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Occlusion of the pig superior sagittal sinus, bridging and cortical veins: multistep evolution of sinus-vein thrombosis

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✓ Cerebral sinus-vein thrombosis may lead to severe hemodynamic changes, elevated intracranial pressure (ICP), and brain edema. It is supposed that progression of the thrombus from the sinus into bridging and cortical veins plays a key role in the development of these pathophysiological changes, but this hypothesis lacks experimental proof. The aim of this study, using a novel animal model of sinus-vein thrombosis, was to evaluate the effects of a standardized occlusion of the superior sagittal sinus and its bridging and cortical veins on hemodynamic alterations, on brain water content, and on ICP in domestic pigs.

In 10 animals, the middle third of the superior sagittal sinus was occluded with a catheter-guided balloon. Five of these pigs received an additional injection of 1 ml fibrin glue into the superior sagittal sinus anterior to the inflated balloon, leading to an obstruction of bridging and cortical veins. In five control animals the balloon was inserted but not inflated. Five pigs underwent cerebral angiography. Four hours after occlusion, the brains were frozen in liquid nitrogen, and coronal slices were examined for Evans blue dye extravasation, regional water content, and histological changes.

Occlusion of the superior sagittal sinus alone did not affect ICP or cerebral perfusion pressure (CPP). The additional injection of fibrin glue caused an obstruction of cortical and bridging veins as well as severe increases in mean (± standard deviation) ICP to 49.4 ± 14.3 mm Hg, compared with 8.3 ± 4.5 mm Hg in sham-treated controls and 7.1 ± 3.9 mm Hg in animals with occlusion of the superior sagittal sinus alone. There was also a steep fall in the mean CPP to 34.2 ± 19.6 mm Hg compared with 96.4 ± 13.8 mm Hg in the control group.

White-matter water content anterior to the occlusion site was elevated to 81.9 ± 3.7 gm/100 gm frozen weight in the fibrin group as compared to 70.7 ± 2.2 gm/100 gm in controls. Posterior to the occlusion site, water content did not differ among the three groups. Angiography demonstrated collateral flow via cortical and bridging veins in animals with occlusion of the superior sagittal sinus alone. Additional fibrin glue obstructed these collateral vessels.

The data suggest a multistep process of pathophysiological alterations in patients with sinus-vein thrombosis and may explain why these patients present with a wide variety of symptoms: minor neurological deficits or headache might indicate thrombosis of the superior sagittal sinus and/or its bridging veins. In subjects with severe symptoms, coma, and increased ICP there may be an additional involvement of tributary cortical veins. The proposed multistep process offers the rationale for heparin treatment of sinus-vein thrombosis even in patients with minor symptoms.

KEY WORDS • **superior sagittal sinus** • **sinus thrombosis** • **edema** • **cerebral perfusion pressure** • **intracranial pressure** • **angiography** • **pig**

BRAIN edema, cerebral infarction, elevated intracranial pressure (ICP), or intracerebral hemorrhage is found in 50% of patients suffering from sinus-vein thrombosis.[3,6,20] The remaining 50% develop only mild symptoms such as headache, dizziness, and visual disorders. The pathophysiological mechanisms responsible for this high variability of symptoms remain unclear so far.

Over the last years, various animal models of sinus-vein thrombosis[2,8,12,14,17,22] have been designed using ligation, coagulation, and/or injection of obstructing or thrombogenic material such as isobutyl-2-cyanoacry-

late, iophendylate, scandium chloride, kaolin-cephalin, or thrombin into the superior sagittal sinus and adjacent bridging veins. Taken together, the results of these studies suggest that the progression of the thrombosis from the superior sagittal sinus to bridging veins and cortical veins may initiate deleterious pathomechanisms which in turn play a crucial role for the clinical course of patients with sinus-vein thrombosis.[3,5,7,9]

Most of the animal models for sinus-vein thrombosis currently available, using either rats, cats, or dogs, are afflicted with methodological problems preventing reproducible results. The anatomy of the superior sagittal sinus of cats and dogs is rather inconstant, with trabeculae and parasinuses in many cases. On the other hand, the anatomy of the superior sagittal sinus in rats appears to be constant[17] but is very tiny, with the consequence that minor manipulations may have extreme effects on intracranial compartments.

Recent clinical data[7] indicate that the time course for growth of the thrombus may last from a few hours to many months, leading to the well-known wide variety of symptoms of sinus-vein thrombosis. In spite of this clinical observation, it is not yet clear how far the growing thrombus must progress within the sinus and its tributaries to cause alterations in cerebral blood flow (CBF), cerebral infarction, brain edema, and elevated ICP.[7,9]

The aim of this study, using a novel animal model for sinus-vein thrombosis, was to evaluate the effects of a standardized occlusion of the superior sagittal sinus alone and together with an obstruction of tributary bridging and cortical veins on cerebral circulation, brain water content, and ICP.

Materials and Methods

Ethical Considerations

All experiments were conducted according to the ethical standards of the United States Public Health Service, and were granted permission by the Bezirksregierung Rheinhessen-Pfalz, Neustadt, Federal Republic of Germany (District Government, Permit No. 177-07/901-22).

Anesthesia

Twenty domestic pigs of either sex, each weighing 25 to 27 kg, were orally intubated under short-time sedation with intramuscular azaparone (1.2 ml/kg). They were then anesthetized intravenously with piritramide (1.2 mg/kg/hr) and pancuronium bromide (0.4 mg/kg/hr), ventilated with a 60% N_2O mixture, and maintained under controlled respiration throughout the experiment. Arterial pO_2 was 95 to 100 mm Hg and pCO_2 was 35 to 45 mm Hg; these pressures were checked by blood gas analysis initially every 15 minutes and later at hourly intervals.

Surgical Preparation

Catheters for monitoring the arterial and central venous blood pressure were inserted through the left femoral vessels. The animals were fixed in a stereotactic frame in the prone position and the anterior third of the superior sagittal sinus was exposed via a small longitudinal craniotomy (5 × 10 mm). Thereafter, a catheter-guided cylindrical balloon with a length of 25 mm and a diameter of 5 mm was inserted and positioned in the middle third of the superior sagittal sinus. Superior sagittal sinus pressure posterior to the occlusion site was continuously monitored by the distal tip of this double-barreled balloon catheter.

A Teflon catheter (0.7 mm outside diameter) inserted into the anterior third of the superior sagittal sinus was used to inject fibrin glue in one experimental animal group or to measure superior sagittal sinus pressure anterior to the occlusion site. A ventricular catheter and a fiberoptic pressure transducer* were inserted through bilateral frontoparietal burr holes to measure intraventricular pressure and cerebral tissue pressure.

Experimental Groups

In 15 animals, a 90-minute control period preceded the experimental phase to establish control values for all pressures recorded. Thereafter, individual animals were assigned to one of the following experimental groups: 1) Group SO, in which the superior sagittal sinus was occluded by inflation of the balloon (five pigs); 2) Group SO+F, in which animals received, 15 minutes after superior sagittal sinus balloon occlusion, an injection of 1 ml fibrin glue anterior to the inflated balloon in order to obstruct frontal bridging and cortical veins (five pigs); and 3) a control group of sham-treated animals, in which the balloon was inserted into the superior sagittal sinus but was not inflated and no fibrin glue was injected (five pigs). All of these groups were treated as follows. At the beginning of each experiment, 2 ml of Evans blue dye (2%) was administered intravenously. Intraventricular pressure, cerebral tissue pressure, superior sagittal sinus pressure anterior and posterior to the occlusion site, mean arterial blood pressure (MABP), and central venous pressure were monitored throughout the experiment. Cerebral perfusion pressure (CPP) was calculated according to the formula: CPP = MABP − mean cerebral tissue pressure.

Four hours after occlusion and continuous pressure monitoring, the animals were sacrificed by bolus injection of 40 ml KCl. The brains were immediately frozen *in situ* by immersion of the head in liquid nitrogen, then cut into coronal slices (Fig. 1) and examined for Evans blue extravasation, for regional cerebral water content, and for histological pathologies. Slices 1 and 2 were located anterior to the balloon and the occlusion site, Slice 3 was located on the site of the balloon, and Slice 4 was located posterior to the occlusion site (Fig. 1).

Cerebral Water Content

From frozen brain Slices 2, 3, and 4 (Fig. 1), tissue samples of white and gray matter of 400 to 500 mg

* Fiberoptic pressure transducer, system 420 R, manufactured by Camino Laboratories, Zeppelin, Pullach, Germany.

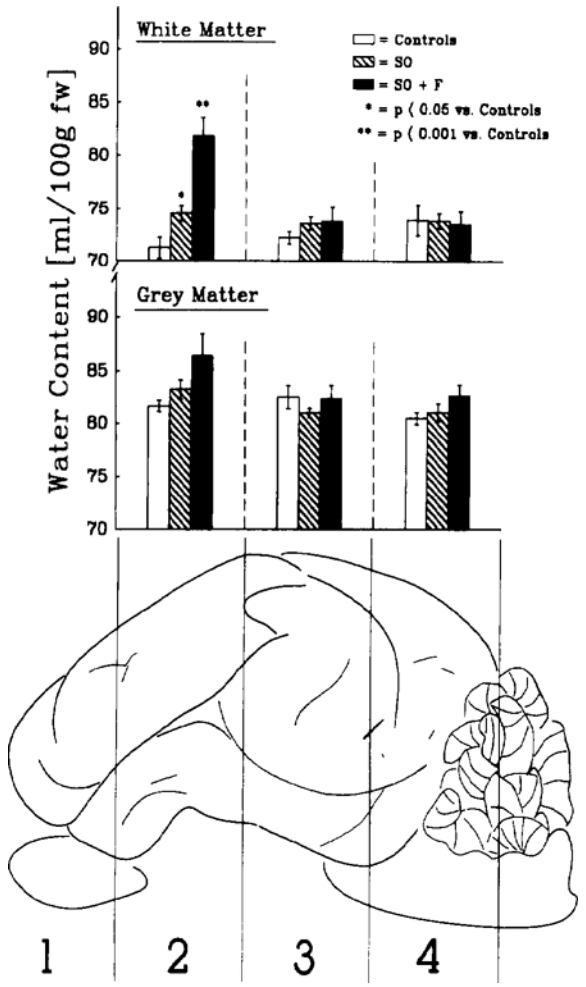

FIG. 1. *Upper Pair:* Graphs showing white- and gray-matter water content of Slices 2 (anterior to occlusion site), 3 (occlusion site), and 4 (posterior to occlusion site) in the three experimental groups. *Lower:* Diagram of slice location. The slices were obtained by coronal sawing of the pigs' heads which were frozen *in situ* in liquid nitrogen.

frozen weight (fwt) each were dried for 3 days at 100°C for determination of dry weight (dwt). Water content was calculated according to the formula:

$$\text{water content (\%)} = \frac{\text{fwt} - \text{dwt}}{\text{fwt}} \times 100.$$

From each animal the means of two samples per slice were used for statistics. Differences between the experimental groups were evaluated by the Kruskal-Wallis test with multiple comparisons on ranks of several independent samples.[19] Slice 1 tissue (Fig. 1) was not examined for water content because it contained only small amounts of white matter which could not be reproducibly separated from gray matter.

Histological Preparation

Samples of each brain slice were immersion-fixed in a 10% formaldehyde solution for 48 hours, dehydrated in an ethanol series, embedded in paraffin, and cut into slices 10 μm thick. Three different stains were applied: hematoxylin and eosin stain, Nissl stain with brilliant cresyl-violet, and fibrin stain according to Weigert's technique modified by the method of Kockel.[13]

Cerebral Angiography

In addition to the experiments described so far, the remaining five animals underwent cerebral angiography. In the Seldinger technique, a No. 5 French multipurpose angiography catheter was percutaneously introduced via the right femoral artery with its tip selectively placed in the right internal carotid artery (ICA). Non-ionic contrast medium (iopamidol and Solutrast 300) was injected manually. Serial digital-subtraction angiographic images† at between 2 and 4 frames/sec were obtained of arterial, parenchymal, and early and late venous phases before inflation of the superior sagittal sinus balloon, immediately after inflation of the balloon, and immediately after injection of fibrin glue into the superior sagittal sinus.

Results

Cerebral Angiography

Cerebral angiography of the pigs' forebrains via the ICA revealed the anatomy of the cerebral venous and sinus system to be very similar to that in man. In the early venous phases, the contrast medium filled multiple cerebral veins that either drained via cortical veins and bridging veins into the superior sagittal sinus or via the internal veins into the sinus rectus and the sinus confluens. From there, further venous outflow continued via both transverse sinuses and, in contrast to the situation in man, via a large spinal epidural venous plexus. The sigmoid sinuses were tiny (Fig. 2a). For this reason it was impossible to introduce the superior sagittal sinus balloon catheter through the jugular veins, so we had to choose a route via a small craniotomy located over the anterior third of the superior sagittal sinus.

Complete obstruction of the superior sagittal sinus was achieved by inflating the balloon. From the moment of complete superior sagittal sinus obstruction, venous drainage by collateral flow via bridging veins and cortical veins could be demonstrated. Retrograde flow in bridging veins anterior to the occlusion site and dilatation of the anterior superior sagittal sinus was seen (Fig. 2b).

The additional injection of fibrin glue led to immediate obstruction of these collaterals and of the anterior superior sagittal sinus with cerebral hypoperfusion of both frontal lobes (Fig. 2c).

Intracranial Pressure

Although the superior sagittal sinus was occluded completely in Group SO for 4 hours, this did not affect

† Politron digital-subtraction angiography system manufactured by Siemens, Erlangen, Germany.

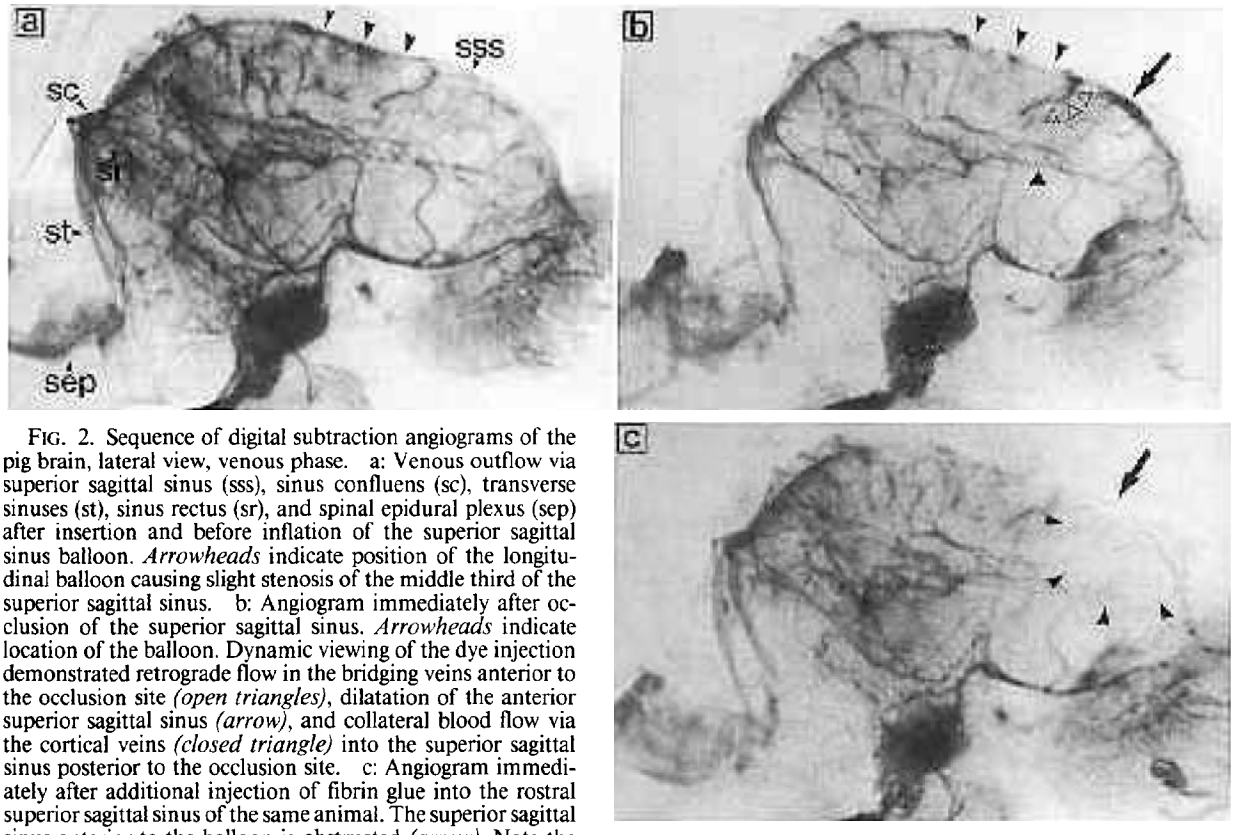

FIG. 2. Sequence of digital subtraction angiograms of the pig brain, lateral view, venous phase. a: Venous outflow via superior sagittal sinus (sss), sinus confluens (sc), transverse sinuses (st), sinus rectus (sr), and spinal epidural plexus (sep) after insertion and before inflation of the superior sagittal sinus balloon. *Arrowheads* indicate position of the longitudinal balloon causing slight stenosis of the middle third of the superior sagittal sinus. b: Angiogram immediately after occlusion of the superior sagittal sinus. *Arrowheads* indicate location of the balloon. Dynamic viewing of the dye injection demonstrated retrograde flow in the bridging veins anterior to the occlusion site *(open triangles)*, dilatation of the anterior superior sagittal sinus *(arrow)*, and collateral blood flow via the cortical veins *(closed triangle)* into the superior sagittal sinus posterior to the occlusion site. c: Angiogram immediately after additional injection of fibrin glue into the rostral superior sagittal sinus of the same animal. The superior sagittal sinus anterior to the balloon is obstructed *(arrow)*. Note the lack of collateral cortical veins and the marked area of hypoperfusion in the frontal lobes *(arrowheads)*.

ICP as could be shown by monitoring the intraventricular pressure (mean ± standard deviation 7.1 ± 3.9 mm Hg vs. 8.3 ± 4.5 mm Hg in controls), cerebral tissue pressure (5.3 ± 6.1 mm Hg vs. 8.1 ± 7.2 mm Hg in controls), CPP (96.4 ± 13.8 mm Hg vs. 103.7 ± 11.2 mm Hg in controls), and superior sagittal sinus pressure anterior to the occlusion site (11.9 ± 5.5 mm Hg vs. 8.3 ± 5.2 mm Hg in controls) (Fig. 3).

The additional injection of fibrin glue caused a severe increase in ICP and a steep fall in CPP. Within 4 hours, intraventricular pressure in Group SO+F rose to 49.4 ± 14.3 mm Hg (in contrast to 7.1 ± 3.9 mm Hg in Group SO) and cerebral tissue pressure rose to 39.4 ± 18.8 mm Hg (in contrast to 5.3 ± 6.1 mm Hg in Group SO), while CPP decreased to 34.2 ± 19.6 mm Hg (in contrast to 96.4 ± 13.8 mm Hg in Group SO) (Fig. 3).

Macroscopic and Histopathological Observations

Macroscopically, the brains of the control animals and those with occlusion of the superior sagittal sinus alone appeared completely normal. Neither hemorrhage nor Evans blue extravasation was detectable. In the frontal cortex and white matter of the fibrin group (Group SO+F), abundant petechial bleeding combined with patchy Evans blue dye extravasations indicated disruption of the blood-brain barrier (Fig. 4a).

These macroscopic findings correlated well with the histological picture. In the control group and in Group SO we could not find any thrombotic clots in the cortical veins, bridging veins, or superior sagittal sinus. The parenchyma exhibited no pathological changes. In contrast to these findings, additional injection of fibrin glue caused an extensive obstruction of bridging and cortical veins related to the frontal and parietal tributaries of the superior sagittal sinus. Compact confluent fibrin material interspersed with thrombotic clots could be seen in the superior sagittal sinus anterior to the balloon as well as in the bridging and cortical veins and even in capillaries (Fig. 4b, c, and d). Edematous areas with swollen perivascular astrocytes, multiple petechial hemorrhages, and spot-like intracerebral hemorrhages of the white and gray matter could be seen in Group SO+F as well (Fig. 4b, c, and d).

Water Content

As suggested by the extravasation of Evans blue dye indicating blood-brain barrier disruption, in Group SO+F, white-matter water content anterior to the occlusion site was significantly elevated to 81.9 ± 3.7 gm/100 gm fwt compared to 71.3 ± 2.2 gm/100 gm fwt in sham-treated controls ($p < 0.001$) (Fig. 1). The gray-matter water content in Slice 2 of Group SO+F was also elevated, to 86.8 ± 3.6 gm/100 gm fwt compared

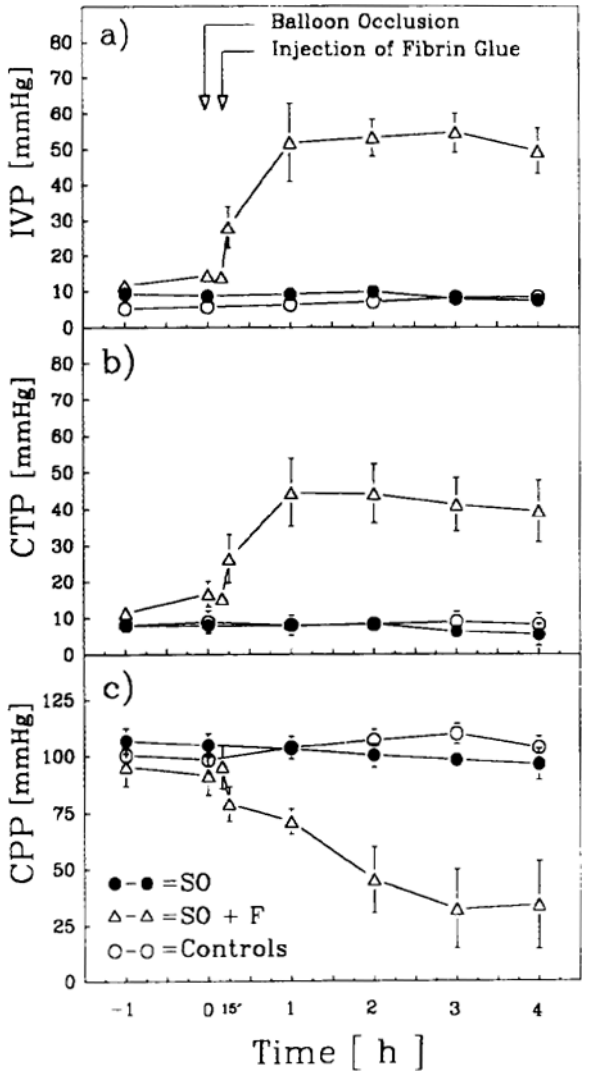

FIG. 3. Graphs showing results of manipulations in the three animal groups. The balloon was occluded in Groups SO (occlusion only) and SO+F (occlusion plus fibrin glue) at time 0; in Group SO+F fibrin glue was injected 15 minutes later. All values are means ± standard deviations. a: Intraventricular pressure (IVP). b: Cerebral tissue pressure (CTP). c: Cerebral perfusion pressure (CPP).

to 81.6 ± 1.2 gm/100 gm fwt in controls (Fig. 1). Occlusion of the superior sagittal sinus alone caused only a moderate increase in white-matter water content to 74.2 ± 2.0 gm/100 gm fwt and in gray-matter water content to 83.5 ± 2.4 gm/100 gm fwt ($p < 0.05$ vs. Group SO+F, $p < 0.05$ vs. controls).

In brain Slice 3, reflecting the site of the balloon, where the superior sagittal sinus and bridging veins but not cortical veins were obstructed, white- and gray-matter water content did not differ significantly among the three experimental groups. Values for white-matter water content in Slice 3 were 72.6 ± 0.9 gm/100 gm fwt in controls, 73.3 ± 1.4 gm/100 gm fwt Group SO, and 73.9 ± 2.8 gm/100 gm fwt in Group SO+F. Gray-matter water content in Slice 3 was 81.6 ± 1.5 gm/100 gm fwt in controls, 80.9 ± 1.2 gm/100 gm fwt in Group SO, and 82.4 ± 2.8 gm/100 gm fwt in Group SO+F (Fig. 1).

White- and gray-matter water content were found to be almost equal in all groups posterior to the occlusion site in Slice 4. White-matter water content was 73.5 ± 3.6 gm/100 gm fwt in controls, 73.7 ± 1.9 gm/100 gm fwt in Group SO, and 73.6 ± 2.6 gm/100 gm fwt in the fibrin group. Gray-matter water content in Slice 4 was 80.5 ± 1.3 gm/100 gm fwt in controls, 80.3 ± 1.0 gm/100 gm fwt in Group SO, and slightly increased to 82.7 ± 2.3 gm/100 gm fwt (not significant) in Group SO+F (Fig. 1).

Discussion

Pathophysiological Intracranial Alterations

Although the causes and the symptoms of sinus-vein thrombosis cover a wide spectrum,[1,3–5,7,15] the reactions of vascular and parenchymal parts of the brain are quite uniform.[5,9] Recently, data on ICP elevation,[6] disturbances of CBF,[16] and appearance of brain edema[5,6,9,20] associated with sinus-vein thrombosis have accumulated that, taken together with improved diagnostic strategies,[4] make adequate therapeutic interventions more feasible.[8,10,11,18,21]

Today it is an accepted fact that, in most diagnosed cases of sinus-vein thrombosis, ICP is elevated to some degree; this has been demonstrated experimentally,[14] clinically, and neuroradiologically.[4,6,7,20] Together with elevated ICP, alterations of regional and total cerebral perfusion may cause disruption of the blood-brain barrier and hypoperfusion with associated cerebral infarction and brain edema.

The Multistep Process of Sinus-Vein Thrombosis

Hitherto, convincing data have not been available regarding the size and extent of a thrombus necessary to initiate the deleterious pathomechanisms causing fatal outcomes in patients suffering from sinus-vein thrombosis. In previous clinical[5,15,20] and experimental studies,[8,12,14] it was a matter of discussion whether a stable thrombus located in any part of the cerebral venous outflow system would give rise to a cascade of pathomechanisms or whether the growth of the thrombus further into the tributary veins would cause deterioration. The results of this study indicate that at least some of the pathomechanisms associated with sinus-vein thrombosis actually evolve as a multistep process which directly correlates with the extent of the thrombus.

The four steps in this process could be characterized as follows. Initially, a floating thrombus incompletely occludes the superior sagittal sinus. This condition may be tolerated without major symptoms as suggested by normal ICP recordings, normal brain water content, and normal angiographic findings in the sham-treated animals that carried a floating, deflated, nonobstructing balloon in their superior sagittal sinus.

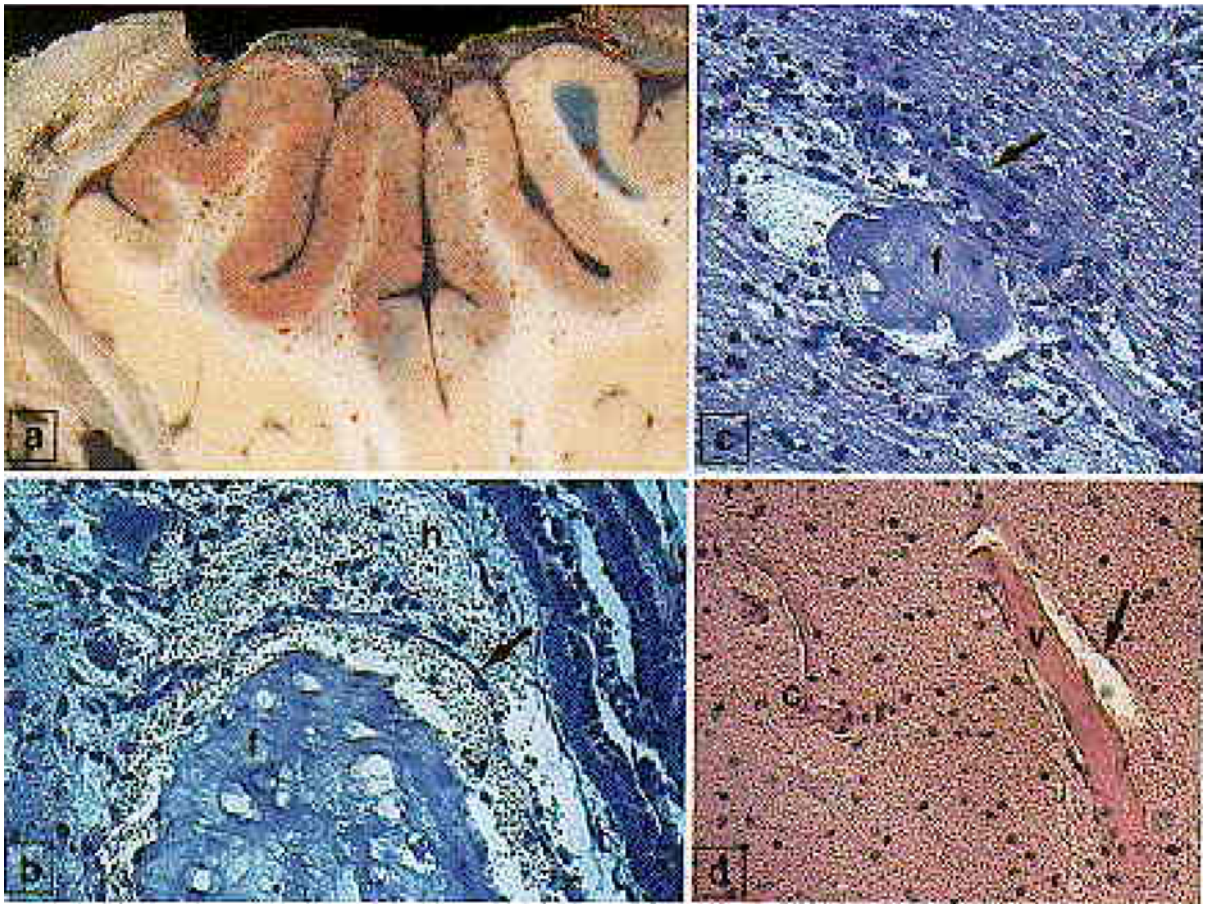

FIG. 4. a: Photomicrograph of a frozen coronal section through the frontoparietal area (Slice 2 on Fig. 1, anterior to the occlusion site) of a Group SO+F animal. Note the petechial hemorrhages and patchy Evans blue dye extravasations in the cortex and subcortical white matter of both hemispheres. b: Photomicrograph of the cerebral vein of a Group SO+F animal showing fibrin clot (f) and perivascular hemorrhage (h) after disruption of the blood-brain barrier. *Arrow* indicates the vessel wall. Nissl stain with brilliant cresyl-violet, × 270. c: Photomicrograph showing two cerebral vessels of a Group SO+F animal. One of the vessels (a small vein) is obstructed by a fibrin clot (f), the other vessel (a small artery, *arrow*) seems to be compressed. Nissl stain with brilliant cresyl-violet, × 165. d: Photomicrograph showing a small vein (v) and a capillary (c) in a Group SO+F animal. These vessels are obstructed by fibrin clots. The *arrow* indicates possible swelling of perivascular astrocytes. H & E, × 165.

In the second step, the thrombus completely occludes the superior sagittal sinus. By analogy, balloon obstruction of the pig superior sagittal sinus causes major changes within the cerebral circulation that are compensated for by the opening of venous collaterals and retrograde flow in the bridging veins anterior to the occlusion site, as demonstrated by angiography (Fig. 2a and b). Intact collateralization thus prevents regional hypoperfusion and brain edema.

In the third step, the growing thrombus occludes bridging veins in addition to the superior sagittal sinus. Venous outflow via collaterals is still possible (Fig. 2b). This is suggested by the fact that in Group SO, in which the cylindrical balloon occluded several bridging veins over a length of 25 mm along the superior sagittal sinus, no increase in ICP occurred, and neither infarction nor edema was found in the underlying tissue (Slice 3).

Once the tributary cortical veins become involved in the process of obstruction, the fourth and final step of the cascade emerges. Lack of sufficient collateralization, regional hyperperfusion with cerebral infarction, and disruption of the blood-brain barrier will damage the cerebral tissue and impair the prognosis of patients.

Clinical and Therapeutic Implications

We would like to emphasize the fact that this laboratory study in pigs concentrates on the occlusion of the middle third of the superior sagittal sinus and of the tributary bridging and cortical veins along the middle and anterior third of this sinus. However, the proposed multistep process of deleterious pathomechanisms may explain to some extent the wide variety of symptoms of cerebral sinus-vein thrombosis, and may suggest at least two implications for the therapy of a

thrombosis in the venous outflow system of the superior sagittal sinus: 1) Based on the results of this study, surgical treatment using thrombectomy or implantation of a sinus-venous bypass might be of benefit only in those cases where the thrombus is localized exclusively in the cerebral sinus and not affecting bridging veins or cortical veins. 2) The best prevention of a progression of sinus-vein thrombosis into cortical veins is to interfere with the growth of the thrombus by anticoagulation. Indeed, experimental and clinical attempts to use heparin in conservative treatment of sinus-vein thrombosis have been most promising.[8,10,11,18,21] In these studies particularly, the number of intracerebral hemorrhages as a possible complication of heparin therapy of sinus-vein thrombosis was lower than generally expected. The rationale for heparin treatment, especially of patients presenting with mild symptoms and with distinct neuroradiological findings, would be to stop further growth of the thrombus. By interrupting the multistep process as early as possible, the clinician treating patients with sinus-vein thrombosis might be "one step ahead of the thrombus."

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