

# A new animal model of cerebral venous infarction: ligation of the posterior part of the superior sagittal sinus in the cat

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## Summary

*Questions under study:* dural sinus occlusion is an infrequent but potentially devastating cause of stroke. The pathophysiological course of events underlying it, as yet incompletely understood.

*Methods:* in a cat model, regional cerebral blood flow (CBF) was measured during control and 2, and 24 hours after superior sagittal sinus occlusion. Around 48 hours after superior sagittal sinus occlusion, experimental settings were terminated by perfusion fixation with 4% paraformaldehyde solution, and haematoxylin and eosin histology.

*Results:* CBF was significantly reduced over the time-period of measurement ( $p < 0.05$ ) covering about 45% of the brain in planes that were affected by occlusion. Histologically, in all cases signs of subacute venous infarction could be demonstrated.

*Conclusions:* based on the newly-developed model of microsurgical ligation of the superior sagittal sinus in cats, we present for the first time

an animal model for cerebral venous infarction that leads to a histologically proven subacute venous infarction with a good reproducibility. The further advantage of this model is the fact that it mimics the clinical situation as far as possible by its inter- and intra-individual variance of extension of the venous infarction and by the slow reduction of CBF over 24 hours. Sequential PET imaging is a favourable, non-invasive method to gain further insight into the pathophysiological characteristics of experimental cerebral venous infarction. Therefore, the new-developed cat-model as demonstrated in this study will be of great value for further and more detailed investigations of cerebral-venous infarctions, and for the experimental evaluation of therapeutic strategies.

*Key words:* cerebral venous infarction; cat; superior sagittal sinus; occlusion; animal model; cerebral blood flow; positron emission tomography

## Introduction

The main objective of neurovascular experimental research is to contribute to a better knowledge of physiological and pathophysiological processes in the cerebral vascular system. Such experimental studies have formed the current concept of varying biochemical and molecular alterations induced by cerebral venous infarction. As the cerebral vasculature represents a dynamic and not a static system, there is an inevitable need for animal models to better investigate such courses of disease during a certain time-window. The advantage of such animal models lies in the fact, that they allow to reproduce cerebral ischaemia under standard conditions, controlling the different variables that may modify these results (duration and location of ischaemia), thus facilitating conclusions by largely eliminating the variability inherent to the clinical setting [1]. Being a relatively large animal, the cat is especially suited as an experimental

model, because use of high-resolution positron emission tomography (PET), as in this study, cannot be successfully applied to smaller animals for investigating cerebral ischaemic alterations. As PET still represents one of the few methods allowing quantitative determinations of various intracellular biochemical and molecular processes in living animals [1], it enables transfer of data from the experimental to the clinical setting [1, 2]. It aids our understanding of the development of such pathophysiological changes, since the crucial step from normal to pathological conditions can be followed and the gaps between early and late changes can be filled in repeat imaging studies [1].

In spite of numerous experimental in vivo and in vitro studies regarding the various changes after cerebral arterial obstruction [1, 3], only little light has so far been shed on the pathophysiological characteristics of cerebral sinus vein occlusion [4].

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Recent publications on experimental sinus vein occlusion have suggested that ischaemic brain tissue damage may only be found in cases of additional involvement of the draining cortical veins [5]. As this does not correspond to clinical experience, in which a single occlusion of the superior sagittal sinus (SSS) can also lead to haemorrhagic venous infarction [6–8], further experimental work is needed to better understand the changes of haemodynamic, metabolic and structural param-

eters after such cerebral sinus vein occlusion. For this reason, the present study was designed to develop a new and single-vein cerebral sinus occlusion model that directly corresponds to clinical conditions, as well as to further elucidate pathophysiological events such as the relationship between regional cerebral haemodynamic disturbance and subsequent histological brain tissue damage.

## Material and methods

The present study was approved by the local Animal Care Committee and the Regierungspräsident of Cologne and is in compliance with the German laws for animal protection.

### Cat sinus vein occlusion model

The experiments were performed using 3 male cats, weighing 3.1–4.7 kg, after fasting of at least 6 hours. Anaesthesia was induced with ketamine hydrochloride (Ketanest, Parke-Davies USA; 25 mg/kg) by intramuscular injection. The left femoral vein and artery were cannulated using polyethylene catheters under loop magnification. The arterial line was used for continuous recording of mean arterial blood pressure and heart rate and the venous line was needed for administration of drugs. The animals were tracheotomised, immobilised with 0.2 mg/kg pancuronium bromide (Pancuronium Inrea, Inrea, USA), and ventilated artificially (FMI, Egelsbach, Germany). General anaesthesia was maintained with 0.6–1.2% halothane in a 3:1-mixture of nitrous oxide-oxygen gas, initially using a face mask. An intravenous infusion of 2 ml/kg/h Ringer's solution containing 5 mg/kg/h gallamine triethiodide for muscle relaxation was maintained throughout the whole experiment. Physiological variables were kept within the normal range known for awake cats [9]. Deep body temperature was kept at 37 °C using a heating blanket feedback controlled by a rectal temperature probe.

The surgical procedure was performed with the animal in the sphinx position, the head in the midline position and fixed in a stereotactic holder. A 20-mm-midline skin incision with an additional 10-mm-skin-incision extending in a v-shape posteriorly was made 30 minutes after induction of general anaesthesia. Subsequently, the myocutaneous flap was dissected down to the pericranium of the temporal fossa: Two burr holes of 3-mm-diameter were drilled parieto-temporally posterior to the coronal suture and temporo-occipitally to the lamboid suture using a dental high-speed drill (Bien Air, Switzerland) under microscopic control (Carl Zeiss, Inc, Germany). The drill-tip was cooled continuously with physiological saline to avoid any thermal injury. By this surgical procedure, a small part of bilateral parasagittal cortex with intact overlying dura mater was exposed. Care was taken to avoid lesions of the sigmoid and superior sagittal sinuses (to prevent the possibility of sinus thrombosis) or the bridging veins. The underlying transparent dura mater was dissected by a small longitudinal cut on both sides of the midline at the location of the initial burr holes. The small dural flap was based towards the SSS. The falx was carefully dissected just below the SSS. The SSS was snared first on the middle part just behind the Rolandic vein and then on the posterior part close to the confluens sinus using loops of 5–0 prolene thread without damage to the

adjacent brain tissue. Initially, the snare was not tightened but the free ends were protected with a silicon tube. Meticulous care was taken to keep the dura intact. The dura mater was protected with a thin layer of cotton and the removed skull was substituted by a cranioplasty that was fixed without sealing the cranium by suturing the temporalis muscle and the skin flap in plane.

### Experimental protocol

Routine monitoring of physiological parameters included measurements of heart rate, MABP, rCBF and ICP. In addition, end-tidal concentration of CO<sub>2</sub> (P<sub>ET</sub>CO<sub>2</sub>; range 3.5–4.5 kPa) and halothane (P<sub>ET</sub>HAL; range 0.8–1.2 kPa) were monitored by use of an infrared gas-analyser (Datex, Helsinki, Finland). All parameters were continuously recorded using a PC-based data acquisition system (Dasy Lab, National Instruments, USA).

PET images of CBF were obtained before and around 2 and 24 hours after SSS occlusion, achieved in the PET scanner by tightening the snare. The details of the CBF measurement are described in our previous report [10].

At the end of each experiment, usually 48 hours after SSS occlusion, experiments were terminated. Thoracotomy was performed under artificial ventilation and the ascending aorta was cannulated. The descending aorta was clamped. After rinsing with 150 ml of 0.9% NaCl with 10 IU heparin within 2 minutes the animals were perfused with 10% formalin. Right atriotomy was performed immediately after starting to rinse. The brain was then left within the skull for eight hours at room temperature. After removal, it was immersed in 4% buffered formalin.

### Positron emission tomography

Serial positron emission tomography (PET) was performed with a 24-ring, high-resolution camera (Siemens/CTI ECAT EXACT HR) with an axial field of view of 15 cm, an in-plane spatial resolution of 3.6 mm full width at half maximum, and an axial resolution of 4.0 mm full width at half maximum [11, 12]. For the assessment of cerebral blood flow (CBF), bolus applications of <sup>15</sup>O-H<sub>2</sub>O were used as has been described and discussed before [12–18]. Starting around 2 hours before SSS occlusion, several consecutive PET studies were performed in each cat.

Analysis of PET data was based on the parametric images of 14 coronal brain slices. The obtained images permitted the identification of the main anatomic structures of the cat's brain and a distinction of grey and white matter. For quantitative analysis, CBF images obtained during control were masked using a CBF threshold of 10 ml/100 g/min to obtain images that represented the whole brain. These masks were used to analyse coronal brain slices in subsequent scans. On coronal slices, regions with a CBF threshold >30 ml/100 g/min were reconstructed, and the ratios between these regions and the whole slices

were calculated. Furthermore, CBF was determined in circular regions positioned in the centre of the affected areas in respective coronal slices.

#### Analysis of histological data

After paraffin embedding, 7- $\mu$ m-thick coronal sections were cut at distances of 2 mm and stained with haematoxylin-eosin or with a combination of Luxol fast blue and cresyl violet.

#### Statistics

Statistical analysis (StatSoft, Oklahoma, USA) was performed using repeated measures ANOVA with Scheffé post-hoc comparison to test variation over time. Statistical significance was defined at  $p < 0.05$ .

## Results

### General physiological parameters

Arterial blood gas levels, pH and haemoglobin concentration in the 3 cats remained within normal physiological limits throughout the experiments. Mean systemic arterial pressure was not significantly altered by the surgical procedure (occlusion of SSS), nor in the later course of the experiments (data not shown).

### Histological studies

Histopathological light microscopic observations demonstrated subacute, focally extensive haemorrhagic necrosis predominantly in the posterior

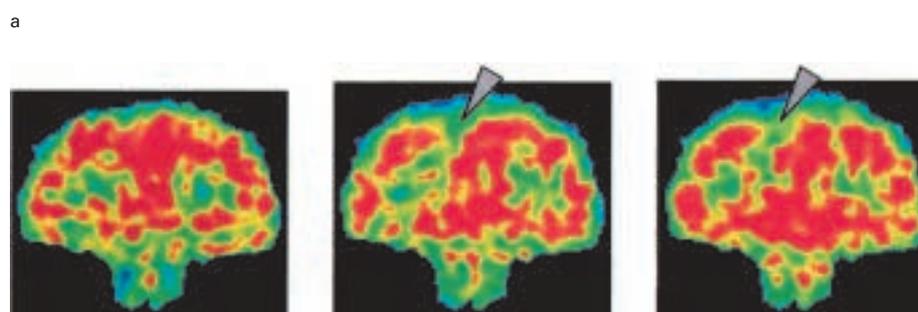
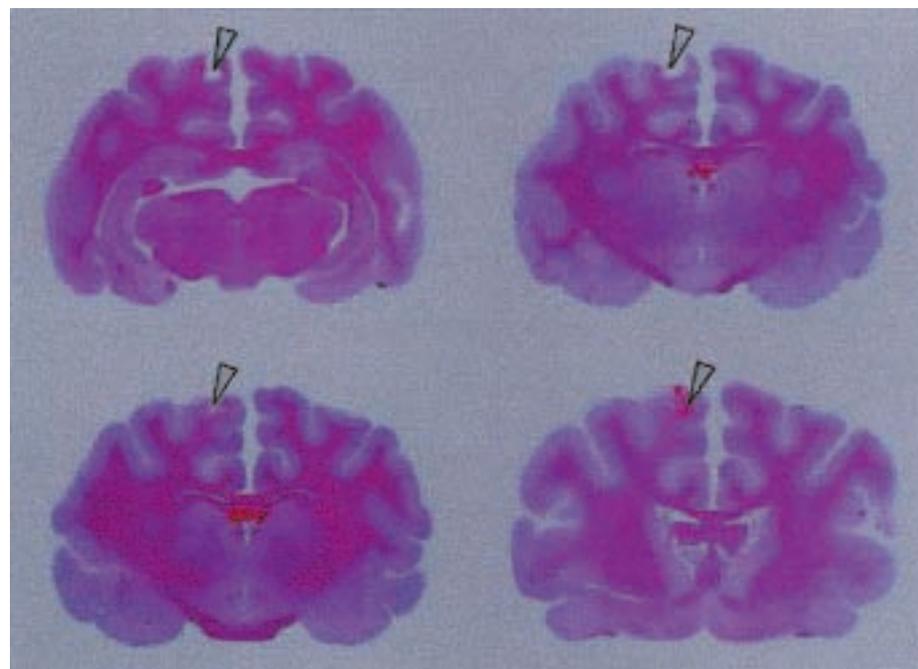
third of the marginal gyrus. This was accompanied by eosinophilic hypoxic-ischaemic neuronal death (see figure 1). Suffering and disintegration of the ischaemic area and pronounced circumlesional swelling of nerve cell bodies was demonstrated. Thrombotic material was always found within the occluded part of the SSS, extending up to 4 mm into the preocclusion SSS and up to 2 mm post-occlusionally into the confluens sinus. The confluens sinus was not totally obliterated by thrombotic material in any case. No thrombotic material was detected in the cerebral veins draining into the SSS or in the straight and transverse sinuses. Dif-

**Figure 1**

Representative histological sections and positron emission tomography images.

a. Representative cross-sections (stained with haematoxylin and eosin) of cat 1, demonstrating subacute haemorrhagic infarct in the marginal gyrus where the superior sagittal sinus was occluded: grey arrows demonstrate region of main infarction.

b. Sequential positron emission tomography images of cerebral blood flow of cat 1, obtained at control and 2 and 24 hours after superior sagittal sinus occlusion: grey arrows demonstrate region of main flow decrease.



control

2 hours

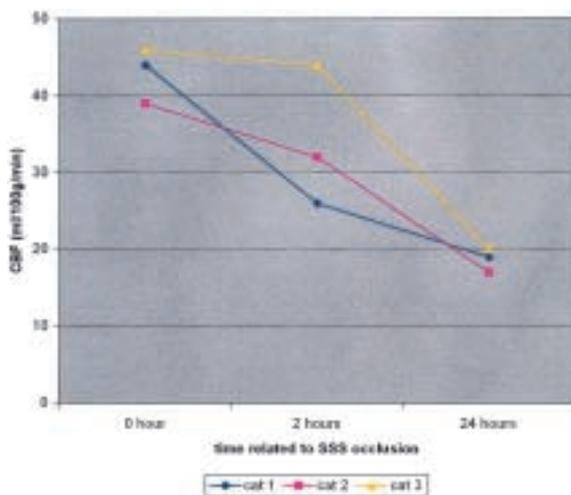
24 hours

b

**Figure 2**

Course of cerebral blood flow, as imaged by positron emission tomography, obtained before, 2 hours and 24 hours after superior sagittal sinus occlusion.

Legend: CBF: cerebral blood flow; SSS: superior sagittal sinus.



ferent degrees of haemorrhagic conversion of the venous infarction were apparent in all of the investigated brains. No microscopic or macroscopic signs of transtentorial herniation could be detected in any of the brains.

Venous infarctions were all found to lie in the vascular territory of the superficial venous drainage in the cortex and subcortical white matter. An infarct extension to the deeper cortical part, as seen in one cat, was shown in a border zone between the vascular territory of the superficial and the deep medullar veins.

### Neurological signs

No neurological signs of increased intracranial pressure or venous infarction could be detected in

any cat that were all anaesthetised throughout the whole study period. All cats survived until the end of the study.

### Positron emission tomography measurements

PET scans obtained during control and approximately 2 and 24 hours after SSS occlusion are illustrated on coronal slices in figure 1. The performed experimental procedure decreased CBF significantly in the vascular territories related to the SSS occlusion.

Mean CBF levels measured before SSS occlusion were 43 ml/100 g/minutes and were significantly higher than 18 ml/100 g/minutes after 24 hours after occlusion (see figure 2) ( $p < 0.05$ ). This is in contrast to the values of 35 ml/100 g/min at 2 hours after occlusion that demonstrated no significant decrease to the control levels.

Mean CBF measured at 24 hours after SSS occlusion was 18 ml/100 g/minutes. The velocity of CBF decrease during the first 24 hours has no influence of final infarct size. Individual infarction as well as their average size in histological slices were in good agreement with regions of impaired flow in PET. There was a significant relationship between the area of reduced rCBF in different PET images and the venous infarction in corresponding histological slices ( $r = 0.842$ ;  $p < 0.01$ ). From the small regression coefficient, it is obvious that venous infarctions were slightly smaller than the area of reduced CBF.

## Discussion

The present experimental study confirms that our newly developed cat model of cerebral venous infarction is reproducible and comparable to the pathophysiological conditions seen under surgical (skull base surgery approach with transient or permanent ligation) or non-surgical (sinus vein thrombosis with/without involvement of bridging veins) circumstances in humans. Previous reports on experimental models of SSS occlusion examining haemodynamic alterations used different animals: cats, rats or gerbils [19–26] (see table 1). Of these in-vivo models, the cat is thought to be an ideal animal as repeated studies of rCBF by PET are possible. The former experimental models have used varied approaches to occlude the SSS, including ligations, injection of thrombogenic material, retrograde embolisation, coagulation or photochemical thrombosis [19–26]. Although simple, thread ligation of the venous sinus – as performed in the present report – combines the advantage over the other methods, that it does not involve the accompanying bridging veins and permits investigating whether or not venous sinus

occlusion alone causes subsequent venous infarction. This hypothesis could not be investigated so far by the formerly used animal models, so that our single-vein occlusion animal model allows further and important insight into the pathophysiological characteristics of experimental cerebral venous infarction.

### Validity of the animal model

A newly developed experimental animal model must be able to meet different requirements to be of further value for investigating pathophysiological events. It must be feasible and easy to perform, and has to introduce very few variables or artifacts allowing for testing a given hypothesis. The cat model of SSS occlusion presented here demonstrated a reproducible experimental course before and after sinus vein occlusion and has led to a histologically proven subacute venous infarction in every case, even though there was reported a success-rate of only about 50% in previous animal models [19, 27–29]. After surgical preparation, but before sinus vein occlusion, no relevant haemody-

**Table 1**

Summary of previous animal studies investigating haemodynamic alterations of cerebral venous infarction since 1990.

Study	Animals used	Anaesthetic used	Occlusion/Induction	Side of Occlusion	rCBF measurement	Result
Kurokawa Y et al. [20]	rat	pentobarbital	retrograde embolisation	SSS + cortical veins	autoradiography at 15 or 30 min after occlusion	symmetrical hypoperfused parasagittal cortex
Ungersböck K et al. [22]	rat	chloral hydrate	kaolin-cephalin suspension	SSS + cortical veins	laser Doppler, at 60 min after occlusion	rCBF reduced to 61% of baseline conditions
Nakase H et al. [19]	rat	chloral hydrate	photochemical	cortical vein	laser Doppler, in 15-min interval for 90 min after occlusion	transient hyperperfusion zone with initial hyperaemia around hypoperfused core; with thrombus growth, CBF to the core diminished to 15–20% of the initial flow values
Otsuka H et al. [24]	rat	chloral hydrate	photochemical	cortical veins	laser Doppler continuously for 75 min after occlusion	rCBF reduced to 66% of baseline conditions
Schaller C et al. [21]	rat	chloral hydrate	photochemical	cortical veins	laser Doppler, at unknown time-point	rCBF reduced to 70% of baseline conditions
Miyamoto K et al. [25]	gerbil	chloral hydrate	photochemical	single SSS at different sites	laser Doppler in 10-min interval for 60 min after occlusion	rCBF decreased to 47% of baseline conditions until, beginning after 30 min
Gotoh M et al. [26]	cat	ketamine	coagulation	SSS + cortical veins	H <sub>2</sub> clearance at 6 and 12 hours after occlusion	rCBF decreased to 46% and 40% of baseline conditions
Kanaiwa H et al. [23]	cat	chloralose/urethane	cianoacrylate	SSS + external jugular vein	H <sub>2</sub> clearance at 15 and 120 min after occlusion	rCBF decreased to 53% of baseline conditions and remained at 42% at 120 min

SSS: superior sagittal sinus; rCBF: regional cerebral blood flow; H<sub>2</sub> clearance: hydrogen clearance; min: minutes.

dynamic or metabolic changes could be demonstrated using PET imaging, suggesting that no adverse effects arose from the surgical preparation or looping of the SSS within the chosen experimental procedure. The present animal model demonstrated a good correlation between the SSS occlusion and the subsequent pathophysiological effects in cats enabling observation of inter-individual differences of cerebral venous flow in certain vascular territories.

### Occlusion technique

Our chosen occlusion technique that does not involve the accompanying bridging or cortical veins represents a new, but important methodological approach. It allows investigation of the pathophysiological course underlying the development of cerebral venous infarction and estimation of the duration of time during which effective restoration of blood flow and interventions to prevent the consequences of biochemical alterations can be successful in ensuring the viability of cerebral tissue. With the experimental setting used in previous animal models, especially detailed information regarding the capacity of venous collater-

als and its influence on the time course of haemodynamic alterations could not be gained (see table 1). Our new method of single sinus vein occlusion without including bridging or cortical veins leading to subsequent venous infarction, suggests that venous hypertension may play an important, but not such a dominant role in the multi-step pathophysiology of cerebral venous infarction [10] as previously assumed. Progressively decreasing rCBF in line with failure of spontaneous compensation by anastomotic pathways of the venous drainage system is a key issue. It is important to note that functional regulation of CBF seems to be more resistant than other regulatory mechanisms, as seen in the inter- and intraindividual varying of infarct extension in the present study. These experimental findings have certainly implications on clinical treatment, as they give new and important insights into the spatial and time-dependent behaviour of still viable ischaemic “penumbra-like” brain tissue after cerebral venous infarction.

Our presented occlusion technique is appropriate, as it is resistant enough to prevent incomplete sinus vein occlusion over the follow-up time, as proved by histological examination, and demon-

strates appropriate size to cause occlusion in a constant site, and prevents distal migration into cortical or bridging veins.

### Advantages of the model

The advantage of the present animal model includes SSS ligation by a relative simple surgical procedure, and an almost intact dura mater to maintain intact cerebral cortex. The possible introduced (patho)physiological variables by the experimental procedure such as the neuroendocrine response to stress or changes induced in intracranial pressure as a result of the wide opening of the dura mater, can be neglected under these experimental conditions. These circumstances give substantial experimental evidence, that local changes of the haemodynamic parameters and subsequent cellular steps are not directly induced by the surgical procedure itself, but are the consequences of sinus occlusion and therefore represent the main source of cerebral venous infarction. The relatively homogenic appearance of subacute, venous infarction is desirable in relation to the reproducibility of the animal model. Its relative interindividual inhomogeneity of the extension of the venous infarction between different animals is related to spontaneous compensation of venous perfusion within the first hours after SSS occlusion and represents another beneficial aspect in relation to the great relevance of transferring the results gained into the clinical setting. The application of PET in experimental models of disease, eg, focal cerebral-venous ischaemia, helps to understand the development of pathophysiological changes, since the crucial step from the normal to the pathological condition can be followed and the gaps between early and late changes can be filled in repeat studies. However, the histological lesion, as demonstrated in the present study, does differ from the well-known picture of a wholly developed cerebral arterial infarction, when defining such infarction as an area of pannecrosis. The area of brain tissue damage resulting from venous ischaemia forms the cellular basis of the mixture of some necrotic cells, intracellular oedema and a variable degree of extracellular oedema, suggesting a completely different pathophysiological pathway for the slow course of venous compared to arterial infarction [10]. Intrasinusoidal venous hypertension undoubtedly plays an important role in the origin of cerebral venous infarction. It produces intracerebral venous congestion, increases intravascular pressure, and lowers cerebral perfusion pressure. This pathophysiological cascade may explain the slow decrease of CBF over 24 hours in the present study.

### From animal experiments to clinical practice

There are substantial differences between small rodents and large mammals in certain aspects of the pathophysiology of venous ischaemia, such as the flow thresholds for the loss of cell function and the extent of the penumbra-like areas. In small animals, a smaller reduction of rCBF is required to cause brain tissue damage, and the area of penumbra-like tissue can be easily and better identified than in large animals or humans [1]. In addition, patients may have cerebro-vascular occlusions at different other sites than the occluded venous sinus that explains additionally the great variation in efficacy of collateral circulation changes from one patient to another [1]. Such anatomical features may influence the interpretation of experimentally gained results related to the conditions seen in humans hindering a direct transfer of experimental to clinical data. However, neuroimaging findings might serve as surrogate targets in the selection of new therapeutic strategies [30, 31].

### Conclusion

We present for the first time an animal model for cerebral venous infarction that leads in every case to a histological proven subacute venous infarction of varying degree, demonstrating the validity of the model. The further advantage of this model is the fact that it mimics the clinical situation through its inter-individual variance of extension of the venous infarction. State-of-the-art imaging modalities, such as PET, represent a useful method to gain further insight into the pathophysiological characteristics of experimental cerebral-venous infarction, especially in the time course of the disease analysed in relation to effects on impaired perfusion within infarcted tissue. Therefore, the newly-developed cat-model, as demonstrated in this study, will be of great value for further and more detailed investigation of the pathophysiological basis of cerebral-venous infarctions, and for the experimental evaluation of therapeutic strategies.

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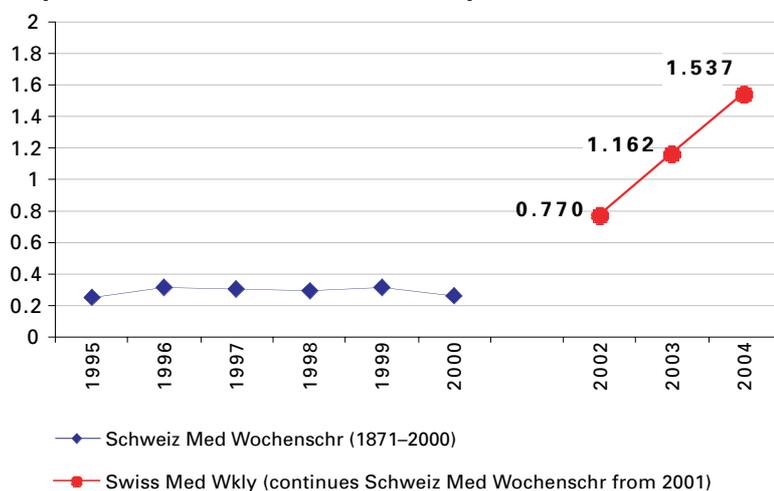
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