Cerebral Blood Flow Alterations in a Rat Model of Cerebral Sinus Thrombosis

K. Ungersböck, MD; A. Heimann, DVM; and O. Kempski, MD, PhD

Background and Purpose: Outcome from sinus vein thrombosis is very variable, with symptoms from headache to coma. Experimental findings suggest that an involvement of cortical veins is necessary to affect the cerebral microcirculation. Laser Doppler flowmetry was used to investigate the regional and temporal changes in local cortical blood flow after experimental occlusion and thrombosis of the superior sagittal sinus and tributary cortical veins in rats.

Methods: Thrombosis was induced by slow injection of kaolin-cephalin suspension after frontal and caudal ligation of the sagittal sinus in rats. Local cerebral blood flow was measured by laser Doppler flowmetry and correlated with parenchymal damage found 24 hours after induction of thrombosis.

Results: Local cerebral blood flow 1 hour after sinus occlusion and induction of thrombosis had decreased to 60.92±29.05% (p<0.01); however, there was a large variability among individual animals. Only five of 12 rats showed histological damage and intracerebral hemorrhages 24 hours after induction of thrombosis. A subgroup analysis revealed that parenchymal damage occurred in concurrence with reduced blood flow values after sinus ligation and injection of the thrombogenic material. Sinus thrombosis alone, without alteration of blood flow, did not cause tissue necrosis.

Conclusions: The data support the contention that sinus vein thrombosis evolves gradually, with major symptoms occurring only if the thrombus expands from the sinus into bridging and cortical veins. Collateral venous outflow pathways are thereby occluded, and local blood flow may become reduced to and below the ischemic threshold. (Stroke 1993;24:563–570)

Key Words • cerebral blood flow • microcirculation • sinus thrombosis • rats

The history, clinical symptoms, and prognosis of cerebral sinus vein thrombosis (SVT) are known to be quite variable.1-3 Reports in the literature suggest that the clinical course of SVT may be less dangerous than generally believed. Also, the diagnosis might be established more often if taken into consideration.1,4 On the computed tomographic scan, suspicious findings such as the empty delta sign may assist the diagnosis,1,7 which, to be confirmed, requires cerebral angiography and possibly magnetic resonance angiography in the future.8 In addition to these diagnostic problems, there is very limited understanding of the pathophysiology of SVT and of the alterations taking place in the cerebral circulation in particular. To our knowledge there are only two clinical investigations in which cerebral blood flow (CBF) was actually measured. Shinohara et al6 examined three patients with SVT and found a slight decrease of regional CBF (rCBF) under resting conditions, a normal response during hyperventilation, but no increase after CO2 stimulation. Schmiedek et al6 studied 10 SVT patients with serial rCBF measurements using the xenon-133 inhalation technique. The authors performed the initial examination during the first week after admission and

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follow-up studies within 6 months. rCBF in the acute stage of SVT revealed subnormal values. In contrast to Shinohara’s findings, acetazolamide increased the flow in all patients to normal or slightly subnormal values. Taken together, these reports demonstrate that rCBF alterations after SVT are less severe than in arterial disease. Both hemispheres are affected, and cerebral reserve capacity may be partially preserved. In all cases these clinical observations were made with a considerable delay after SVT.

The purpose of the current experiments was to elucidate the pathophysiology of the cortical microcirculation during the early onset of SVT using laser Doppler flowmetry (LDF). Regional as well as time-dependent alterations of the local CBF (LCBF) were studied in a rat model of SVT first described by Deckert et al.10 LDF provides noninvasive, continuous information on the microcirculatory blood flow with a sample volume of 1–2 µL, i.e., with a rather high spatial resolution. The present study made use of the advantages of LDF with 1) the high temporal resolution offered by LDF when used continuously at one stationary cortical location and 2) the gain of additional information on regional cortical flow heterogeneities by moving the probe at the beginning and the end of the experiment to many locations with a micromanipulator. This “scanning” procedure allows one to establish frequency histograms of LCBF values and, by returning to identical points of

From the Department of Neurosurgery (K.U.) and the Institute for Neurosurgical Pathophysiology (A.H., O.K.), Mainz University School of Medicine, Mainz, FRG.

Address for correspondence: Prof. Dr. O. Kempski, Institut für Neurochirurgische Pathophysiologie, Johannes Gutenberg-University Mainz, Langenbeckstrasse 1, W-6500 Mainz, Germany.

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measurement, to detect even subtle flow changes over a larger area of the cortex.

**Materials and Methods**

Male Wistar rats (250–350 g) were premedicated intraperitoneally with 0.5 mg atropine. Anesthesia was introduced with ether and continued by injection of chloral hydrate (36 mg/100 g body wt i.p.). Spontaneous ventilation was maintained. Body temperature was monitored by a rectal probe and maintained at 37°C with a feedback-controlled heating pad. Blood pressure in the tail artery was continuously monitored with an intra-arterial catheter connected to a pressure transducer. The head was fixed in a stereotaxic frame (Stoelt-Ing Co., Wood Dale, Ill.). After a 1.5-cm midline skin incision a longitudinal cranial window (9 mm×1.5 mm) was drilled between the coronal and lambdoid sutures. The drill tip was cooled continuously with saline to avoid thermal injury to the cortex. The superior sagittal sinus (SSS) and bilateral parasagittal cortex were exposed, and extreme care was taken to keep the dura intact. All surgery was performed under an operating microscope (Zeiss, FRG). Using a micromanipulator, a 0.8-mm laser Doppler needle probe was positioned over the parietal dura, and the cranial window was filled with warm saline. After stable conditions had been achieved, LCBF was measured at multiple locations in a scanning procedure by means of the micromanipulator. Special attention was paid to avoid movement artifacts: each measurement was started only after 10 seconds in an absolutely stable position. After scanning, the probe was located in the middle section of the left parasagittal cortex for continuous monitoring. After 20 minutes the SSS was ligated with a 9.0 suture, first in the rostral and then in the dorsal part. After 30 minutes the sinus was punctured with a 27-gauge needle just in front of the dorsal ligation. A kaolin-cephalin suspension (100 μL; a partial thromboplastin time reagent; Boehringer Mannheim, FRG) was injected into the sinus over 5 minutes: to do so, 10 μL was slowly injected every 30 seconds. One hour later the needle was withdrawn. The continuous CBF monitoring was discontinued, and the multipoint scanning was repeated at identical coordinates. Thereafter the skin wounds were closed, and the animal was allowed to recover from anesthesia. After 24 hours the rat was killed and submitted to perfusion fixation.

**Results**

After injection of kaolin-cephalin suspension, thrombosis of the SSS could be detected through the operating microscope as a grayish black discoloration of the sinus. In eight of 12 rats thrombosis appeared complete, and after retraction of the injection cannula from the sinus there was no bleeding. In three rats thrombosis was incomplete, with minor bleeding after removal of the cannula, which was immediately stopped by hemostatic material. The sinus appeared completely unaffected in only one animal. In this case the venous hemorrhage from the puncture site could only be stopped by tamponage.

Mean arterial pressure (MAP) as measured via the tail artery was 79.25±5.61 mm Hg before ligation of the sinus. Within the first 5 minutes after ligation the pressure slightly increased to 86.69±9.55 mm Hg but returned to the control level within 10 minutes. During the fractionated injection of kaolin-cephalin suspension there was a short-lasting pressure drop, which was most pronounced after 3 minutes, when MAP reached 58.42±8.61 mm Hg. Pressure normalized again after 10 minutes. At the end of the experiments MAP was 81.33±11.06 mm Hg. MAP in the control group was 75.33±5.5 mm Hg at the beginning and 77.60±7.74 mm Hg at the end of the experiments.

The continuous measurement of LCBF by LDF demonstrated a rapid drop of LCBF after ligation of the sinus (Figure 1, insert). A new plateau was reached 10 minutes after sinus ligation with 68.23±33.31% of the control value (p<0.05 versus sham-operated controls). After the injection of kaolin-cephalin there was a further decrease of LCBF to 58.96±30.82% after 10 minutes and 49.89±22.51% after 30 minutes. Thereafter, LCBF increased again gradually and was 60.92±29.05% at the end of the experiments. In the control group LCBF decreased slightly during the whole observation period and was 90.15±18.79% at the end of the experiments (Figure 1, insert). Red cell velocity changed in parallel to the LCBF alterations, whereas volume fraction was stable during the whole experiment in the sham-operated as well as in the experimental group.

A more detailed analysis of the individual LCBF curves, however, proves that the calculation of mean values in this case is quite misleading. There was a tremendous variability among individual animals (Figure 1), which explains the high standard deviations of the LCBF values. LCBF decreased rapidly after sinus ligation in only six rats and recovered slightly in two rats thereafter. In the remaining six rats there was only a small LCBF decrease after sinus ligation, with a further decrease after the injection of kaolin-cephalin. In five animals from this subgroup LCBF showed a tendency to...
recover within 60 minutes, whereas there was a further decrease in one rat. At the end of the observation period LCBF varied between 28.82% and 110.78%, suggesting that SVT led to a rather heterogeneous disturbance of the cortical microcirculation. This inhomogeneity was reflected in the outcome, i.e., parenchymal damage.

The brains of all animals were examined for histological damage 24 hours after induction of SSS thrombosis or sham operation. In the latter group a small unilateral lesion was found in only one animal in the parietodorsal cortex, probably inflicted during fixation and removal of the brain. In all other sham-operated animals pathological alterations were not observed.

In the experimental group, on the other hand, signs of histological damage were present. Thrombotic material was always found within the sinus. Five of 12 rats exhibited parenchymal damage such as subarachnoid bleeding, local parenchymal hemorrhage, and circumscribed areas with necrotic nerve cells in the cortex, typically located in the parasagittal area, with large vacuoles from swollen cells. The remaining seven rats from the experimental group showed no or only minor histological changes and showed dilated veins.

Taken together, the effects of SSS thrombosis were not very dramatic, with the spontaneous formation of two subgroups, one in which damage was absent (group A) and another with discrete signs of neurological damage (group B). The observation of the spontaneous formation of two subgroups with and without histological damage allowed us to retrospectively test whether blood pressure and microcirculation were different for the two groups and whether these parameters are linked to outcome from SSS thrombosis.

Blood pressure on sinus ligation showed a significant rise in group A rats without histological damage, a reaction absent in group B rats. The injection of kaolin-cephalin solution caused a pressure drop in both subgroups, which, however, was statistically significant only in group B rats. Group A rats had a somewhat higher blood pressure during the entire experiment than group B rats (Figure 2).

Mean LCBF in group A rats decreased only slightly after sinus ligation as well as after injection of kaolin-cephalin suspension (Figure 3). The reduction was 22.8% after 3 minutes and 24.8% 25 minutes after sinus occlusion; after induction of thrombosis flow was somewhat more depressed to 60.9% of control after 3 min-
utes, 76.9% after 10 minutes, and 78.74% after 1 hour (i.e., 90 minutes after sinus occlusion). In group B rats, on the other hand, the sinus occlusion–induced LCBF decrease was considerable, and it was even more pronounced after induction of thrombosis (Figure 3). Ligation of the sinus caused a drop of LCBF of 47.6% after 3 minutes and of 48.8% after 25 minutes. The additional injection of kaolin-cephalin suspension led to a further reduction of LCBF to 41.4% after 3 minutes, 30.05% after 10 minutes, and 34.7% after 1 hour. The minimum was 25.9% after 20 minutes. The difference between both groups was statistically significant (Figure 3). The correlation of outcome and LCBF is particularly evident if the CBF recordings from individual rats in Figure 1 are studied in detail. Clearly, group A rats (Figure 1, left panel) exhibit LCBF values above 28 arbitrary units with a tendency to increase, whereas group B rats (Figure 1, right panel) all have low CBF values below 22 arbitrary units.

Red cell velocity showed a pattern similar to that of LCBF, with a pronounced decrease in group B rats after sinus occlusion, which also was statistically significant compared with group A. The reduction of red cell velocity after injection of kaolin-cephalin suspension did not last long in group A, whereas it did not recover at all in group B (Figure 4).

Volume fraction was generally lower in group B than in group A rats (0.364±0.026 arbitrary units versus 0.419±0.008 arbitrary units; Figure 5). A statistical analysis, however, did not reveal significant differences between the groups, except for a short-lasting 7% reduction of volume fraction immediately after sinus ligation in group B. The similar 9–12% reduction after induction of thrombosis was not significant. At the end of the experiment, volume fraction was normal in both groups.

The regional scanning of the cortical microcirculation over the parasagittal cortex revealed flow values to scatter over a wide range in individual animals as well as in the total population, from an observed minimum of 12 arbitrary units to a maximum of 220 arbitrary units. The data obtained are dependent on the position of the laser Doppler probe. Lateral dislocations of the probe position by only 0.2 mm, corresponding to one fourth of the probe diameter, may falsely reflect severe flow changes. The calculation of the flow values in a frequency histogram results in an asymmetric distribution with two maxima, one at 40–70 arbitrary units and one at 90–120 arbitrary units.

The rCBF scanning 90 minutes after SSS ligation and after thrombosis demonstrated a shift of the maxima in the histogram to the left, i.e., toward lower values. Only the regions with a control flow greater than 120 arbitrary units were unaffected (data not shown). Since the second scan at the end of the experiments was performed over the same locations as that at the beginning of each experiment, it was possible to calculate the LCBF change for each point. When a frequency histogram was calculated for these changes, it became evident that in the sham-operated rats, the mean change was negligible at only 5.85±2.53% (mean±SEM). The frequency histogram (Figure 6a) assumes a Gaussian distribution, in which the standard deviation incorporates errors due to misplacement of the Doppler probe.
as well as random changes of CBF. In group B rats, a dramatic shift of the distribution to the left was found with a mean reduction of LCBF of $-41.82 \pm 3.64\%$ (Figure 6c). In group A rats, the flow reduction of $-5.5 \pm 3.19\%$ was far less impressive and hemodynamically insignificant (Figure 6b).

**Discussion**

Only every second patient suffering from SVT develops severe clinical symptoms such as brain edema, elevated intracranial pressure, intracerebral hemorrhage, or cerebral infarction, whereas the remaining 50% of patients present with surprisingly mild complaints, with headache, dizziness, or visual complications only.\(^1\) This wide variability of the clinical course has long been unexplained. Recent experimental findings,\(^{10,16-18}\) however, suggest that it is the progression of the thrombosis from the sinus to the bridging and cortical veins with the complete obstruction of venous collaterals that initiates a fatal outcome. Data derived from a pig model of sinus occlusion\(^{13,18}\) supported the contention that thrombosis of the sinus alone is not sufficient to cause cerebral hypoperfusion; clearly, an additional occlusion of bridging veins and tributary cortical veins was necessary to prevent venous outflow via collaterals and to induce parenchymal damage.

Although the evidence for such a stepwise evolution of the pathophysiology of SVT is quite strong, so far there are few experimental data correlating blood flow and outcome. Sato et al,\(^9\) after clipping of the SSS in dogs, found a decrease in rCBF in the gray matter with hyperemia of the subcortical substance. Fujita et al,\(^20\) also using the hydrogen clearance technique, reported the absence of rCBF changes when cortical veins were not involved and a reduction down to 30% when cortical veins were affected.

The current study made use of the LDF technique to evaluate the effects of SVT on the cortical microcirculation in a rat model of SVT. The model\(^19\) was chosen because it has a variability of outcome high enough to allow for a correlation with CBF changes: similar to human disease, about half the rats injected with kaolin-cephalin suspension after sinus ligation develop histological defects. This is an advantage over other animal models of SVT that are also based on ligation or clipping of the sinus, injection of glue, or polymerization of synthetic material. Most of these models either do not produce histological changes at all or have dramatic all-or-nothing effects with increases of intracranial pressure and intracerebral hemorrhages. Thus, in the previously used pig model,\(^17,18\) the occlusion of the sinus by a balloon did not produce parenchymal damage, edema, or an elevated intracranial pressure, whereas the additional injection of fibrin glue led to a drastic reduction of the cerebral perfusion pressure associated with edema and intracerebral bleeding.\(^18\) Similarly, Kannuki et al\(^21\) in a cat model of SVT using the injection of cyanoacrylate/iophendilate found no histological changes in 14 animals with only a partial block of venous outflow, whereas in eight completely occluded animals they found focal ischemic neuronal changes and intracerebral hematomas.

The use of kaolin-cephalin suspension (a reagent available for the partial thromboplastin time reaction) has the advantage that sinus and veins are not just mechanically occluded but a true thrombotic process is initiated, which may or may not expand into bridging and cortical veins. This accounts for the realistic variability of the model as a prerequisite for correlations with cortical blood flow.
LDF was chosen because it offers discrete advantages for studies of changes of the LCBF. LDF yields not only measures of LCBF but also of the volume fraction occupied by moving particles, i.e., red cells, as well as their velocity. Actually flow is calculated from these two variables. LDF may be used continuously and noninvasively; in rats even the translucent dura may be kept intact. The technique has an excellent spatial resolution, which is an advantage if, in an analogy to tissue Po2 measurements, LCBF can be measured in many locations to reflect the blood flow distribution on the cortical surface. A disadvantage is the fact that an absolute calibration of LDF is still impossible, although LDF of the cortical microcirculation has been correlated with the hydrogen clearance and the microsphere techniques. These studies could demonstrate a good correlation with relative CBF changes. However, data still have to be expressed in arbitrary units, since absolute flow values did not correlate very well. With the current experience it is proposed that this lack of correlation with absolute values is due to the differing sampling volumes of the methods compared: LDF has such a good spatial resolution that even a lateral dislocation of the Doppler probe of 0.2 mm may result in a doubling of flow recordings. This, on the other hand, is not surprising, if one recalls the high variability of vessels and vessel diameters found on the cortical surface. As a consequence, extreme readings may point to pathophysiological events, or, just as probable, to a placement of the laser probe at an anatomical site with extreme flow conditions. In the present study an attempt was made to overcome this drawback by introducing a scanning technique to establish a frequency histogram of blood flow values over a given cortical surface area. By probing many locations, the technique more realistically reflects regional flow, but with a loss of temporal resolution. The combination of both methods (local and regional LDF) is helpful in excluding erroneous data resulting from involuntary movements of the Doppler probe or from misplacement over large vessels, and it provides valuable additional information on the spatial dimensions of focal inhomogeneities of blood flow.

Changes in the microcirculatory parameters of flow, volume fraction, and velocity after sinus occlusion and injection of thrombogenic material show that in venous obstruction, disturbances of the microcirculation may occur with very individual kinetics and severity. The flow drop often found (Figures 1 and 3) results from a reduction in red cell velocity (Figure 4), probably due to the increase of venous outflow resistance. Interestingly, no major change of the volume fraction was seen (Figure 5) during the observation time. Volume fraction is a measure of moving versus nonmoving, fixed structures under the Doppler probe and hence depends on the density and diameter of perfused vessels and on microhematocrit. The only significant difference between groups A and B occurred immediately after sinus ligation, when volume fraction briefly decreased in group B (with histological damage) but increased in group A. This phenomenon might be explained by a short but complete stasis in certain sections of the microcirculation within the sampling volume before venous outflow normalized via collaterals in group B. Stasis would reduce the density of perfused vessels and cause volume fraction to decrease. A similar but statistically not significant reduction of volume fraction was observed with a 10-minute delay after injection of the thrombogenic material in group B, and this reduction might indicate the thrombotic occlusion of parts of the microcirculatory bed.

The individual variability of microcirculatory disturbances correlates well with the histological findings (Figure 1). The present results as well as observations reported by other groups point to the fact that SVT leads to a limited restriction of the cerebral perfusion that, in many cases, remains above the ischemic threshold. In this respect SVT has features reminiscent of the ischemic penumbra, where blood flow remains just above the ischemic level and function is temporarily lost. Blood supply is just sufficient to support neuronal survival. Any further disturbance, such as a short drop of the cerebral perfusion pressure, may have dramatic consequences. Arterial blood pressure, the determinant of perfusion pressure, was also a critical parameter for outcome from SVT in the current experiments. Those animals that did not develop tissue necrosis later showed an increase in arterial blood pressure on sinus occlusion and had a less impressive reduction of flow and red cell velocity than animals with a worse outcome. Moreover, the regularly observed pressure drop after injection of the thrombogenic material was statistically significant only in the group of animals that had subsequent tissue damage.

Apart from the differences in arterial blood pressure, the changes of LCBF after sinus occlusion may explain why certain animals develop parenchymal damage. In these rats, the ligation of the sinus alone reduced LCBF significantly more than in group A rats (Figures 1 and 3). As mentioned previously, the brief reduction of volume fraction in group B might be taken as an indication of temporary stasis occurring in parts of the microcirculation. The major difference between groups A and B, therefore, could be a better collateralization of venous outflow in those animals that did not develop parenchymal damage. In group B, the already impaired flow conditions should have facilitated the growth of the thrombus into cortical veins after the injection of thrombogenic material. The data illustrate nicely that it is the co-occurrence of risk factors, in this case reduction of flow and presence of thrombogenic material, that is necessary to cause SVT.

The results of the present study again demonstrate that a thrombus within the venous system of the brain becomes critical for the parenchymal blood supply only if bridging and cortical veins are involved. Occlusion of the SSS is not sufficient to block venous outflow. This is emphasized by the observation that all but one rat developed a macroscopically visible thrombus within the sinus after ligation and injection of kaolin-cephalin suspension, but only five of the 12 rats showed histological damage. A thrombus was actually found in all those histological specimens, where the sinus was successfully embedded together with the brain. Most important, parenchymal damage occurred only in animals in which local cortical blood flow was significantly affected by the thrombus. This is best seen when the regional CBF scans for subgroups A and B are compared (Figures 1 and 3).
Similar observations have now been made in pigs, rats (the present study), and dogs and suggest that in man SVT also evolves in a stepwise manner. Initially, a floating thrombus occludes the SSS incompletely without major symptoms. In progression, the sinus is completely occluded, causing major hemodynamic changes with the opening of venous collaterals and occurrence of retrograde flow in bridging veins. At this point, hypoperfusion still may be lacking. Involvement of bridging veins still permits venous outflow via collaterals. Only the additional occlusion of tributary veins leads to a significant disturbance of the microcirculation, with local ischemic foci developing together with petechial bleedings and disruptions of the blood–brain barrier. To which degree SVT progresses in a patient depends not only on the individual venous anatomy but on the simultaneous presence of risk factors favoring the growth of a thrombus, such as lesions or inflammations of the vessel wall, elevated hematocrit, or high estrogen levels.

In conclusion, the present results support the contention that the cause of neurological deficits after SVT is a malperfusion of those cerebral tissues where draining cortical veins are occluded. An occlusion of the sinus alone is not sufficient to reduce LCBF to critical levels. Even if cortical veins are affected, the tissue hypoperfusion does not necessarily reach the ischemic threshold, which explains the often observed remission of severe neurological deficits after SVT. Therefore, outcome is determined by the efficacy of the microcirculatory bed to communicate with collateral outflow pathways and will benefit from measures to eliminate additional risk factors. In addition to heparinization and attempts to lyse the thrombus, treatment to improve the cerebral microcirculation might be considered during the therapy of patients with SVT.

References

Editorial Comment

This article uses a new, interesting model of sagittal sinus thrombosis, exhibiting a dichotomy in histopathological findings that correlated well with changes in local cerebral blood flow. As such it may mimic the human situation in which clinical symptoms range from some headache to death. However, a puzzling problem still remains: the animals with histopathological damage had the largest decrease in blood pressure right after the...
injection of kaolin. First, what is the cause for this hypotension? Second, is the larger blood pressure drop a consequence of a more severe injury, or is it conversely the cause of stasis so that the clot can expand into the tributaries to the sagittal sinus and then does more secondary damage? It would be interesting to try to answer these questions, even though the drop in blood pressure probably does not occur in the human situation, in which sinus thrombosis occurs more gradually. We agree with the authors that the use of the laser Doppler frequency histogram improves the reliability of the temporal resolution. One wonders if a good correlation of absolute flow values with other methods may be obtained by using the average of the many values obtained in this way.

J. Paul Muizelaar, MD, PhD, Guest Editor
Department of Neurosurgery
Medical College of Virginia
Richmond, Va.
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K Ungersböck, A Heimann and O Kemspki

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