterial blood gas levels, and hematocrit.[28,29,31] Thus, reducing the dosage in old animals improved survival while still providing adequate conditions for the experiment.

The second problem that we encountered was that the skull bone adhered tightly to the dura in aged rats and separation was impossible without causing subdural or subarachnoid hemorrhage. This problem was resolved by thinning the parietal skull bone to translucency for photochemical occlusion, fluorescence angiography, and CBF monitoring. This technique allowed observation of the cerebral surface and cortical vessel structure without inducing dural and cerebral damage or any effect on intracranial pressure. Taken together, the combination of photochemical thrombotic vein occlusion and LD scanning technique used here had distinct advantages for small aged animals because it was less invasive and was simple to perform.

Several physiological changes occur in humans with increasing age. Some reports have demonstrated that CBF is lower[38] and blood pressure higher[21] in aged rats than in young ones, whereas others have shown no statistically significant intergroup differences in CBF and blood pressure.[5,17,35] In the current study, no significant differences were found in those parameters and other physiological variables, such as arterial blood gas levels, between the different age groups.

It is well known that the aged brain has potential susceptibility to stress[18,36] and is severely damaged by cerebral ischemia. Some reports have associated aging with an altered catecholamine level,[9,39] a decline in the quantity and sensitivity of dopamine receptors,[4,16] a reduction in neurotrophic factors,[45] a decrease in the neuron/glial cell ratio,[3,25] reduced levels of nerve growth factor[22] and nerve growth factor receptor,[14] and a decrease in *N*-methyl-D-aspartate receptor density[44] and function.[15] Furthermore, there is some evidence to suggest decreased blood–brain barrier transport of glucose[26] and amino acids,[34] reduced metabolic rates for glucose[23] and oxygen,[32] and decreased oxidative metabolism in the mitochondria in the aged brain.[6,13,41,42] A decline in red blood cell deformability may contribute to reduced blood filterability in the aged.[8] Reduced infiltration of macrophages into cerebral infarcts and hypertrophy of astroglial fibrils surrounding these infarcts in the aged rat have been reported in an embolic stroke model. These results suggest that immunological response may also decline with age.[12]

Venous infarction is an increasingly recognized cause of postoperative complications in aged patients. Nevertheless, there has been no report on CVCDs in aged patients or in experimental animals; therefore, very little is known about the pathophysiological condition. In the current study we documented the pathological development of CVCDs in aged experimental animals, which was concomitant with a deterioration in outcome; the degree of venous ischemia (early and extensive hypoperfusion of circumscribed brain areas drained by the occluded vein), the frequency of venous infarction, and the infarct size were significantly greater in aged than in young animals. As to the mechanism potentially responsible for the observed age-related differences in vulnerability to venous infarction, the fact that half the dose of rose bengal dye was enough to occlude the cortical vein in aged rats, together with the observation that the size of venous thrombus after 90 minutes was significantly larger in old than in young rats (Table 2) suggest that the equilibrium between thrombogenic and thrombolytic factors in old rats is shifted toward thrombogenesis. This may be due to changes on the endothelial surface. Documented morphological changes in the cerebral vasculature of aging rats include thinning of the endothelium, reduction in capillary lumen diameter, and decreasing number of capillary endothelial cells.[1,2] These structural and blood coagulative changes (such as reduced blood filterability)[8] associated with advancing age might result in the shift of the thrombogenic/thrombolytic equilibrium seen in the present experiment. As shown in Table 2, the relative deficiency in venous collateral circulation associated with age might also contribute. This is the first study in which the influence of advancing age on cerebral venous infarction has been evaluated. However, the question arises whether age in an animal is comparable to a given age in humans, because the life span of animals is much shorter than that of humans. The normal life expectancy of a Wistar rat is 2 to 3 years, and an age of 80 to 100 weeks in rats corresponds to 50 to 60 years in humans, which is when cerebrovascular diseases often occur.[24] The aged rats used in this experiment are only a few years old and significant atherosclerosis did not occur. Other differences between aged rats and older humans might exist. Therefore, caution is required before the results are extrapolated to aging humans. Notwithstanding, the differences in vulnerability to

CVCDs between the two age groups are certainly noteworthy. Identification of the mechanisms involved require further study.

In this study, changes in rCBF following venous occlusion correlated well with the subsequent tissue damage. Similar observations have been reported after occlusion of one and two adjacent cortical veins; two-vein occlusion caused more extensive hypoperfusion and greater venous infarction than single-vein occlusion.[30] The pattern of blood flow decline in elderly animals bears a striking resemblance to that seen after two-vein occlusion in young rats.[30] These findings suggest that ischemia is a significant pathophysiological consequence of CVCDs and that CBF monitoring may be a promising tool for the prediction of critical CVCDs.

In a recent simulation study conducted by Kempski, et al.,[20] the number of measurements necessary to assess rCBF by local LD recording was evaluated, revealing that sample sizes larger than 25 obtained by LD scanning are necessary to obtain more reliable information on rCBF. Thus, an LD scanning technique to register LD flow signals from multiple locations may partly overcome the problem of spatial heterogeneity while maintaining a high temporal resolution. Moreover, a study recently performed in our laboratory demonstrated that LD scanning estimates can be calibrated for absolute CBF in milliliters per 100 grams per minute by comparing the findings of LD scanning with hydrogen clearance. Using data obtained from that study, a final flow of 28.6 $\pm$ 4.9 ml/100 g/min can be calculated for the aged group compared with 46.2 $\pm$ 22.5 ml/100 g/min for young rats 90 minutes after single-vein occlusion. Therefore regional flow even in aged rats is still above the threshold level assumed to cause infarction in the penumbra zone. However, from the slope of the flow change, it may be assumed that the flow decrease continues longer than the 90-minute observation time and finally reaches a critical level.

## Conclusions

This study emphasizes the importance of age in a model of venous infarction; neuronal injury after cerebral vein occlusion is greater in rats of advanced age than in younger animals. The age-related susceptibility might be attributed to the fact that aging leads to a greater fall in blood flow in brain areas drained by the occluded vein.

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