Commentary on:
A New Thrombosis Model of the Superior Sagittal Sinus Involving Cortical Veins
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Toward a Better Model of Cerebral Venous Sinus Thrombosis

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Cerebral venous sinus thrombosis (CVST) is an important cause of stroke and disability, particularly in young patients. A lack of understanding of the pathophysiology of CVST contributes to the ongoing morbidity and relative inadequacy of current treatment options. The disease is relatively rare, affecting 3–4 people per 1 million overall and 7 per 1 million children. It represents 0.5%–3% of stroke cases (2, 28, 32).

Animal models of this disease may provide insight into its pathophysiology as well as guide future treatment methods. Several animal models of CVST have been developed in various species. However, no single model exists that adequately recreates the range of pathology seen in humans. An ideal model of CVST should provide 3 key elements: (i) mimic the pathophysiologic milieu in which CVST occurs in humans; (ii) follow the pattern of thrombosis, infarction, hemorrhage, and pathology observed in humans; and (iii) provide a platform to develop and test new treatment modalities. Li et al. present a new model in their study. We review this research in the context of the animal models developed and studied to date.

CVST IN HUMANS

To develop a model that mimics CVST in humans, an understanding of the natural history, risk factors, pathology, and prognosis of CVST is necessary. The largest prospective study to date, ISCVT (International Study on Cerebral Vein and Dural Sinus Thrombosis), is a multinational observational study that followed 624 patients with symptomatic CVST with a median 16-month follow-up (11). These results have been verified by several other large series (15, 16, 24). Risk factors for development of CVST include female gender, oral contraceptive use, thrombophilia, puerperium, pregnancy, malignancy, and infection. ISCVT demonstrated an 8.8% mortality rate and a 12.6% significant morbidity rate (modified Rankin score $\geq$2) in patients presenting with symptomatic CVST (11). Additionally, morbidity increases with the presence of a parenchymal lesion on imaging and increases further with the presence of intraparenchymal hemorrhage (10, 20). Other factors associated with worse long-term outcome include age, male gender, deep cerebral vein thrombosis, coma, mental status disorder, infection, and cancer (5, 11).

In terms of disease management, apart from supportive measures and hydration, the mainstay of treatment for acute CVST is systemic anticoagulation with heparin, a therapy that has been shown in 2 small, randomized trials to be safe but that may not confer a significant morbidity or mortality benefit (3, 17). Low-molecular-weight heparin may confer a slight benefit over unfractionated heparin (4, 19). However, mortality remains high, with reports ranging from 8%–14% in modern series (7). Although endovascular targeted thrombolytic therapy with recombinant tissue plasminogen activator has not been compared with systemic anticoagulation in

Key words
- Cortical vein
- Hemorrhage
- Infarction
- Superior sagittal sinus
- Thrombosis

Abbreviations and Acronyms
CBF: Cerebral blood flow
CVST: Cerebral venous sinus thrombosis
$HbSO_2$: Hemoglobin oxygen saturation
ISCVT: International Study on Cerebral Vein and Dural Sinus Thrombosis
MRI: Magnetic resonance imaging
SSS: Superior sagittal sinus

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a randomized trial, and its safety profile has not been evaluated in a prospective fashion, several small case series suggest there may be an advantage to this technique in patients with declining clinical status despite adequate systemic anticoagulation (9, 25). Endovascular mechanical thrombectomy has been reported, but indications for use, safety profile, and efficacy have not been extensively studied (8, 18).

CVST can be divided based on 2 mechanisms with distinct clinical courses. First, thrombosis of the venous sinuses alone typically manifests with symptoms of elevated intracranial pressure such as headache and papilledema owing to inadequate venous outflow and occurs in approximately 20% of cases (11). Second, thrombosis of the cerebral veins leads to localized brain edema and venous infarction and can progress to hemorrhage (32). It is unclear whether these 2 mechanisms are independent and what causal relation they have to each other. Direct thrombosis of the sinuses may occur without cerebral vein involvement; it may lead to cerebral vein thrombosis, or thrombosis of the sinus may be a secondary result of cerebral vein thrombosis (12).

EARLY CVST MODELS

Beck and Russell (1) in 1946 were the first to attempt a model of sinus occlusion. They occluded the superior sagittal sinus (SSS) in dogs, cats, and rabbits with clips or silk ligatures and injected thrombin or the chemical coagulant ethanolamine oleate; however, they were unsuccessful in creating a thrombus in the sinus or cortical veins or in producing any neurologic change. Other early models of CVST involved artificially occluding the sinus by injecting sclerosing agents such as ethanolamine, sodium morrhuate, lard oil, hot paraffin, isobutyl-2-cyanoacrylate, iophendylate, and scandium chloride, or by heat coagulation or tamponade with muscle or cotton (13, 14). A significant drawback of these models is that often an artificially created thrombus does not result in a similar pattern of clot formation, propagation, or resolution as seen in humans. Subsequent models have focused on creating a more physiologic induction of thrombus by using a combination of stasis (either by balloon or ligation) combined with injection of prothrombotic agents such as thrombin or kaolin cephalin. What these early models did demonstrate was that progression of thrombus from the SSS to bridging and cortical veins was likely necessary to produce changes in the brain parenchyma such as edema, infarction, and hemorrhage (14).

DECKERT MODEL

Deckert et al. (6, 13) sought to create a more natural thrombus, and their technique served as the basis of future models. In Sprague-Dawley rats, 2 cranial windows were made: one over the confluens sinuum and one over the anterior SSS. Stasis was induced by ligating the SSS just anterior to the confluence and 1 cm anteriorly. Thrombus was induced by injection of kaolin cephalin (a reagent used in inducing clot for the partial thromboplastin time reaction) directly into the isolated sinus. Induction of thrombus led to a significant increase in intracranial pressure and increase in local brain tissue impedance. Histologic, electroencephalographic, and clinical changes were seen only in cases where thrombus extended into the cerebral veins, which was not consistently seen in all cases. Subsequent heparinization reversed the tissue perfusion impedance. This model demonstrated normal pathophysiologic creation of thrombus and, in some cases, extension to the cortical veins.

Using this model, Ungersbock et al. (33) measured local blood flow in the isolated portion of the sinus using laser Doppler flowmetry. They demonstrated that thrombosis was not always accompanied by a significant decrease in blood flow. Cortical vein thrombosis and subsequent infarction or hemorrhage was contingent on decreased flow and not solely sinus thrombosis. These authors hypothesized that the presence of variable venous outflow collaterals in rats led to the variation in thrombosis and flow patterns. This finding was supported by a model developed by Fries et al. (14) in pigs, in which balloon occlusion of the middle third of the SSS did not cause elevated intracranial pressure or infarct unless accompanied by fibrin glue injection causing cortical and bridging vein thrombosis.

Nakase et al. (22, 23) applied laser Doppler flowmetry regional cerebral blood flow (CBF) measurement, regional hemoglobin oxygen saturation ($HbSO_2$) assessment using microspectrophotometry, and fluorescein angiography to the Deckert model to investigate the relationship between local and regional blood flow and concomitant $HbSO_2$. They divided their results into 3 groups based on angiographic findings: SSS occlusion only, SSS with cortical vein thrombosis, and a sham operated group. As seen in the prior studies, cortical vein thrombosis was necessary for parenchymal changes. In the cortical vein thrombosis group, regional $HbSO_2$ and regional CBF decreased immediately after sinus venous thrombosis. The reduction of $HbSO_2$ preceded the decrease in regional CBF and was a sensitive predictor of subsequent cerebral vein thrombus and infarction. The authors concluded, as Ungersbock et al. (33) had, that local variations in venous collateral drainage might be responsible for the difference in response to SSS occlusion and subsequent cerebral vein thrombosis and infarct. The blood pressure in animals tolerating CVST was significantly higher (15%) than in animals sustaining infarction or the sham-operated group, suggesting certain rats had a greater compensatory response to the change in regional CBF, which rescued them from ischemia. This mechanism remains unexplained.

Magnetic resonance imaging (MRI) in the Deckert model, studied by Rother et al. (26), corroborates many of the previously discussed findings. Infarct and hemorrhage were seen only in animals with cerebral venous thrombosis. Additionally, histopathologic changes correlated well with MRI findings. A portion of animals in this study was given recombinant tissue plasminogen activator after induction of CVST. These animals demonstrated a gradual improvement in diffusion-weighted imaging signal, and the area of infarct measured on histopathology correlated to the final, improved diffusion-weighted imaging signal area on MRI, further supporting the role of anticoagulation or thrombolysis in the management of CVST.

Taken together, the studies based on the Deckert model support the hypotheses that maintaining hydration and cerebral perfusion pressure is critical to limiting ischemia, and that the expeditious use of anticoagulation may limit the progression of thrombus to the cortical veins.

ROTTGER MODEL

A limitation of the Deckert models is the reliance on ligation of the SSS to create the thrombus. Although both SSS and subsequent cortical vein thrombosis can be studied with these techniques, the study of therapy is limited by the permanence of ligation.