# SUPPLEMENTAL MATERIAL

# Intracranial Dural Arteriovenous Fistulae

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*Keywords:* Intracranial, Dural Arteriovenous Fistula, Shunt, Cortical Venous Drainage, Borden-Shucart, Cognard, Zipfel, Barrow

*Running Header:* Intracranial Dural Arteriovenous Fistulae

**Abbreviations:* AVM = Arteriovenous Malformation; CCF = Carotid-Cavernous Fistula; dAVF = Dural Arteriovenous Fistula; CS = Cavernous Sinus; CVD = Cortical Venous Drainage; DSA = Digital Subtraction Angiography; ECA = External Carotid Artery; FLAIR = Fluid-Attenuated Inversion Recovery; ICA = Internal Carotid Artery; ICH = Intracerebral Hemorrhage; MRI = Magnetic Resonance Imaging; mRS = Modified Rankin Scale; NHND = Non-Hemorrhagic Neurological Deficit; SRS = Stereotactic Radiosurgery; TAE = Trans-Arterial Embolization; TVE = Trans-Venous Embolization.

## ***Treatment Options:***

*Endovascular Treatment:* With refinement of microcatheter technology and newer liquid embolic agents, endovascular therapy is often the first line of treatment for the majority of intracranaial dAVFs.[1] The goals of endovascular therapy are related to dAVF location, angioarchitecture, and mode of presentation. For *dAVFs with CVD presenting with ICH* or NHND, the goal of treatment is rapid cure of the fistula via occlusion of the proximal segment of the draining vein to eliminate the risk of repeat ICH or worsening NHND. For *dAVFs with CVD presenting with more benign symptoms* such as tinnitus, the goal of treatment is also cure of the fistula, though endovascular treatment can be initiated in a more elective fashion given the less aggressive natural history associated with these patients. For *dAVFs without CVD presenting with intolerable symptoms* such as tinnitus, the primary goal of treatment is palliation of these symptoms given the benign natural history associated with these patients. This palliation is often achieved via partial embolization and flow reduction without necessarily obtaining complete radiographic obliteration of the dAVF. In selected cases, as discussed in the following paragraphs, endovascular therapy can also be utilized to reduce dAVF flow in preparation for surgical obliteration or in association with radiosurgical treatment.

Schematically, endovascular treatment can be divided into three main categories: (1) Transarterial embolization; (2) Transvenous embolization; and (3) Combined approaches. When utilized for curative purposes, the transarterial approach involves distal microcatheterization of arterial feeders and embolization with liquid embolic agents (**Supplementary Figure IA**), while the transvenous approach involves distal microcatheterization of the proximal draining vein or the involved dural sinus and embolization with liquid embolic agents or coils (**Supplementary Figure IB**). Once again, the sine qua non condition to achieve protection against future ICH or NHND from the dAVF is complete obliteration of the proximal portion of the draining vein (i.e. CVD).

Transarterial embolization to achieve complete dAVF obliteration while preserving a patent dural sinus can be pursued in two main anatomic situations: (1) When the dAVF drains into a parallel channel within a patent dural sinus that is compartmentalized; and (2) When the dAVF drains into a venous pouch immediately adjacent to a major patent dural sinus that is not compartmentalized. With recent development of large compliant balloons, an alternative to this standard transarterial approach has emerged—a strategy that combines transarterial liquid embolization under "the protection" of a balloon advanced through a retrograde, transvenous route and inflated during injection of the liquid embolic agent. In such a manner, the balloon preserves sinus patency while the liquid embolic agent occludes the pathological shunts within the walls of the sinus. In cases where a transfemoral approach to distal arterial feeders is impaired by extreme tortuosity of the feeding arteries or the presence of an isolated sinus, percutaneous puncture of parietal and occipital transosseus perforating arteries and surgical exposure of the isolated sinus, respectively, can be utilized to facilitate distal access to the dAVF. Importantly, as most dAVFs involving a major dural sinus do not have CVD, have a benign natural history, and carry very low rates of upconversion to dAVFs with CVD, it is critical that the risks of any potentially hazardous maneuver are carefully weighed against the possible benefits.

An alternative to transarterial embolization is a transvenous endovascular approach to reach the proximal draining vein and deliver liquid embolic material and/or coils to occlude this CVD to eliminate the risk of ICH and NHND. With newer endovascular techniques, the transvenous approach to occlude an involved patent dural sinus is rarely utilized and employed mostly for dAVFs of the parasellar (cavernous sinus) region.

*Microsurgical Treatment:* While endovascular embolization is the first-line treatment for many dAVFs, open microsurgery is often necessary when lesions are unable to be treated successfully or safely via endovascular techniques. Factors contributing to endovascular treatment failures include difficult venous and/or arterial access, incomplete fistula obliteration with recruitment of additional feeders, recanalization of embolized vessels, fear of non-target embolization, and challenging anatomical location. Specific examples where surgical intervention is often required include lesions located at the anterior fossa floor, tentorial region, and the superior sagittal sinus. For anterior fossa floor dAVFs, ethmoidal branches of the ophthalmic artery are typically the primary arterial feeders (**Figures 1C and 3**). As such, embolization carries risk of unintentionally sacrificing the ophthalmic artery with subsequent central retinal artery occlusion and ipsilateral vision loss.[2] Although many tentorial dAVFs can be treated with endovascular embolization using liquid embolic agents,[3] surgical disconnection can still be required in situations where safe distal catheterization of the arterial feeders is not possible or in cases of incomplete obliteration/recurrence after endovascular treatment. For superior sagittal sinus dAVFs, difficulties with arterial access and inability to safely sacrifice the posterior sinus may preclude safe and effective endovascular therapy.

Historically, surgical treatment of dAVF has involved direct ligation of dural arterial feeders and arterialized draining veins; complete resection of the dAVF including all of the involved dura; packing, occlusion, and/or resection of the offending dural sinus; skeletonization and arterial devascularization of the offending dural sinus (**Supplementary Figure IIA**); or combinations thereof.[4, 5] However, significant morbidity and mortality was associated with many of these techniques. Therefore, a more targeted surgical approach has emerged as the safest and most efficacious strategy for treating dAVFs having CVD. This involves selectively disconnecting the CVD by ligating the arterialized vein(s) as close to the fistula as possible (**Supplementary Figure IIB**).[4, 5] The primary goal of this surgical approach is complete disconnection of the most dangerous aspect of dAVFs—the CVD. Feeding dural arteries encountered during the exposure are also coagulated and divided. Non-arterialized cortical veins adjacent to the fistula, on the other hand, must be preserved to avoid the risk of venous infarction. The safety and long-term efficacy of this more selective surgical approach has been validated by multiple single-institution case series.[6-8] Importantly, partial dAVF treatment without complete elimination of the CVD fails to protect the patient against future ICH and NHND and may increase the risk of these neurological events due to venous outflow obstruction and worsening cortical venous hypertension.

While surgical corridors and strategies vary widely depending on dAVF location and complexity, most approaches utilize the safest and most efficient route to the arterialized CVD.[2, 9] Indocyanine green video-angiography[10] and intra-operative DSA[11] are invaluable tools to verify complete disconnection of the CVD and potentially total dAVF of the dAVF and reduce the necessity for dAVF retreatment.

*Radiosurgical Treatment:* SRS is a viable treatment option for carefully selected dAVFs, particularly those located in the cavernous sinus and the transverse/sigmoid sinuses.[12] Typically, a dose of 20 to 30 Gy is delivered to the dAVF at the 50% isodose line with dynamic planning to avoid sensitive surrounding neural structures. The use of SRS in the treatment of dAVF remains somewhat controversial, related in part to the paucity of large case control studies to support its routine use (in contrast to the endovascular and microsurgical treatment of dAVFs). Despite this shortcoming, a growing body of literature has supported the use of SRS as a primary treatment modality in carefully selected patients with dAVFs or in combination with embolization and/or microsurgery.[13] Good candidates for SRS include patients harboring dAVFs without CVD and without intolerable or progressive symptoms of increased sinus drainage (e.g., tinnitus), as symptom resolution would be expected to occur over a period of 1-3 years after radiosurgery. Patients harboring dAVFs with CVD may also be treated with SRS, though this should be reserved for those presenting incidentally or with benign symptoms of increased sinus drainage (e.g., tinnitus) or those having significant medical comorbidities or especially complex dAVF anatomy that preclude safe endovascular or microsurgical therapy. Importantly, patients harboring dAVFs with CVD and presenting with aggressive symptoms of ICH or NHNDs are not good candidates for SRS given the latency period (≥ 1-3 years) required for fistula obliteration and the unacceptably high risk of ICH and NHND during that time.

## ***Treatment Outcomes:***

*Endovascular Outcomes:* In our series of 23 patients with Borden-Shucart type I fistulae (13 of which underwent endovascular embolization for disabling symptoms), dAVF obliteration was achieved in 4 (31%) patients and palliative flow reduction was achieved in 9 (69%) patients.[14] All patients with residual symptoms had undergone palliative, rather than curative, therapy. We observed a 0.0% rate of ICH, NHND, and dAVF-related deaths over a follow-up period of 5.6 years. No treatment-related complications occurred. One patient experienced spontaneous resolution of a partially-treated dAVF and 2 patients with partially-treated fistulas had symptomatic upconversion to a more aggressive lesion (0.8% annual risk of upconversion).[14] Signorelli et al.[15] published their series on 45 patients with intracranial dAVFs, 29 (64%) of which underwent transarterial embolization, transvenous embolization, or combination endovascular therapy. They documented a 65% rate of angiographic obliteration. One endovascular complication (ICH requiring craniotomy for evacuation) was noted. Chandra et al.[16] treated 41 dAVFs using single-agent Onyx embolysate. They observed an immediate angiographic obliteration rate of 95% with only a 2% rate of permanent neurological complications. Most (85%) fistulae were treated in a single session.

Based upon these and other single-institution retrospective case series, it appears that endovascular embolization (1) carries a low risk of peri-procedural complications, (2) is effective in ameliorating dAVF-related symptoms, and (3) affords excellent rates of angiographic obliteration. However, these results also indicate that re-treatment due to incomplete fistula obliteration and/or recanalization (particularly in patients with palliative flow-reduction for dAVFs without CVD) is sometimes necessary.

*Microsurgical Outcomes:* Gross and Du[17] reported a surgical series of 24 patients with Borden-Shucart type III lesions treated with microsurgery. They observed an angiographic obliteration rate of 96% after a mean follow-up time of 2.1 years. The permanent surgical morbidity and mortality rate was 17%. At last follow-up, 13 patients were asymptomatic (modified Rankin Scale [mRS] 0) and 18 patients were independent (mRS 0-2). One patient died from perioperative edema. Importantly, the microsurgical details of how the dAVFs were obliterated (e.g., selective disconnection of the CVD vs. more traditional approaches of complete dAVF excision with resection/occlusion of the involved sinus) were not included in this study. Liu and colleagues[18] reported a surgical series of 23 dAVFs with CVD in which nearly all were treated with a strategy of selective disconnection of the CVD. They documented a 100% rate of angiographic obliteration (mean follow-up = 45 months) with no permanent surgical morbidity or mortality. Kakarla et al.[19] reported a surgical series of 53 dAVFs with CVD in which the majority of patients were treated via selective disconnection of the CVD (though more traditional methods including sinus packing/obliteration, complete resection of fistula, and skeletonization of involved dural sinus were also employed). They noted that most patients (92%) had good or excellent outcomes, though the permanent surgical morbidity and mortality rate was 13%.

Van Dikj and colleagues[6] reported on a surgical series of 70 dAVFs with CVD and directly compared outcomes in those treated with selective disconnection of the CVD (n=52) vs. those treated with complete surgical resection of their dAVF (n = 18). They found that patients who had selective disconnection of the CVD had similar angiographic and clinical outcomes in long-term follow-up but had fewer rates of peri-operative complications (55.6% and 5.8%, respectively). There were no lasting adverse sequelae or mortalities in either surgical group. Wachter et al.[20] reported on a surgical series of 42 dAVFs with CVD in which the majority of patients were treated by selective disconnection of the CVD (n = 31). The authors achieved an angiographic obliteration rate of 97.6% for those fistulae not involving a dural venous sinus with an overall low rate of temporary and permanent surgical morbidity for all treated dAVF (11.9% and 7.1%, respectively; no mortalities). The rate of peri-operative morbidity was reduced to 4.8% when only the dAVF treated by selective CVD disconnection were considered. Al-Mahfoudh and colleagues[21] reported on a surgical series of 25 dAVFs with CVD in which all patients were treated with selective disconnection of the CVD. They observed excellent rates of post-operative angiographic obliteration (100%) with a low incidence of temporary peri-operative morbidity (4%) and mortality (0%).

In total, these single-institution retrospective case series suggest that dAVFs with CVD can be treated via microsurgical approaches with very high rates of angiographic obliteration / CVD disconnection, but with significant rates of permanent morbidity and mortality. They also suggest, however, that a surgical strategy of selective disconnection of the CVD offers outstanding protection against future ICH and NHND with substantially less surgical risk of peri-operative neurological deficits.

*Radiosurgical Outcomes:* One of the first reports of SRS treatment of dAVFs was from Barcia-Salorio and colleagues[22] in 1982 where they described the radiosurgical treatment of 4 patients with spontaneous, symptomatic CCFs. In a later series of 25 patients with CCFs treated with SRS,[23] the authors observed that most low-flow CCFs (e.g., Barrow Type B, C, and D; or parasellar dAVFs) had high rates of angiographic obliteration (e.g., 100%, 75%, and 86%, respectively; average of 7.5 months after SRS) with resolution of clinical symptoms (average of 2.4 months after SRS), while high-flow CCFs (e.g., Barrow Type A) did not demonstrate the same rate of treatment success. They concluded that high-flow, direct CCFs are likely best treated by endovascular means while indirect CCFs—or parasellar dAVFs—can be effectively treated via SRS.

Since then, radiosurgical data from numerous other authors have supported these early observations. Soderman and colleagues[24] documented their extensive 25-year experience with intracranial dAVFs (n = 58) treated by SRS. After 2 years, the authors noted a 68% fistula obliteration rate with significant flow attenuation in another 24% of cases. Based upon these results, they concluded that SRS is an effective therapy for dAVF with a low risk of complications. They acknowledged that SRS was most appropriate for dAVFs without CVD with intolerable clinical symptoms, but likely not for fistulas with CVD given the high rate of incomplete obliteration and the latency of protection against ICH and NHND. Park et al.[25] reported on their series of 20 dAVF patients (8 dAVFs without CVD and with intolerable symptoms; 11 dAVFs with CVD and without ICH or NHND) treated with SRS alone. They reported a complete angiographic cure rate of 90% (n = 18) with subtotal cures of 10% (n = 2) at a mean follow-up time of 21 months. Notably, all symptomatic patients experienced complete relief of their presenting symptoms, and only one had a temporary complication after the procedure. In our experience, radiosurgery with or without particle embolization is very effective for dAVFs of the transverse/sigmoid sinus (usually Borden-Shucart Type I fistulae) and the parasellar region, but less effective for dAVFs with exclusive CVD (without drainage into a dural sinus).

*Multi-Modality Outcomes:* Some dAVFs with CVD are most effectively managed via a combination of endovascular, surgical, and/or radiosurgical therapy. For example, a high-flow fistula with eloquent arterial feeders may be partially embolized for flow reduction prior to microsurgical disconnection to reduce peri-operative complications. While several authors have shown this combination therapy to be quite effective (obliteration rates ~100%),[19, 26] the patient is subjected to the complication rates of both procedures and, therefore, the overall morbidity and mortality may be higher than either procedure alone. Similarly, Pollock et al.[27] published their series of 20 patients with cavernous sinus dAVF treated with SRS alone (n = 7) or SRS with transarterial embolization (n = 13). They found that SRS with transarterial embolization was more effective than SRS alone with regard to timing of symptom relief, but long-term angiographic obliteration rates were similar between groups.

## *Supplementary Table I:*

***Supplementary Table I: Classification Scheme for CCFs (Barrow Classification)***

| *Type* | *Arterial Supply* | *Drainage* | *Hemodynamics* | *Type of Fistula* | *Etiology* |
|---|---|---|---|---|---|
| A | Intracavernous ICA | CS | High-flow | Direct | Traumatic/Iatrogenic >> Spontaneous |
| B | Intracavernous ICA branches | CS | Low-flow | Dural | Spontaneous |
| C | Meningeal ECA branches | CS | Low-flow | Dural | Spontaneous |
| D | Intracavernous ICA branches and meningeal ECA branches | CS | Low-flow | Dural | Spontaneous |

CCF = Carotid-cavernous fistula; CS = Cavernous sinus; ECA = External carotid artery; ICA = Internal carotid artery

## *Figure Captions:*

*Supplementary Figure I:* Endovascular treatment of intracranial dAVF. In TAE, femoral arterial access is obtained (A) and a microcatheter is advanced anterogradely into the meningeal feeding artery as close to the fistulous connection as possible (A, upper panel). Embolization with liquid embolic material is performed (A, lower panel) to completely obliterate the fistula. In TVE, femoral venous access is obtained (B) and a microcatheter is advanced retrogradely through the venous system to the site of the fistula (B, upper panel). Embolization with liquid embolic agents and/or coils is performed (B, lower panel) to obliterate the fistula.

*Supplementary Figure II:* Microsurgical management of intracranial dAVF. Historically, craniotomy for skeletonization of the offending dural venous sinus and arterial devascularization (A, upper and lower panels)—with or without packing or resection of the sinus—was performed. A more targeted and equally efficacious surgical approach involves selective surgical disconnection of the CVD as close as possible to the site where the arterialized vein exits the dural venous sinus (B, upper and lower panel).

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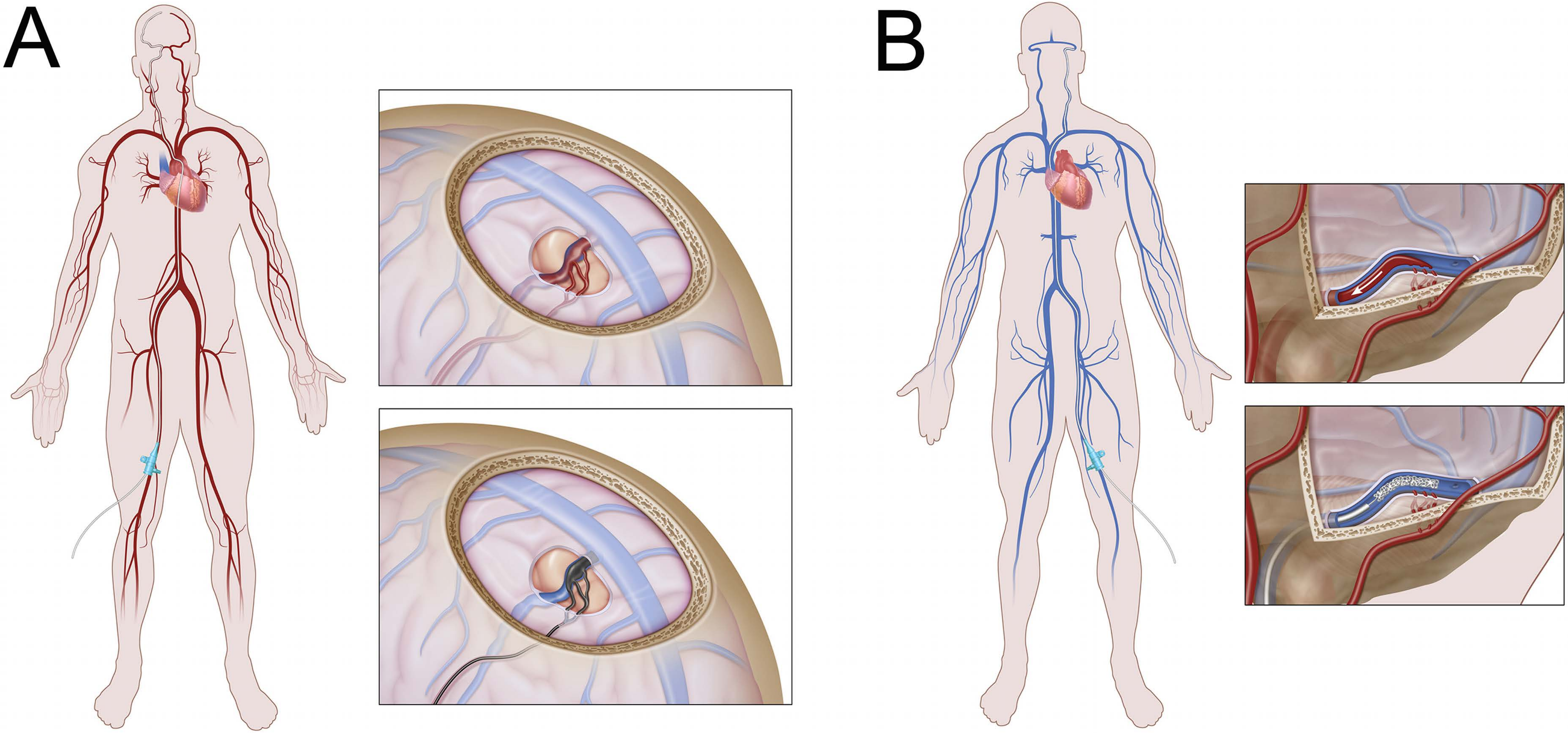
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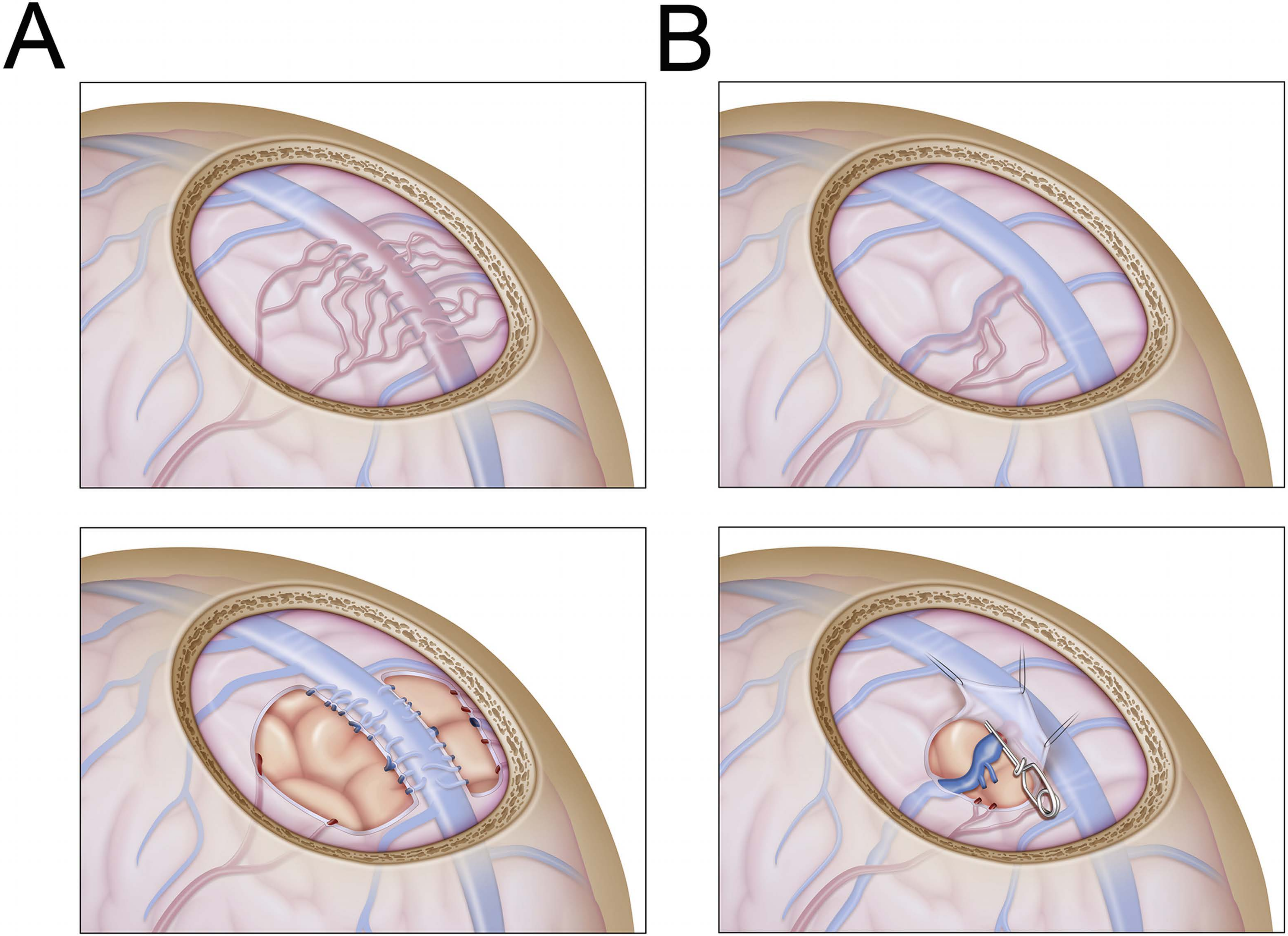
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