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Microcirculatory alterations in a Mongolian gerbil sinus-vein thrombosis model

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Summary *Background and purpose*. The pathophysiology of sinus-vein thrombosis (SVT) is still controversial in patients and experimental animals, the microcirculatory alterations in particular. This study was designed to develop a new sinus-vein thrombosis model and to further elucidate pathophysiological events such as the relationship between local and regional cerebral blood flow and haemoglobin oxygen saturation ($HbSO_2$), changes of the microvasculature, leukocyte behaviour and brain tissue damage. *Methods*. In a first experimental series, animals were divided into two groups which resulted from different procedures of inducing SVT. In the SSS middle occlusion group (SMO group), SVT was induced by the ligation of the superior sagittal sinus right in the middle between the bregma and the confluence sinum. In the SSS posterior occlusion group (SPO group) the ligation was performed close to the confluence sinum. Regional cerebral blood flow (rCBF) was assessed at 36 identical locations by laser-Doppler flowmetry together with regional haemoglobin oxygen saturation ($HbSO_2$). In a second series of experiments SVT was induced by ligation of the SSS close to the confluence sinuum (SVT group) to study effects on the cortical microcirculation. A sham operation was performed in six animals (sham group). In both groups, an intravital microscopic double tracing technique was utilised for evaluating microvessel structures and leukocyte behaviour. The images were recorded on videotape for evaluating alterations of microvessel (venules, arterioles and capillaries) diameters and numbers of leukocyte rollers and stickers by a digital video analyser. Animals were sacrificed for histological evaluation after 5 days. *Results*. The posterior sinus ligation caused a significant decrease of rCBF and $HbSO_2$ and brain tissue damage which was not seen in the SMO group. Alteration of rCBF and $HbSO_2$ were positively correlated with infarct size in the SPO group only, where venous infarction was easily reproduced. Therefore, it is suggested that this model is suitable for studying SVT in Mongolian gerbils. Intravital microscopy of the cortical microcirculation revealed no significant changes of vessels diameter in the sham group, whereas a significant dilation of veins and capillaries was seen in the SVT group. Numbers of leukocyte rollers and stickers were positively correlated with infarct size. *Conclusion*. Microcirculatory alterations and brain tissue damage from SVT in the Mongolian gerbil depend on the SSS occlusion site. The newly established mongolian gerbil sinus-vein thrombosis model has advantages compared to previously reported sinus-vein thrombosis models such as easy handling, easy technique, highly reproduciblity, and good observation of microcirculatory event. The model allows for studies of cerebral low-flow conditions such as expected to occur in an ischaemic penumbra zone. © 2001 Harcourt Publishers Ltd

Keywords: sinus-vein thrombosis, microcirculatory alterations, mongolian gerbil

INTRODUCTION

The pathophysiology of sinus-vein thrombosis (SVT) is still controversial in patients and experimental animals, the microcirculatory alterations in particular. The experimental study of the subject is limited by the lack of a reproducible SVT model permitting access to the cerebral microcirculation. This study was designed to develop a new sinus-vein thrombosis model and to further elucidate pathophysiological events such as the relationship between local and regional cerebral blood flow and haemoglobin oxygen saturation ($HbSO_2$), changes of the microvasculature, leukocyte behaviour and brain tissue damage.

MATERIAL AND METHODS

The present study was conducted according to the German animal protection legislation and was reviewed by the regional ethics committee (Bezirksregierung Rheinhessen-Pfalz). Gerbils which had an epileptic attack during the experimental preparation were excluded from this study.

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Gerbil SVT model

Twenty-eight male Mongolian Gerbils (55–90 g body weight) were premedicated with 0.3 mg atropine sulfate. Anesthesia was introduced with ether and continued by intraperitoneal injection of chloral hydrate (36 mg/100 g body weight).

Spontaneous ventilation was maintained. Body temperature was monitored by a rectal probe and maintained at 37°C with a feedback controlled homeothermic blanket control unit (Harvard). Polyethylene catheters (outer diameter 0.61 mm, inner diameter 0.28 mm) were inserted into the left femoral artery and femoral vein under an operating microscope (OPMI-1-FR, Zeiss). The arterial line served for continuous recording of arterial blood pressure via a pressure transducer (Model CL-810231, Gould). The venous line was used for administration of fluid. All gerbils were mounted on a stereotaxic frame (Stoelting Co.,Wood Dale, USA).

After a 2.0 cm midline skin incision, two longitudinal cranial windows, each of 5×4 mm were made between coronal and lamboid sutures bilaterally with a high-speed drill (Microtron, Aesculap) under an operating microscope. During the craniotomy, the drill-tip was cooled continuously with physiological saline to avoid thermal injury to the brain cortex. The SSS cranial to the later ligation site and bilateral parasagittal cortex were exposed and meticulous care was taken to keep the dura intact (Fig. 1).

lCBF was measured using a Vasomedics laser flow blood perfusion monitor (model BPM 403a) with a 0.8-mm needle probe.

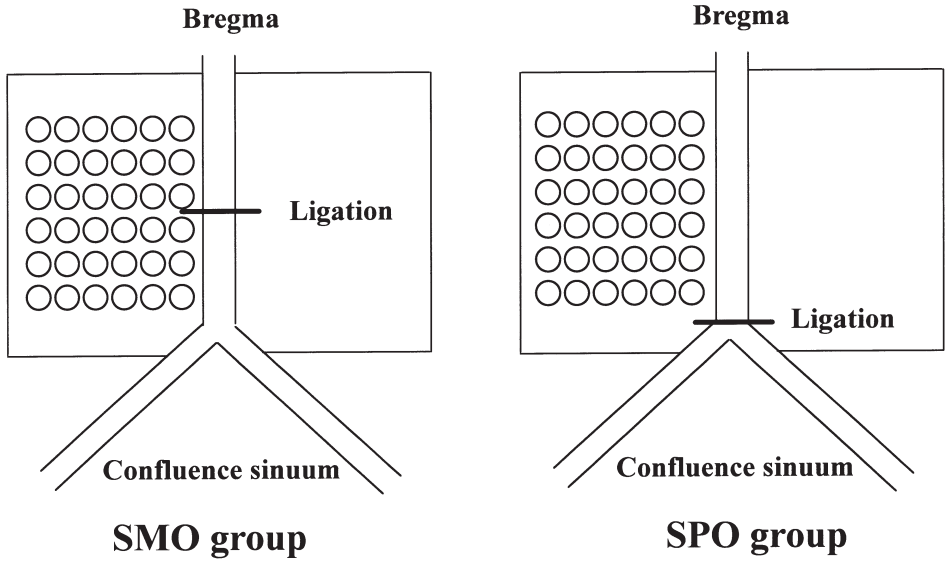

Fig. 1 Schematic drawing of the site of superior sagittal sinus ligation. Right; SMO group, Left; SPO group.

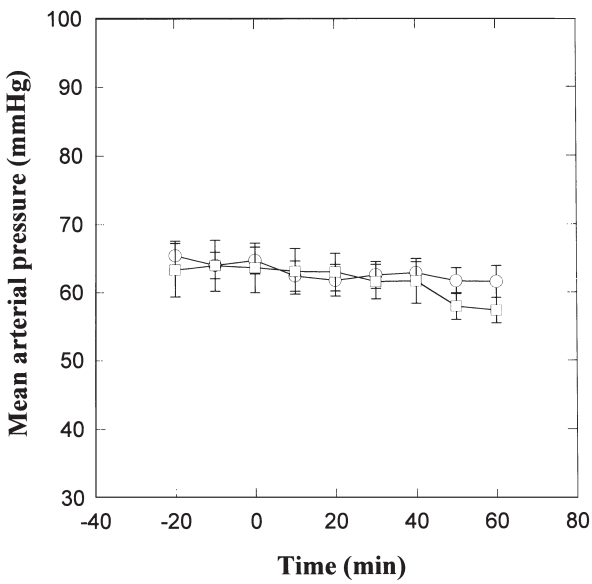

Fig. 2 Graph showing sequential changes in mean arterial blood pressure in SMO group and SPO group. There were no significant difference between those two groups.

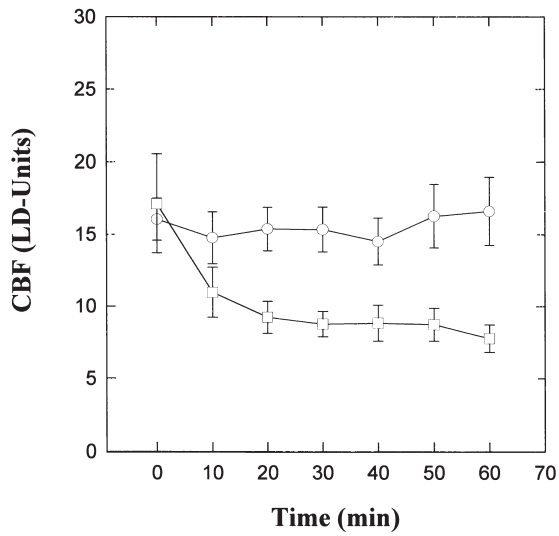

Fig. 3 Graph showing sequential changes in rCBF in SMO group and SPO group. The values are expressed in LDUs (mean ± SE of median lCBF from 36 location in each animal). In SPO group, rCBF significantly decreased after the SSS ligation compared with SMO group ($P<0.01$). A significant decrease of rCBF ($P<0.05$) started at 30 min after SSS ligation until the end of experiment.

lCBF was expressed in LD units. The LD system used has a reproducibly low biological zero, and with the scanning technique described below data from individual animals and locations may be compared.

The local tissue $HbSO_2$ was measured with EMPHO (Erlangen micro-lightguide spectrophotometer, Bodenseewerk Geraetetechnik GmbH). The local $HbSO_2$ is expressed in percent. The EMPHO monitor system consists of four modules: a light source, a micro-lightguide, the detector, and a computer. Parallellized light from a xenon high-pressure lamp is transmitted to the tissue surface by a central fiber surrounded by a hexagon of six detecting fibres. Light transmitted by these detecting fibres passes a fast rotating interference band-pass filter disk (502–628 nm) and then illuminates a photomultiplier.

The raw spectrum thus obtained is corrected online with the dark spectrum and with the spectrum obtained from excitation light reflected from a mirror at a set distance. The response spectrum is used for the evaluation of the tissue spectra from which local $HbSO_2$ is calculated. So, the spectra are digitalised in 2-nm increments from 502 to 628 nm. The relative amounts of oxyhaemoglobin and deoxyhaemoglobin normalised for light scattering are estimated as parameters using an iterative best-fit procedure based on the theory of Kubelka and Munk. These are relative concentrations because of light scattering, but they do permit calulation of the percentage of oxyhaemoglobin saturation.[1]

lCBF and local $HbSO_2$ were measured at 36 (6×6) identical locations in a scanning procedure by means of a computer-controlled micromanipulator. Thus, the random registration of 36

individual measurements results in one scanning procedure with information from 36 different locations, each at a distance of 500 μm.[2–5]

SVT was induced by SSS ligation technique.[4] Animals were divided into two groups, the SSS middle occlusion group (SMO group, $n=20$) and the SSS posterior occlusion group (SPO group, $n=8$) by means of the different sites of SSS ligation. In the SMO group, the SSS was ligated in the middle between bregma and confluence sinuum using 10-0 monofilament nylon suture. Skull bone above the ligation site was drilled out before ligation. Ligations were performed with meticulous care to avoid adjacent brain tissue damage. In the SPO group, the SSS was ligated just close to the confluence sinuum using 10-0 monofilament nylon suture. These procedures were performed under the operating microscope.

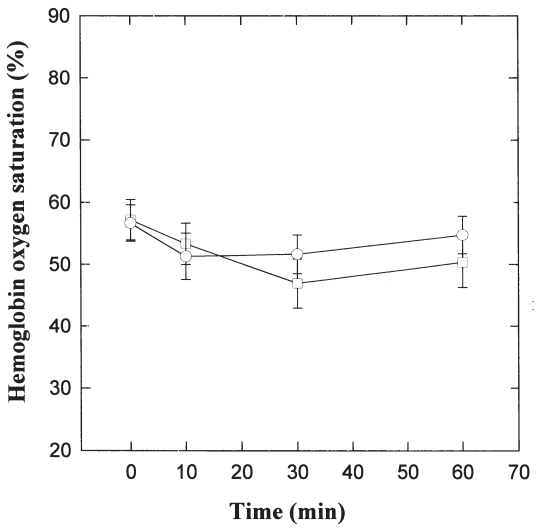

Fig. 4 Graph showing sequential change in local $HbSO_2$ in SMO group and SPO group. The values are expressed as a percentage of hemoglobin oxygen saturation (mean ± SE of median $HbSO_2$ from 36 location in each animal). No significant change of local $HbSO_2$ was seen in SMO group. In SPO group, maximum and highly significant decrease of local $HbSO_2$ was seen 30 min after SSS ligation ($P<0.05$). An incomplete recovery of $HbSO_2$ was seen 60 min after SSS ligation but local $HbSO_2$ value at 60 min was still significantly lower than baseline values ($P<0.05$).

Afterwards, the lCBF multiple scanning was repeated at 36 identical coordinates every 10 min up to 60 min after the SSS ligation. On the other hand, the $HbSO_2$ multiple scanning was repeated at 36 identical coordinates at 10, 30 and 60 min after the SSS ligation. After the experiments, the resected bone flaps were repositioned on the bilateral parietal regions and the operative wounds were closed. The animals were returned to individual cages and allowed to recover from anaesthesia.

Thereafter, the animals were allowed free access to food and water. Body weight was measured before operation and every day after operation to assess the intensity of ischaemic events.[2]

Gerbil SVT microcirculation study

Twenty Mongolian gerbils (48.6–78.2 g body weight) were premedicated and anaesthetised in the same fashion as described above. According to the results from the first experiments, Gerbil SSS posterior occlusion model was choosen for this series of experiments (SVT group, $n=14$). The polyethylene catheter was inserted in the left. femoral vein for administration of fluid and fluorescence agents. The animals were mounted on a stereotaxic

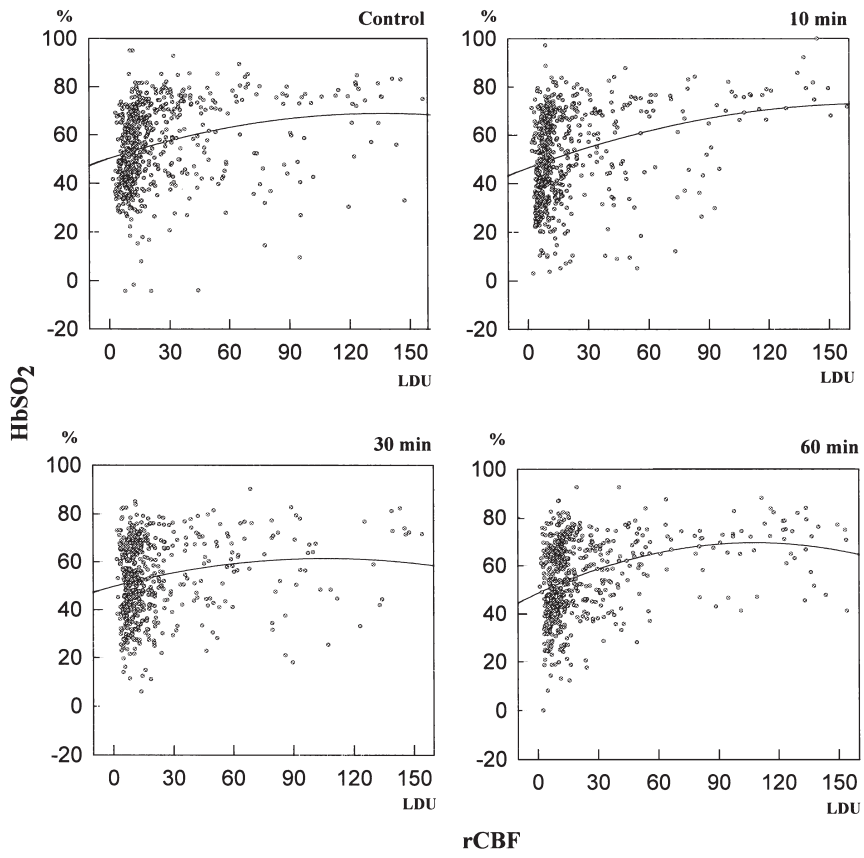

Fig. 5 Graph showing distributions of rCBF and local $HbSO_2$ as measured in identical cortical locations in SMO group. The distribution shows no change before and after SSS ligation in this group. Lines indicate single degree polynomial function regression lines.

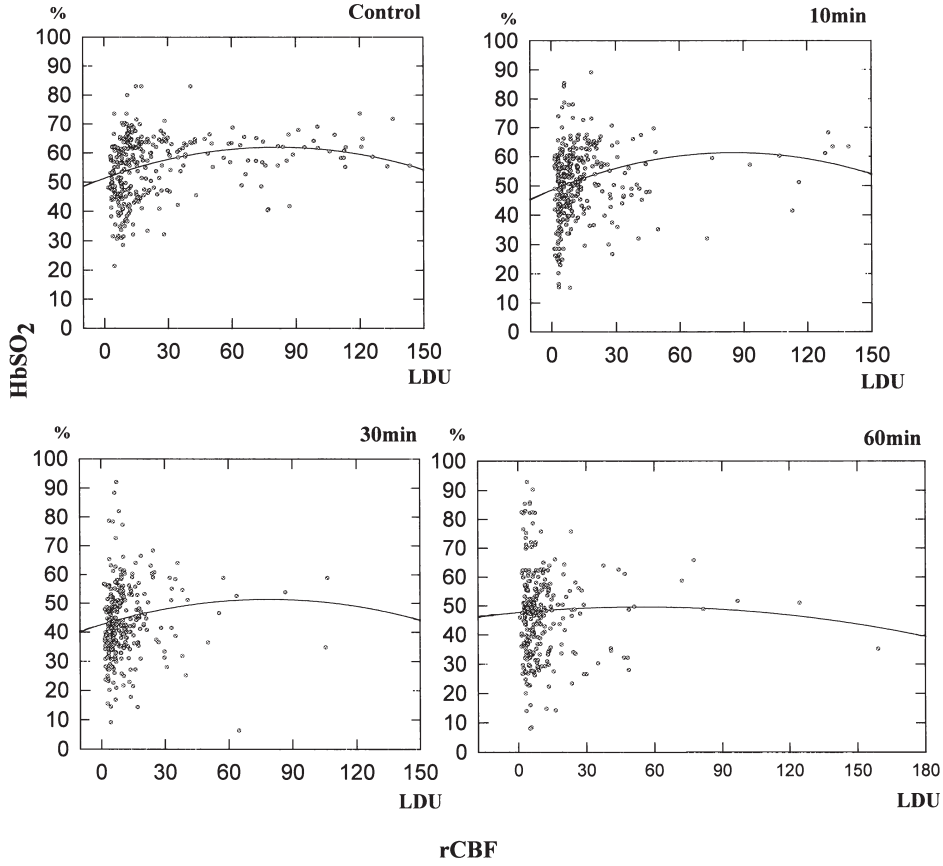

Fig. 6 Graph showing distributions of rCBF and local $HbSO_2$ as measured in identical cortical locations in SPO group. After SSS ligation both rCBF and local $HbSO_2$ have decreased and locations with low rCBF (<40 LDU) and low local $HbSO_2$ ($<30\%$) values increased. Lines indicate single degree polynomial function regression lines.

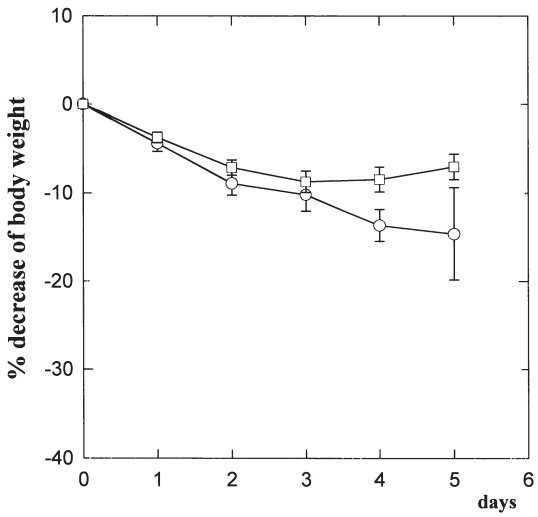

Fig. 7 Graph showing sequential change in percent decreasement of body weight compared with the body weight before and after SSS ligation in SMO group and SPO group. The value are expressed as a percentage of the decreasement of mean body weight (mean $\pm$ SE). Open circle; SMO group, Open square; SPO group Mean body weight of the SMO group decreased initially but began to recover 4 days after operation. In the SPO group mean body weight further decreased throughout the 5 days after operation.

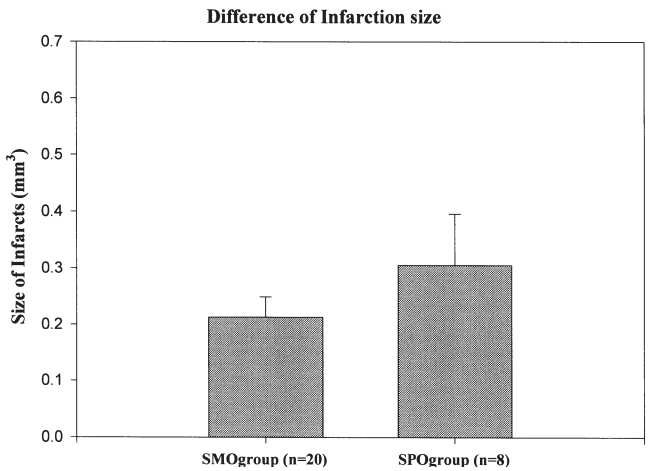

Fig. 8 Bar graph showing total infarct volume in SMO group and SPO group.The values are expressed as mm^3 (mean $\pm$ SE). The total infarct volume of the SPO group was significantly larger than that of the SMO group. ($0.306 \pm 0.090\ mm^3$ versus $0.159 \pm 0.057\ mm^3$, $P<0.05$)

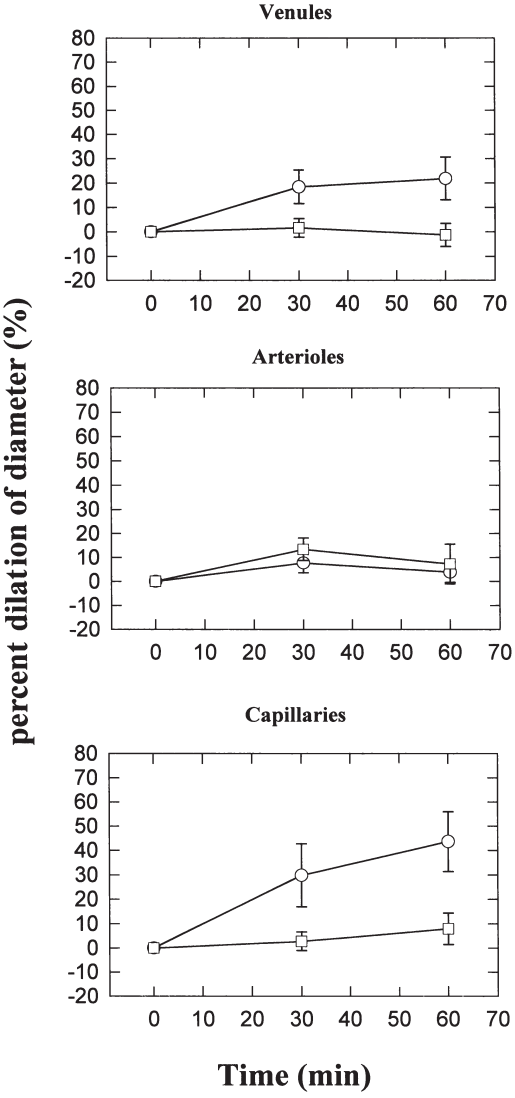

Fig. 9 Graph showing sequential change in percent dilataion of vessels (venule, arteriole, capillary). The values are expressed as percentage of dilation compared with the diameter before and after SSS ligation.The diameters of venules, arterioles and capillaries in the sham group revealed no significant change throughout experiments. In the SVT group baseline diameters of venules, arterioles and capillaries were $89.84 \pm 8.65\,\mu m$, $29.12 \pm 1.97\,\mu m$ and $7.10 \pm 0.66\,\mu m$, respectively. Venules were dilated significantly at 30 and 60 min ($105.39 \pm 10.32\,\mu m$ and $107.73 \pm 10.44\,\mu m$) after induction of SVT ($P < 0.05$ versus baseline). Capillaries also were significantly dilated 60 min after induction of SVT ($9.4 \pm 0.81\,\mu m$) ($P < 0.05$ versus control).

frame (Stoelting). After a 2.0 cm midline skin incision was made, bilateral parietal cranial windows (5×4 mm) were made between the coronal and lamboid sutures with a high-speed drill (Microtron Aesculap) under the operating microscope (OPMI-1-FR, Zeiss). During the drilling, the drill tip was cooled with physiologial saline to avoid thermal injury to the cortex.

The dura was kept intact. Thereafter, the animals were transferred to a stereotaxic frame positioned on a computer-controlled intravital microscope stage. Intravital microscopy was used to study microcirculatory events at five identical locations in each animal. Duration of the observation at each location was limited to 2 min to avoid photothermal injury of the brain cortex. The intravital microscope (Axiotech Vario 100HD,G/180403 Carl Zeiss) furnished with an illumination system (AttoArc, HBO 100W), flourescence filters (510–560 and 450–490 nm) and 3CCD digital camera (STEMMER VS450) was used for fluorescence angiography, which was carried out before, 10, 30 and 60 min after induction of SVT. After control images were taken, SVT was induced. The SSS was ligated just close to the confluence sinuum, using 10-0 monofilament nylon suture with meticulous care to avoid adjacent brain tissue damage. The images were recorded by a time lapse video cassette recorder (HS-S5600E[RS], Mitsubishi) via a 3 CCD digital camera and an image processor (Argus-10 image processor, Hammamatsu).

Recorded video images were evaluated offline with an image analysis system (Cap image, Dr Zeintl Ingenieurburo, Heidelberg). This system consists of three modules, a computer-controlled videorecorder, a frame grabber and software (Cap image version 5.03). 0.02% FITC-Dextran (MW 150.000) and 0.005% Rhodamin-6-G were used for fluorescence angiography (double staining technique). FITC Dextran (MW 150.000) was used for observing the vessel structures, flow alteration and thrombus formation through a fluorescence filter (510–560 nm).[6]

Rhodamine-6-G was used for staining activated leukocytes and platelets. Therefore, leukocyte behaviour was observed through a fluorescence filter (450–490 nm).[7] Fluorescence angiographies were performed before and 30 and 60 min after induction of SVT. Afterwards, using the video analysis system, vessel diameters were measured and numbers of leukocyte rollers and stickers were counted at 30 and 60 min after induction of SVT. Diameters of venules, arterioles and capillaries were measured before, 30 and 60 min after induction of SVT. Venules, arterioles and capillaries were classified by their diameters (venules: 50–120 μm, arterioles: 20–40 μm, capillaries: 5–10 μm) 'stickers' were defined as the activated leukocytes which sticked on the inner wall of vessels longer than 20 s and 'rollers' were defined as those leukocytes which were slowly rolling for more than 50 μm along the inner wall of vessels. Numbers of stickers and rollers were counted at five identical areas before, 30 and 60 min after induction of SVT.

Histological analysis

Five days after operation, gerbils from both experimental series were submitted to perfusion fixation with 4% paraformaldehyde under general anaesthesia with chloral hydrate. The brains were carefully removed from the skull and were prepared for histological evaluation. Sections were stained with haematoxylin and eosin (H & E) and Luxol Fast Blue (LBF). Infarction area was defined as the area with low staining in H & E stain and infarction areas were measured by a computer image analyser. (OK image Ver1.0)

Statistical analysis

Data were expressed as mean S.E. (standard error) of the median lCBF and $HbSO_2$ from the 36 data sets from each gerbils. ANOVA for multiple comparison or the Mann-Whitney rank-sum test was used for between group comparisons. Time sequences were evaluated by ANOVA followed by Dunnett's test for repeated measures.

Statistical significance was accepted at an error probability of $P < 0.05$.

Mongolian gerbils are very sensitive animals and easily influenced by their environment. Even if a gentle care was taken for handling gerbils, some of them showed seizure when environment was changed. These animals were excluded from the experimental study.

RESULTS

SVT model

Arterial blood gases were not measured in this experimental series because Mongolian gerbils are rather small and repeated blood sampling may easily induce hypovolaemia. Mean arterial blood

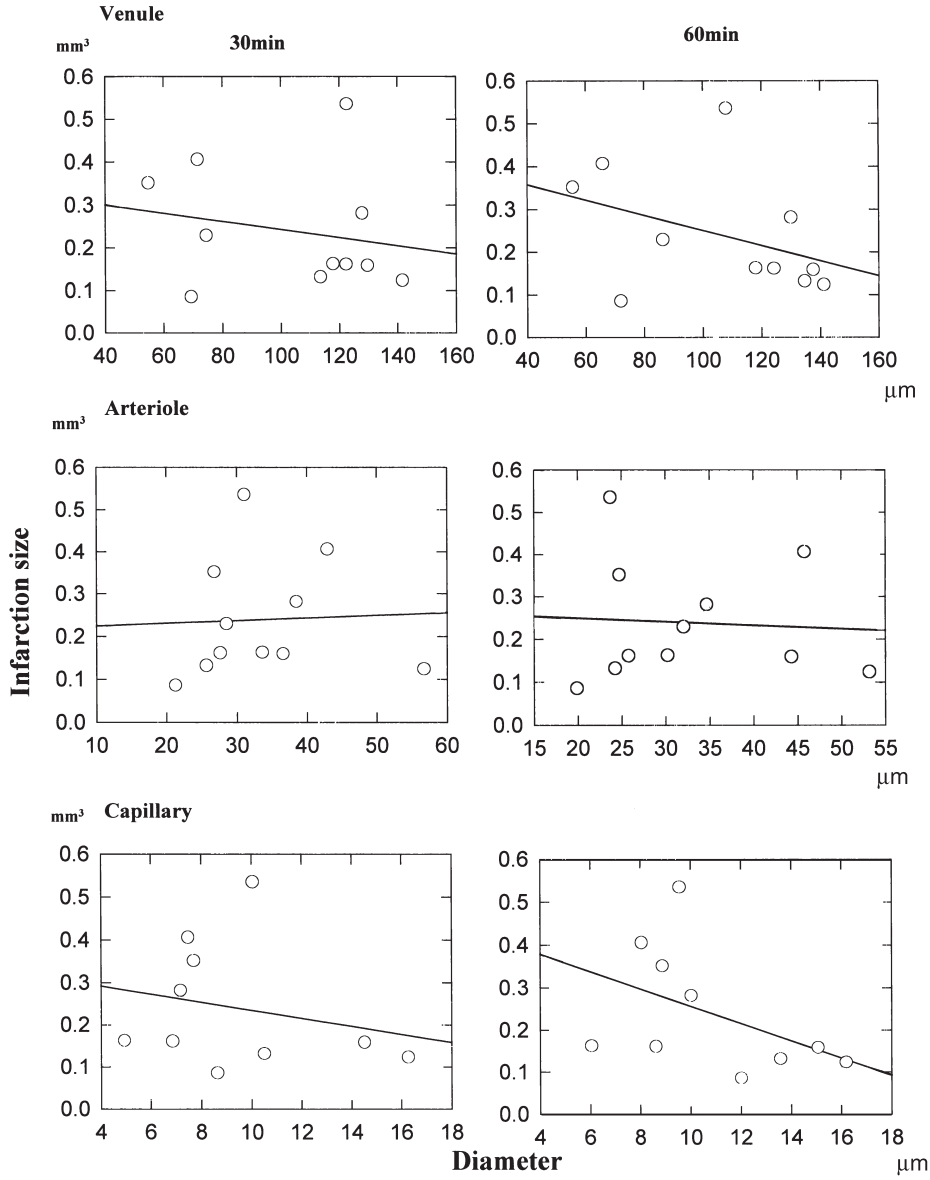

Fig. 10 Graph showing distribution of vessel diameter and total infarct volume in the SVT group. Plotting vessel diameters at the end of acute experimental stage and total infarct volumes after 5 days in the SVT group revealed negative correlations in venules and capillaries.

pressure showed no significant change throughout the experiments in both, the SMO and the SPO group (Fig. 2).

The calculation of median rCBF values from 36 locations in each animal showed no change in the SMO group estimated by ANOVA for repeated measures. In the SPO group, rCBF significantly decreased after the SSS ligation compared with SMO group ($P<0.01$). The baseline rCBF value of the SPO group was 17.1 ± 3.4 LD units. A significant decease of rCBF ($P<0.05$ versus control) started at 30 min after occlusion of SSS until the end of experiment. The rCBF 60 min after occlusion of SSS was 7.8 ± 2.9 LD units (Fig. 3).

The median of the local $HbSO_2$ values from 36 locations in each animal showed no significant change in the SMO group. The control $HbSO_2$ values in SPO group was $57.2\pm3.2\%$, the maximal and highly significant decrease was seen 30 min after occlusion of SSS ($P<0.05$). Thereafter, an incomplete recovery of $HbSO_2$ was seen 60 min ($50.3\pm4.1\%$) after occlusion of SSS, but $HbSO_2$ at 60 min still was significantly below baseline values ($P<0.05$). Compared with data from the SMO group, no significant differences were seen (Fig. 4).

Before occlusion of SSS, there were no differences between the distributions of lCBF and local $HbSO_2$ of the SMO and the SPO group. After occlusion of SSS, the distributions in SMO group did not change, whereas both lCBF and local $HbSO_2$ decreased substantially in the SPO group (Figs 5 and 6).

Mean body weight of the SMO group decreased initially but began to recover 4 days after operation. In the SPO group mean body weight further decreased throughout the 5 days after operation. This suggests that the intensity of ischemic events was seen higher in the SPO than in the SMO group (Fig. 7) .

Five days after operation, histological examination was performed. Macroscopic and histological examination demonstrated that the brains of SMO group appeared small parasagittal infarction without haemorrhage and the cortical veins were not occluded. The thrombus in the SSS was seen just in the front and rear of the ligation site.

In SPO group, large bilateral parasagittal infarction was seen in all gerbils. The SSS was completely occluded in all girbils and the

thrombus was extened to the cortical veins. Petechial haemorrhage around the dilated capillaries was observed in some gerbils.

The total infarct volume of the SPO group was significantly larger than that of the SMO group. ($0.306 \pm 0.090\,mm^3$ versus $0.159 \pm 0.057\,mm^3$, $P < 0.05$) (Fig. 8). There were no correlations in the distributions of total infarction volume and lCBF or $HbSO_2$ measured 60 min after occlusion of SSS in the SMO group. In the SPO group, however, these distributions showed negative correlations, suggesting that animals which showed low lCBF and $HbSO_2$ at 60 min after occlusion of SSS also showed large infarctions.

Microcirculation study

The diameters of venules, arterioles and capillaries in the sham group revealed no significant change throughout experiments. In the SVT group baseline diameters of venules, arterioles and capillaries were $89.84 \pm 8.65\,\mu m$, $29.12 \pm 1.97\,\mu m$ and $7.10 \pm 0.66\,\mu m$, respectively. Venules were dilated significantly at 30 and 60 min ($105.39 \pm 10.32\,\mu m$ and $107.73 \pm 10.44\,\mu m$) after induction of SVT ($P < 0.05$ versus baseline). Capillaries also were significantly dilated 60 min after induction of SVT ($9.4 \pm 0.81\,\mu m$) ($P < 0.05$ versus control) (Fig. 9).

Plotting vessel diameters at the end of the acute experiments and resulting total infarct volumes after 5 days in the SVT group revealed negative correlations for venules and capillaries. This suggests that animals where vessels had a better capacity to dilate had smaller infarct volumes (Fig. 10).

Stickers and rollers were observed with the videorecording system (Fig. 11). The numbers of stickers and rollers and total infarction volume revealed positive correlations suggesting that large numbers of rollers and stickers were followed by large infarct volumes. No histological damage was found in the sham group (Fig. 12).

DISCUSSION

Gerbil SVT model

The pathophysiology of sinus-vein thrombosis (SVT) is still controversial in patients and experimental animals, the microcirculatory alterations in particular. Moreover, the experimental study of the latter is limited by the lack of reproducible SVT models.

Previous reports on SVT models used different animals. Rats, cats, pigs have been studied so far. The method of occluding the superior sagittal sinus also varied, including ligations of sinus, infusions of thrombotic materials into the sinus, or balloon

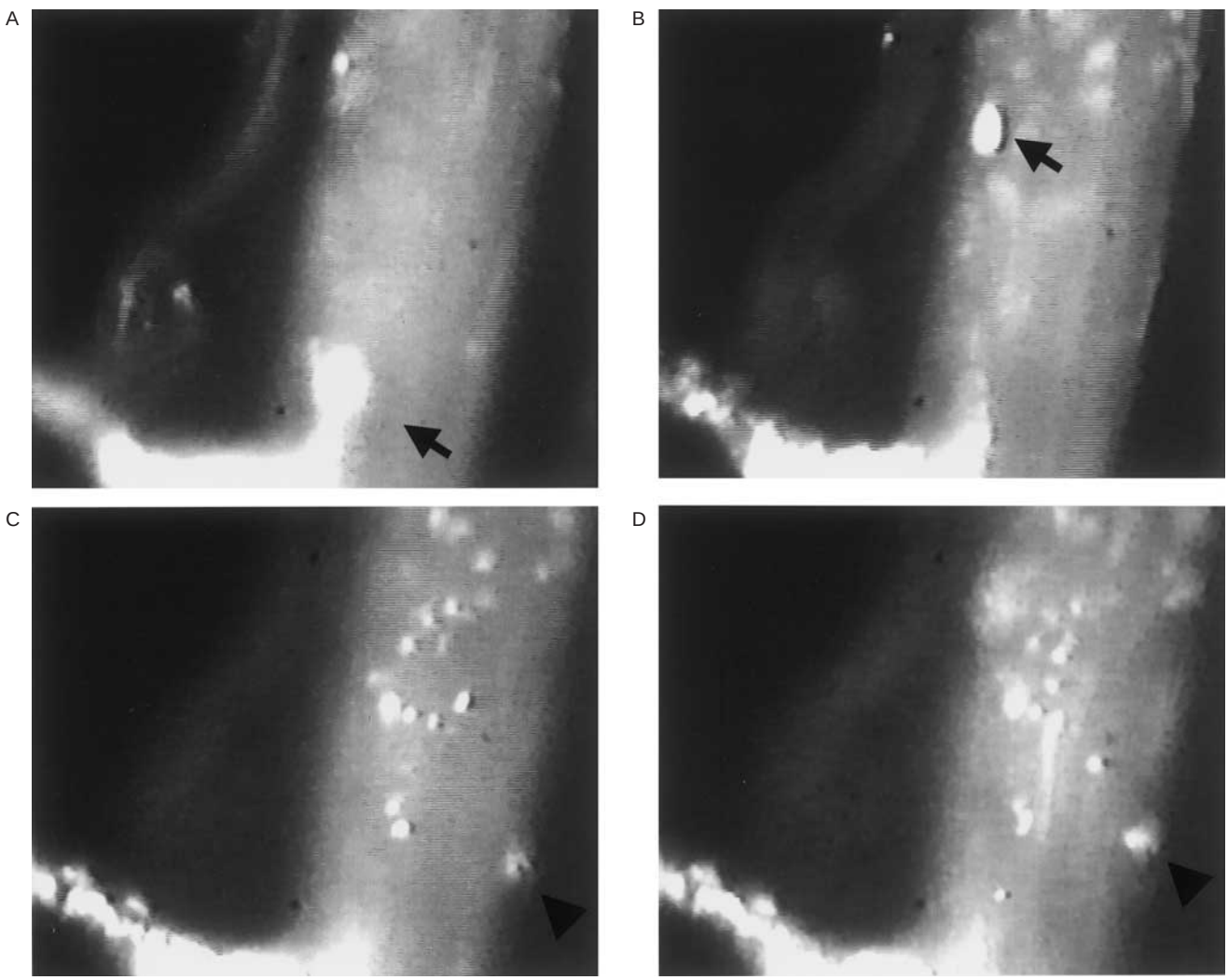

Fig. 11 Video photograms shows stickers and rollers in venule. (A) An activated leukocyte (white arrow) began rolling along inner wall of venule. (B) Rolling over 50 μm along the inner wall of venule. (C) An activated leukocyte (white arrow head) sticked on the venule wall. (D) 20 seconds after sticking.

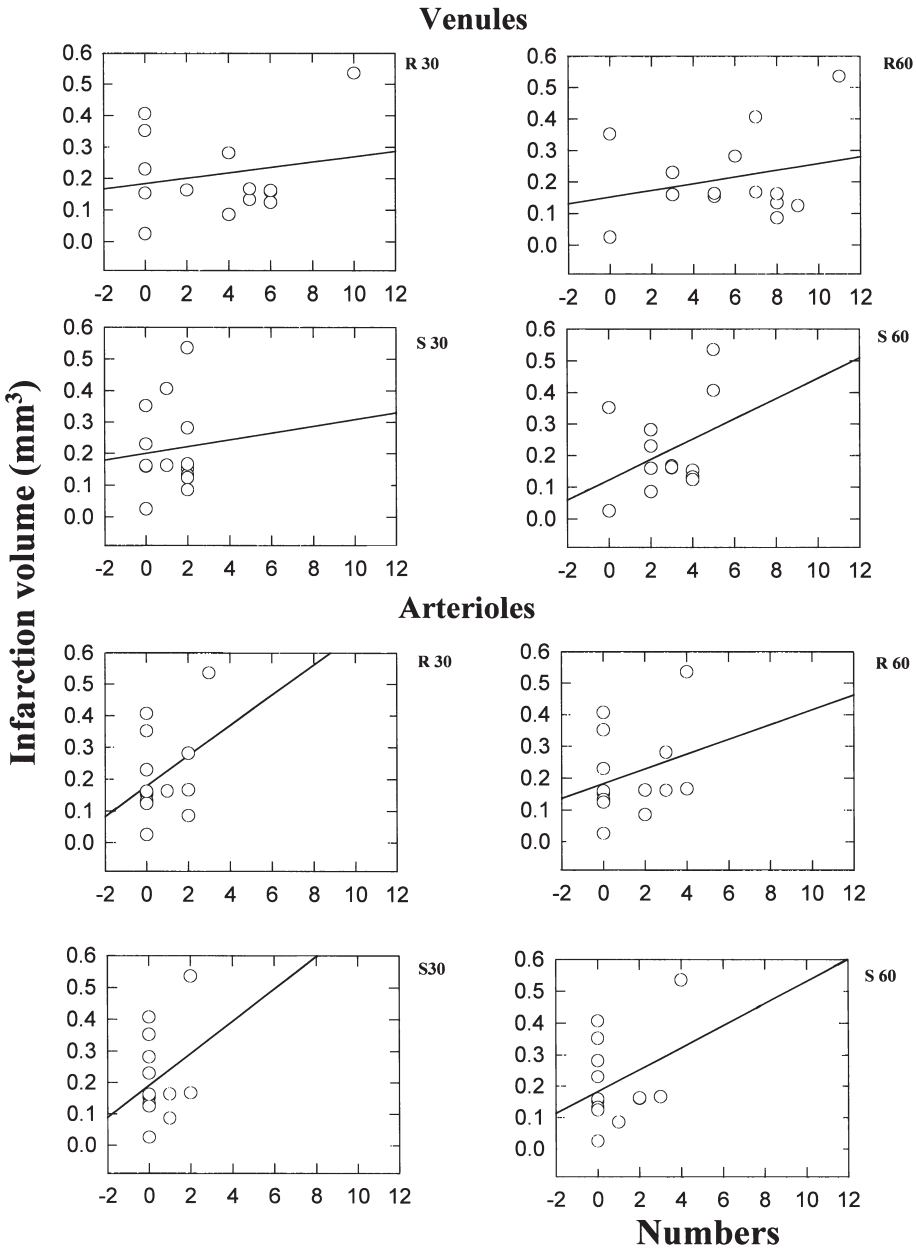

Fig. 12 Graph showing distribution of the numbers of stickers and rollers and total infarct volume in venules and arterioles in 30 and 60 min after SSS ligation. R indicates rollers,S indicates stickers.The distribution revealed positive correlations suggesting that large numbers of rollers and stickers were followed by large infarct volumes.

occlusion of the sinus.[4,5,8–10] In our present experiments, we tried to produce a new and reproducible SVT model that has advantages for studying the microcirculation duing SVT events. Gerbils are paricularly suited since the cerebral microcirculation can be studied without opening the dura, a procedure which can easily disturb the microcirculation in rats and other experimental animals.

The first trial of the present experiments was to evaluate differences of lCBF and local tissue oxygen saturation using scanning technique, by ligating the SSS at different sites. With a medial ligation, lCBF and local tissue oxgen saturation showed variable alterations. It is suggested that there are enough collateral venous pathways to prevent brain tissue damage from SVT events. On the other hand, CBF and oxygen saturation significantly decreased in their median value in SPO group. Nakase et al. reported that local tissue oxygen saturation decrease is detected before decrease of lCBF in a rat SVT model, and, therefore, is a good indicator of ischaemic events duing sinus-vein thrombosis.[4] They concluded that this decrease of tissue haemoglobin oxygen saturation at normal lCBF is due to collateral drainage of desaturated blood. Their rat SVT model was produced with a similar technique as used in our study but included an injection of thombogenic material into the sinus. In our study, however, an initial decrease of local tissue oxygen saturation was not seen, as an indication that infarction evolved as a consequence of a lack of collateral reflux pathways in gerbil brain.

Microcirculation study in the gerbil SVT model

Thorball reported that FITC-Dx 150 provoke an anaphylactic reaction in most rat strain expected for Wistar Fourth rat and Thorball reported significant blood pressure decrease in S-D and Wistar rats 45 min after infusion of FITC-Dx 150.[11] In the first set of experiments in the microcirculatory study, blood pressure was continuously measured during FITC-Dx 150 infusion. Blood

pressure showed no significant decrease during the infusion. This shows that FITC-Dx 150 is well tolerated by Mongolian gerbils.

Mongolian gerbils have a thin, translucent dura mater which permits observation of the microcirculation by light microscopy. This is an anatomical advantage against Wistar rats.[7] Double tracing technique using FITC-Dx 150 and Rhodamine 6G allowed for an easy study of microcirculatory events and with this technique low concentrations of FITC-Dx 150 and Rhodamine 6G are sufficient for observation.

Significant dilatation of venules and capillaries and no significant dilatation of arterioles suggests that venous congestion in SVT occurs at the post-arteriolar level.

The distribution of vessel diameters and total infarction volume in SVT group revealed negative correlations in venules and capillaries. This result suggests that animals with a better capacity of vessels to dilate had a reduced total infarct volume.

Del Zoppo et al. reported that polymorphonuclear leukocytes occlude capillaries following middle cerebral artery occlusion and reperfusion in baboons, and capillary-obstructing polymorphonuclear leukocytes play the key role during early microvascular injury or the 'no-reflow' phenomenon.[12] Hallenbeck et al. reported that isotope labeled leukocytes accumulate in the ischaemic core within 4 h after reperfusion in canine air embolism model.[13] During ischaemia, activation of leukocytes may result in release of chemotaxis factors. During reperfusion, interaction of leukocytes with platelets may result in metabolism of arachidonic acid through lipoxygenase and cyclooxygenase pathway producing prostanoids and oxgen radicals.[12–14] In our experiments, rolling and sticking of leukocytes were observed through rodamine 6G staining microangiography. Capillary and venule obstruction by leukocytes was also observed. And the distributions of numbers of stickers and rollers and total infarction volume revealed positive correlations. Our results – this is the first report concerned with polynuclear leukocyte behaviour in sinus-vein thrombosis – suggest that polymorphonuclear leukocytes indeed play a role in microvascular injury.

In conclusion, brain damage from SVT in the Mongolian gerbil depends on the SSS occlusion site. In contrast to the rat, gerbils do not have enough collateral pathways to prevent tissue damage after caudal sinus occlusion. The newly established Mongolian gerbil sinus-vein thrombosis model has advantages compared to previously reported sinus-vein thrombosis models such as easy handling, easy technique, highly reproduciblity, and good observation of microcirculatory events. The model allows for studies of cerebral low-flow conditions such as expected to occur in an ischaemic penumbra zone.

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