Mechanical thrombectomy and intravascular imaging for cerebral venous sinus thrombosis: a preclinical model

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OBJECTIVE Although the majority of patients with cerebral venous sinus thrombosis (CVST) will improve with anticoagulation therapy, a portion of patients will either present in a comatose state or continue to deteriorate clinically despite early anticoagulation. In these cases, along with treating the underlying thrombophilia, timely thrombolysis may be beneficial. Repurposed arterial thrombectomy devices may not perform as expected in the cerebral venous sinus, and there are currently no preclinical endovascular thrombectomy (EVT) models for CVST. Contrary to arterial stroke research, preclinical models utilized to test various endovascular techniques and devices are lacking. The purpose of this research was to develop a reliable preclinical animal model for the testing of endovascular strategies to treat CVST.

METHODS Five consecutive male Yorkshire swine weighing 45 kg were utilized. Thrombosis of the superior sagittal sinus was induced with a bovine thrombin injection via a microcatheter under distal balloon occlusion for 15 minutes. Combined arterial injections and superselective sinus injections confirmed the extent of thrombosis. EVT was subsequently performed using a second-generation stent retriever, followed by intravascular optical coherence tomography (OCT) imaging to assess the luminal environment after thrombectomy.

RESULTS Thrombosis of the superior sagittal sinus, EVT, and subsequent OCT imaging were technically successful in 4 of the 5 swine. Recanalization of the sinus with a second-generation stent retriever was successful after one attempt in 3 of 4 swine (75%), and 1 swine required two attempts. OCT imaging after thrombectomy revealed regions of residual sinus luminal thrombus despite complete angiographic recanalization. Thrombosed bridging cortical veins were also observed before draining into the sinus, along with patent cortical veins.

CONCLUSIONS The authors describe a preclinical model to assess endovascular techniques and devices for the treatment of CVST. Repurposed devices from arterial stroke may not perform as expected, given the unique features of venous sinus thrombosis. Residual bridging cortical vein thrombus and residual sinus thrombus, visualized on intravascular OCT, may be present despite complete sinus recanalization on angiography, and this may be the etiology of the poor clinical outcome despite technical success. In the setting of bridging cortical vein thrombus after successful sinus thrombectomy, direct chemical thrombolysis may be warranted to dissolve the remaining clot. This model may be helpful in developing and testing a new generation of devices designed specifically for CVST treatment.

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KEYWORDS cerebral venous sinus thrombosis; mechanical thrombectomy; cortical vein thrombosis; optical coherence tomography; vascular disorders

CEREBRAL venous sinus thrombosis (CVST) is a rare type of stroke accounting for 1% of all strokes.¹ Anticoagulation remains the cornerstone of treatment for CVST.² The majority of patients will clinically improve with systemic anticoagulation; however, up to 13% experi-

ence ongoing morbidity and mortality.³ In 2015, Siddiqui et al. conducted the largest systematic review comprising 185 patients undergoing endovascular thrombectomy (EVT) for medically refractory CVST.⁴ Overall, 84% of patients had a favorable outcome (modified Rankin Scale

ABBREVIATIONS CVS = cerebral venous sinus; CVST = CVS thrombosis; EVT = endovascular thrombectomy; OCT = optical coherence tomography; SSS = superior sagittal sinus.

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scores 0–2) and 25% of patients had no or partial recanalization of the sinus.⁴ In the analysis, the AngioJet rheolytic catheter (Boston Scientific) was the most commonly used thrombectomy device in 40% of procedures. This device, along with several other devices used to treat CVST (e.g., Fogarty Embolectomy Device and wires), has become less commonly utilized as the technology and techniques for EVT have evolved considerably over the past decade.⁵

Currently, there are limited data regarding recanalization rates and outcomes in patients with CVST undergoing thrombectomy with modern endovascular devices. The Society of Neurointerventional Surgery 2018 guidelines reported insufficient evidence to recommend optimal endovascular devices or approaches (pharmacological thrombolysis, direct aspiration, stent retriever, balloon thrombectomy, balloon angioplasty and stenting) for medically refractory CVST.⁶ We hypothesize that repurposed arterial thrombectomy devices may not perform as expected in the CVS. Several anatomical differences exist between the CVS and arteries, including increased luminal diameter and vessel wall structure. The sinus wall is composed of endothelium and elastic lamina, lacking the smooth muscle found in arteries.⁷ Furthermore, contrary to arterial stroke research, the preclinical models used to test various endovascular techniques and devices are lacking.

To our knowledge, there are no preclinical EVT models for CVST. The purpose of this research was to develop a reliable preclinical animal model for the testing of endovascular strategies to treat CVST. We describe a swine model of endovascular cerebral sinus thrombosis, subsequent EVT, and intravascular imaging with optical coherence tomography (OCT) to assess the luminal environment after EVT. It was hypothesized that direct visualization of residual sinus thrombus, sinus injury, and bridging cortical vein thrombosis could be possible with OCT.

Methods

All experiments were conducted according to the policies and standards established by our institutional animal research ethics board. Five consecutive male Yorkshire swine weighing 45 kg were used. There was no prescreening imaging of venous anatomy for any animal. All procedures were carried out under general anesthesia with continuous hemodynamic monitoring.

A dedicated animal interventional radiology suite equipped with a single-plane C-arm (Philips) was used for all procedures. Ultrasound-guided right femoral punctures were performed. A 6-Fr sheath was inserted into the right common femoral artery and another 6-Fr sheath into the right femoral vein. A 6-Fr Envoy (Codman) guide catheter was navigated into the right ascending pharyngeal artery under the roadmap technique, ensuring that the guidewire did not enter the rete mirabile to avoid vasospasm of these vessels. A cerebral angiogram was obtained demonstrating the venous drainage system. Next, a second 6-Fr Envoy guide catheter was navigated into the right internal jugular vein.

Cerebral venous drainage in swine is similar to that in humans; however, the sinuses drain primarily via the spinal venous plexus and not the internal jugular vein.⁸

FIG. 1. Swine CVS. **A:** Combined arterial and venous diagnostic angiography injections via a guide catheter in the ascending pharyngeal artery (green arrowhead) and the internal jugular vein (red arrowhead), revealing the connection between the internal jugular vein and sigmoid sinus (blue arrowheads) and the SSS (yellow arrowheads). **B:** The Transcend microwire is stationed in the proximal third of the SSS (yellow arrowheads) via the right internal jugular vein (red arrowhead). Figure is available in color online only.

Therefore, to reveal the connection between the internal jugular vein and sigmoid sinus, a simultaneous hand injection of contrast via the Envoy guide catheter stationed in the right internal jugular vein was performed during the late-venous-phase pump injection from the ascending pharyngeal artery (Fig. 1A). Under the roadmap technique, a 0.014-inch Transcend microwire (Stryker) was navigated into the superior sagittal sinus (SSS) (Fig. 1B).

Sinus Thrombosis

An SL-10 microcatheter (Stryker) was navigated into the SSS using the Transcend wire. Superselective angiographic runs were performed using the SL-10 to reveal the sinus anatomy (Fig. 2A). A HyperForm balloon (Medtronic) was also navigated into the sinus under the roadmap technique and stationed just proximal to the SL-10 tip (Fig. 2B). The balloon was inflated, and contrast injection

FIG. 2. Swine CVST. **A:** Supraselective microcatheter injection of the SSS (yellow arrowheads) outlining the sinus. **B:** A deflated HyperForm balloon with proximal (purple arrowhead) and distal (blue arrowhead) markers is visible, along with the proximal (red arrowhead) and distal (green arrowhead) markers of the SL-10. **C:** Inflated HyperForm balloon (blue arrowheads) and proximal (red arrowhead) and distal (green arrowhead) markers of the SL-10. **D:** Sinus occlusion confirmed with a microcatheter injection just proximal to the balloon occlusion (blue arrowheads), showing contrast pooling only proximal to the balloon (yellow arrowheads). Figure is available in color online only.

tions via the SL-10 microcatheter confirmed occlusion of the sinus (Fig. 2C and D). After confirmation, 150–200 U swine thrombin (Sigma-Aldrich) was slowly injected over 20 minutes through the SL-10 microcatheter while the balloon remained inflated. After 20 minutes, the balloon was deflated and removed. Arterial pump runs and superselective sinus runs confirmed the sinus thrombosis (Fig. 3A and B). If insufficient thrombosis was achieved, the above steps were repeated.

Endovascular Thrombectomy

EVT was performed within 1 hour of sinus occlusion. A Trevo-18 microcatheter (Stryker) was navigated into the sinus beyond the occlusion. A 6 × 25-mm Trevo XP Stent Retriever (Stryker) was deployed for 5 minutes (Fig. 3C). The stent was subsequently retrieved into the Envoy guide catheter and removed to examine for thrombus (Fig. 3D). Additional arterial pump injections were done to confirm successful thrombectomy (Fig. 4A). Successful thrombectomy was defined as complete recanalization of the sinus using standard anteroposterior and lateral angiography. If

FIG. 3. EVT for sinus occlusion. **A:** The HyperForm balloon has been removed, and microcatheter injection reveals filling of the proximal sinus (yellow arrowheads) and sinus occlusion. The distal SL-10 marker (green arrowhead) is visible along with the catheter outline (blue arrowheads). **B:** Venous-phase cerebral angiography injection via the ascending pharyngeal artery revealing the occluded sinus segment (red arrowheads) with ongoing filling of the proximal SSS (yellow arrowheads) and torcular herophili (green arrowhead). **C:** Second-generation stent retriever (green arrowheads) is unsheathed in the sinus to perform EVT of the occluded SSS. **D:** The retrieved thrombus within the stent retriever. Figure is available in color online only.

ongoing occlusion or residual thrombus remained, additional attempts were made to remove the thrombus.

OCT Imaging

Intravascular OCT imaging was performed before and immediately following thrombectomy. The Dragonfly OCT catheter (Abbott Vascular) was used for image acquisition. The OCT catheter was navigated into the sinus via the monorail technique over the Transcend microwire (Fig. 4B). The following steps were sequentially followed for image acquisition: 1) loading an automated injection pump with 150 mL mixture of 50:50 contrast and saline (the pump is connected to the Envoy catheter in the ascending pharyngeal artery; this is used to clear the blood within the sinus lumen during OCT image acquisition); 2) injecting 3 mL/sec for 8 seconds total (24 mL total) via the pump; and 3) enabling the manual OCT pullback mode and initiating the pullback manually once the lumen begins to clear. The OCT catheter performs the motorized automated pullback of 54 mm total. The OCT imaging

FIG. 4. Postthrombectomy angiographic and OCT images. **A:** Angiogram demonstrating patency of the sinus (yellow arrowheads) after thrombectomy. **B:** The OCT catheter is navigated into the sinus via the monorail technique over a 0.014-inch wire. The distal marker (green arrowhead), lens marker (blue arrowhead), and fiber-optic wire (red arrowheads) are visible. Figure is available in color online only.

frequency is 100 frames per second, with a total of 540 cross-sectional images generated per pullback. Following successful imaging, the swine were euthanized with high-dose phenobarbital.

Results

Thrombosis of the SSS, mechanical thrombectomy, and subsequent OCT imaging were technically successful in 4 of the 5 swine. In the remaining swine, there were suspected valves in the bilateral internal jugular veins that could not be crossed with either a microwire or microcatheter. Various techniques and attempts, including venous injections with saline to collapse the valves, were unsuccessful. In the remaining 4 swine, access into the sinus was straightforward. Thrombosis was induced in 3 of 4 swine with a single thrombin injection, and 1 swine required a second injection of 100 U over 20 minutes. Recanalization of the sinus with a second-generation stent retriever was successful after one attempt in 3 of the 4 swine, with 1 swine requiring two attempts. OCT imaging after thrombectomy revealed regions of normal sinus anatomy (Fig. 5A). A thin layer of endothelium over dense connective tissue was observed, with bridging cortical veins draining into the sinus (Fig. 5A). In addition, regions of residual sinus luminal thrombus were observed despite complete angiographic recanalization (Fig. 5B). Thrombosed bridging cortical veins were also observed (Fig. 5C and D) before draining into the sinus.

Discussion

We describe the first preclinical animal model for CVST and mechanical thrombectomy. Using intravascular OCT, the luminal environment can be visualized after thrombectomy to assess the efficacy of the endovascular technique and devices used for recanalization. With this study, we were able to confirm the presence of ongoing thrombosis of bridging cortical veins despite recanalization of the CVS as one putative reason for poor patient outcome despite a successful procedure.

The goals of management of CVST include treating the

FIG. 5. OCT images of the CVS. **A:** OCT image obtained before mechanical thrombectomy, showing the normal sinus anatomy. Draining cortical veins (blue arrowhead) into the sinus and bridging cortical veins adjacent to the sinus (green arrowheads) are visible. **B–D:** OCT images obtained after thrombectomy, showing evidence of residual sinus luminal thrombus (red arrowheads), patent cortical veins (green arrowheads), and evidence of ongoing thrombosed bridging cortical veins (yellow arrowheads). Bar = 2 mm. *OCT lens artifact. Figure is available in color online only.

underlying thrombophilia, controlling raised intracranial pressure when present, halting the propagation of venous thrombosis, and recanalizing the sinus. Two randomized trials have shown that the initiation of early anticoagulation with unfractionated heparin or low-molecular-weight heparin appears to be safe and is associated with a decreased risk of morbidity and mortality.^{9,10} We hypothesize that in patients presenting with CVST without severe neurological deficits, and therefore unlikely to have a high burden of venous congestion and raised intracranial pressure, halting the progression of sinus thrombus with anticoagulation should allow the circulatory system time to remove the thrombus physiologically. The majority of patients (approximately 87%) will fall in this category and have good outcomes.³ However, a portion of patients will either present in a comatose state or continue to deteriorate clinically despite early anticoagulation. In these patients, it is likely that the burden of sinus and bridging cortical vein thrombus has exceeded the brain's ability to compensate, leading to significant compromise of venous drainage, venous infarcts, and raised intracranial pressure. In these cases, along with treating the underlying thrombophilia, timely thrombolysis (not merely halting propagation of sinus thrombus with anticoagulation) may be beneficial.

Several authors have described endovascular thrombolysis in this group of patients whose conditions deteriorate despite anticoagulation or who present with coma,

altered mental status, intracranial hemorrhage, or deep venous thrombosis.^{11,12} These small case series may be subject to publication bias. The only proposed randomized controlled trial to assess if endovascular thrombolysis improves the functional outcome of patients with a severe form of CVST was halted in 2017 due to futility.¹³

We suggest that, before this important clinical question is assessed in a trial, reliable preclinical testing of techniques and devices must be undertaken. Considering CVST's unique pathophysiology and large clot burden, the simple repurposing of arterial thrombectomy techniques and devices does not seem to work as intended. CVST is its own disease and may require a tailored approach. The literature describing device testing for arterial stroke is vast and comprehensive, and it is likely that the same level of innovation will be required to refine devices and techniques for CVST treatment.¹⁴ For example, venous clot shape, composition, total burden, and the interaction with devices, sinus wall anatomy, and overall dimensions may differ significantly from arterial stroke models.

Furthermore, in this study, evidence of residual sinus luminal thrombus was observed along with ongoing thrombosis of bridging cortical veins despite recanalization. This was seen on intravascular OCT but not apparent on cerebral angiography. Mechanical thrombectomy with a stent retriever may be able to recanalize the sinus but will not be effective in addressing thrombus in adjacent bridging cortical veins. Modern devices cannot access cortical veins safely, and the risk of perforation is likely high. We hypothesize that if a bridging cortical vein thrombus is observed after mechanical thrombectomy, direct intrasinus chemical thrombolysis may be warranted to dissolve the remaining clot. Patency of the sinus without patency of bridging veins (particularly if the vein drains an eloquent or large portion of the cerebral cortex) is unlikely to be beneficial. In addition, residual thrombus within the sinus may lead to reocclusion. These findings highlight the utility of intravascular imaging to visualize the luminal environment after thrombectomy.^{15,16}

The majority of previously published animal models of CVST surgically expose the SSS and produce sinus thrombosis via surgical ligation, injection of thrombotic material directly into the sinus, or topical application of ferric chloride. Wang et al. are the only researchers to have described a transvenous technique to occlude the sinus.¹⁷ They described prescreening swine with cerebral angiography and performed occlusion of the sinus in specimens with favorable anatomy, found in half of their animals. As the techniques and endovascular devices have improved over the past decade, we describe a technique to reliably thrombose the sinus and perform thrombectomy without prescreening. We acknowledge that primate anatomy most closely resembles cerebral venous drainage in humans; however, there are significant limitations in access to primates, and it is difficult to justify primate experiments for device or technique testing. Furthermore, this preclinical model was used to examine the efficacy of a second-generation stent retriever with respect to sinus recanalization. Other thrombectomy devices such as aspiration catheters, balloons, and combination techniques can be tested, given the relatively straightforward access

into the sinus. Pharmacological therapy with thrombolytics could also be assessed. If large-bore devices are tested, larger swine may be needed to accommodate the catheters.

There are several limitations to this preclinical model. The proposed preclinical CVST model describes sinus occlusion and subsequent thrombectomy and intravascular imaging. Although sinus recanalization is an important metric in the treatment of CVST, its use as a surrogate for clinical outcome is limited. Future studies are needed to evaluate which patients would benefit most from endovascular treatment for CVST based on neurological outcome. The thrombus in the swine sinus did not occur spontaneously, and therefore the thrombus may have different composition and mechanical properties compared with spontaneous human thrombus. Furthermore, to conduct the experiments, at a minimum a C-arm with roadmap capabilities is required, along with an experienced neurointerventionalist.

Conclusions

We describe a preclinical model to assess endovascular techniques and devices for the treatment of CVST. Repurposed devices from arterial stroke may not perform as expected, given the unique features of venous sinus thrombosis. Residual bridging cortical vein thrombus and residual sinus thrombus, visualized on intravascular OCT, may be present despite complete sinus recanalization on angiography, which might be the etiology of poor clinical outcome despite technical success. This model may be helpful in developing and testing a new generation of devices designed specifically for CVST treatment.

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Disclosures

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author Contributions

Conception and design: Pasarikovski, Keith, Ramjist, Dobashi, Priola, da Costa, Kumar, Yang. Acquisition of data: all authors. Analysis and interpretation of data: Pasarikovski, Ku, Keith, Ramjist, Dobashi, da Costa, Kumar, Yang. Drafting the article: Pasarikovski, Ku, Keith, Priola, da Costa, Kumar, Yang. Critically revising the article: Pasarikovski, Ku, Priola, da Costa, Kumar, Yang. Reviewed submitted version of manuscript: Ku, Keith, Ramjist, Dobashi, da Costa, Kumar, Yang. Approved the final version of the manuscript on behalf of all authors: Pasarikovski. Administrative/technical/material support: Yang. Study supervision: Yang.

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