Use of a New Indocyanine Green Pooling Technique for Improved Visualization of Spinal Dural AV Fistula: A Single-Center Case Series

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■ BACKGROUND: **Intraoperative indocyanine green video angiography (ICG-VAG) is a useful tool in cerebral vascular surgery. In spinal procedures such as dural arteriovenous (AV) fistula, use of ICG-VAG is limited due to lower perfusion pressure. Therefore, we developed a new pooling technique with adapted workflow to improve intraoperative visualization.**

■ METHODS: **Patients operated on spinal dural AV fistulas using ICG-VAG were prospectively included. A new workflow for ICG-VAG was applied: 1) temporary clip placement at the suspected fistula point, 2) ICG administration during 100% oxygenation, 3) ICG pooling proximal of temporary clip, 4) clip removal/observation of vascular filling. Case records, clinical data, magnetic resonance imaging, digital subtraction angiography (DSA), and clinical outcome were analyzed retrospectively.**

■ RESULTS: **A total of 11 patients (median age 68 years, average course of disease 15 months) were included. Optimized, inverted workflow resulted in considerable pooling of ICG in the supplying feeder of the AV fistula in all cases. Complete obliteration was confirmed in 10 of 11 patients by postoperative DSA. However, 1 patient had an additional, preoperative radiologically undetected small feeder that enlarged until postoperative DSA and made successful reoperation necessary. After the median follow-up of 33.2 months, the Aminoff-Logue scale was decreased in all patients, and the McCormick score (modified Rankin score) was improved in 9 (8) patients and remained stable in 2 (3) patients.**

■ CONCLUSIONS: **Procedure modification in terms of ICG pooling enabled us to detect more easily the pathologic vascular architecture. ICG-VAG is a useful adjunct in the surgical treatment of spinal dural AV fistula because it is a real-time, noninvasive, and radiation-free technique with adequate image resolution.**

INTRODUCTION

Spinal dural arteriovenous fistulas (dAVFs) are usually located in the dural leaflets, typically at the intervertebral foramen.[1] Neurologic impairment from spinal dAVFs is attributed to arterialization of intramedullary veins with subsequent venous congestion, and infarction in some cases. The diagnosis of spinal dAVFs is often delayed because of the appearance of unspecific syndromes and the challenging clinical subsumption.[2] The treatment of spinal dAVFs requires interruption at the arteriovenous (AV) transition point, either by surgical occlusion or by endovascular embolization. As a safe, convenient, and reproducible technique, the uses for indocyanine green video angiography (ICG-VAG) have expanded rapidly into the realms of tumor surgery, bypass surgery, and carotid endarterectomy.[3-8] Recently qualitative ICG-VAG has been further enhanced by the new capability of flow analysis, based on fluorescence intensity measurements.[4] Intraoperative ICG-VAG has been implemented in spinal surgery to localize arterial feeders and the draining veins.[6,9-12] Furthermore, at the end of obliteration or resection, ICG may show a residual nidus or remnant AV shunting. However, the use of ICG-VAG in spinal surgery is limited due to a lower perfusion pressure in spinal

Key words
- Dural AV fistula
- Indocyanine green
- Video angiography
- Visualization

Abbreviations and Acronyms
AV: Arteriovenous
dAVF: Dural arteriovenous fistula
DSA: Digital subtraction angiography
ICG: Indocyanine green
ICG-VAG: Indocyanine green video angiography
MRI: Magnetic resonance imaging
mRS: Modified Rankin score

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vasculature and the sometimes complex anatomy and the low flow in smaller feeding arteries. Consequently, the ability to distinguish between the arterial and venous phase is often complex. Even more, sometimes a complex angioarchitecture of multiple feeders contributes to a dAVF.[13,14] The conventional ICG application before placing the clip commonly does not clearly show the feeding artery, and also, ICG remained in the suspected feeding arteries and was not completely washed out. Therefore, we sought to improve ICG-VAG in these cases by introducing ICG administration with "pooling" proximal to the clip to improve intraoperative visualization of the fistula point. Here, we report the applicability, side effects, and clinical outcome of a new ICG application protocol for spinal vascular lesions such as dAVFs.

MATERIALS AND METHODS

Patient Description

From May 2013 until January 2017, 11 consecutive patients with spinal dAVF were operated using the modified ICG-VAG application technique. Informed consent was obtained from each patient. This study was approved by the institutional review board (project no. 17-821) of the University of Munich, Germany. We conducted a prospective analysis of ICG application in patients with spinal dAVF. Demographic information, case records, radiological images, and operative outcome were traced, reviewed, and analyzed retrospectively. All patients who underwent AV fistula in this study underwent preoperative magnetic resonance imaging (MRI) (GE signa HDx 3T scanner) and digital subtraction angiography (DSA, Advanix; GE Healthcare, Little Chalfont, Buckinghamshire, United Kingdom). Also, all patients received postoperative MRI and DSA to verify if the occlusion of the dAVF was successful. Side effects and number of ICG applications were recorded. Postoperative clinical outcome was assessed daily during hospitalization and then after 3 months, 6 months, and every year. Clinical outcome was assigned by the modified Aminoff-Logue scale, the McCormick score, and the modified Rankin score (mRS). The last clinical follow-up was performed in May 2018.

Surgical Technique

All patients were treated by hemilaminectomy, the dura was opened, and the vascular anatomy of the malformation was exposed. During the operative procedure, somatosensory- and motor-evoked potentials were recorded in all cases. The fluorescent dye (indocyanine green, Verdy; Diagnostic Green GmbH, Aschheim-Dornach, Germany) was administered intravenously (10 mg per dose) during surgery. All operations were performed using a microscope-integrated infrared sensitive monochrome video camera (OPMI Pentero with INFRA-RED 800). The resulting video data were analyzed using the FLOW 800 imaging software (Carl Zeiss Surgical, Oberkochen, Germany). The following protocol was implemented under intraoperative monitoring (see Figure 1): 1) exposure of the arterialized medullary vein, 2) temporary clip placement at the suspected fistula point, 3) ICG administration and waiting for fluorescence signal in small peripheral arteries, 4) pooling of fluorescent ICG proximal of temporary clip, and 5) clip removal and observation of vascular filling. All patients underwent general anesthesia with propofol and remifentanil. Before administration of ICG (maximum cumulative dose <2 mg/kg body weight) patients were mechanically ventilated with pure oxygen for 5 minutes. ICG was given at a dose of 10 mg as a bolus injection, mechanical ventilation was halted for 10 to 20 seconds, and ICG-VAG was performed. During the procedure, oxygen was applied by apneic oxygenation and monitored by pulse oximetry. ICG-VAG was repeated if the intraoperative finding of the fistula point was not evident. After identification of the fistula point, the arterialized medullary vein was obliterated by coagulation. A final ICG-VAG was performed to confirm successful occlusion of the dAVF.

Video

Video available at www.sciencedirect.com

Statistical Analysis

For comparison between pre- and postoperative outcome, the χ^2 test was performed for categorical variables and the *t*-test for median scores. Logistic regression analyses were used to verify independent risk factors for the clinical outcome. Statistical significance was accepted at $P < 0.05$.

RESULTS

Patient Characteristics

From May 2013 until May 2016, 11 patients with a spinal dAVF (8 male, 3 female, median age 68 years with range 44–84 years) underwent surgical treatment using the new ICG pooling technique. Patient characteristics are given in Table 1, and the case of an exemplary patient is illustrated in Figure 2. In the preoperative MRI, perimedullary venous congestion was found in all patients and edema could be identified in 10 of 11 patients (83.3%). The median delay between symptom onset and clinical diagnosis was 16 months (median, range: 2–24 months). Diagnosis was confirmed in all cases via spinal DSA, where the fistula point was demonstrated. The location of the spinal dAVF was predominantly thoracic (9/11 patients, 81.8%) and lumbar and sacral (1/11 patients, 9.1%), respectively. Symptoms were basically lower limb numbness (10 patients, 90.9%), paraparesis (7 patients, 63.6%), ataxia (7 patients, 63.6%), and urinary/defecation dysfunction (5 patients, 45.5%). Two patients received unsuccessful endovascular therapy before surgery.

Surgical Results Using the New ICG Pooling Technique

The new protocol for administration of ICG was applied during a period of 100% oxygenation and a short breathing arrest during the fluorescence detection in the microscopic field. We applied ICG during ventilator arrest to avoid any movement during ICG-VAG and to avoid the impact of the intrathoracal pressure change, which could also affect the low flow in smaller feeding arteries. The optimized workflow resulted in considerable pooling of fluorescence signal in the supplying feeder of the AV fistula in 10 of 11 cases. Thereby, the imaging quality was improved compared with the standard protocol by receiving better ICG fluorescent signal due to pooling of the fluorescent dye proximal to the temporary clip (see Figure 3 and Video 1). The median ICG dose was 20 mg (range: 20–50 mg). No adverse reactions after ICG administration were seen. Complete obliteration

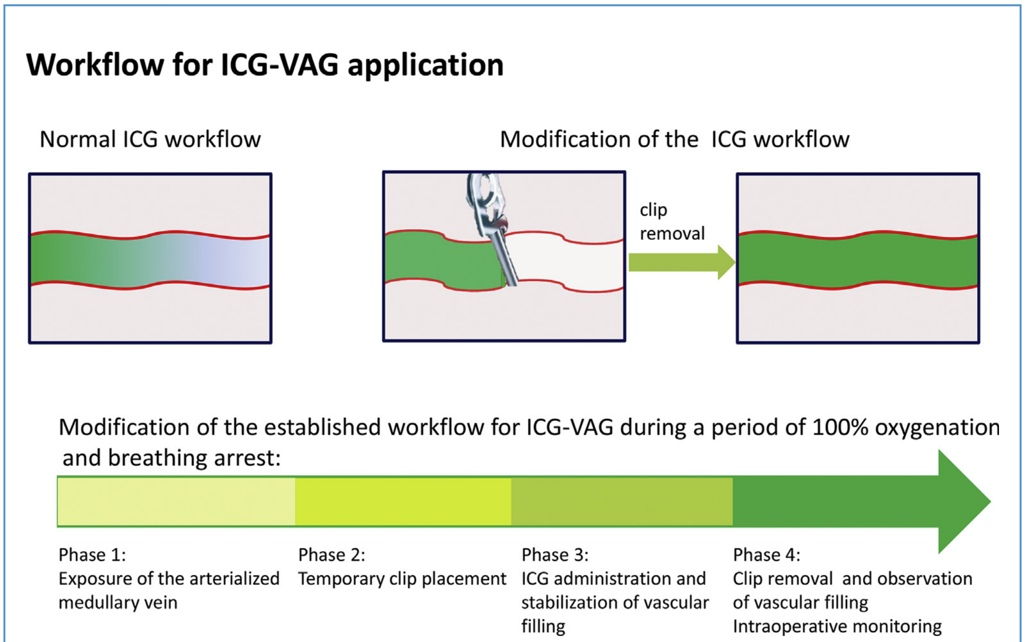

Figure 1. Workflow of the modified indocyanine green video angiography (ICG-VAG) application protocol.

was confirmed in 11 patients by postoperative DSA. However, in 1 patient, an additional, preoperative radiologically undetected small feeder was invisible during the first operation and enlarged under flow rearrangement until control angiography on the fifth postoperative day. This made reoperation necessary. This feeder was localized at the caudal part of the hemilaminectomy and could be identified as a second feeder after flow rearrangement in the ICG control. The second feeder was obliterated and the postoperative angiography showed no remaining feeder.

Neurologic Outcome

After a median follow-up time of 33.2 months (range: 2.2–16.0 months), the Aminoff-Logue scale decreased in all patients ($P < 0.278$), the McCormick score improved in 9 patients and remained stable in 2 patients ($P < 0.039$), and mRS decreased in 8 patients and remained stable in 3 patients ($P < 0.135$) (Figure 4). The outcome was defined favorable when the McCormick score was I–II and mRS was 0–2. In the logistic regression model, there were no favorable prognostic factors for outcome, which was predictable according to the small sample size.

DISCUSSION

The long-term results of our study confirm data of other groups in terms of demographic characteristics, clinical presentation, perioperative morbidity, and clinical outcome.[13-17] Male predominance, mainly thoracal location of the dAVF and the diagnosis in the sixth decade, is in line with other studies.[15-17] The clinical presentation included paraparesis, ataxia, and urinary/defecation dysfunction.[1,3,17] Unfortunately, the median delay between symptom onset and clinical diagnosis was still long with an average delay of 12.6 months, demonstrating the highly frequent misdiagnosis of this disease.[13] Previous reports showed a correlation between the severity of neurologic deficits, the delay of clinical diagnosis, and functional recovery.[18-20] A total of 81% of the patients showed an improvement of the neurologic deficits measured by the McCormick score, and 73% of the patients presented with a better mRS after long-term follow-up. In all cases, the diagnosis was made by angiography. We included the clinical data to rule out that the modification of an intraoperative (diagnostic) procedure might also have a negative impact on overall outcome. The clinical results of our series are in line with other studies on this rare disease, allowing us to conclude that the new ICG pooling technique does not alter the clinical outcome.

Recent reports demonstrated the use of dynaCT rotational angiography to detect the relationship of the fistulous point with the osseous structures in dual-volume mode in spinal dAVF.[21] However, this method is especially used for interventional fistula occlusion, where a precise location of the feeders and the relationship with the osseous structures is mandatory. Spinal angiography remains the gold standard for the diagnosis of the dAVF and contrast-enhanced magnetic resonance angiography might be useful for surgical planning.[22] However, intraoperative angiography will eventually only show that there is a detectable remaining flow in dAVF, but might not demonstrate if there are small additional feeders due to a lower perfusion pressure in spinal vasculature. Also, the technical effort is more demanding compared with ICG-VAG. Regarding therapeutic options, a recent meta-analysis showed that despite gaining popularity of endovascular therapy for spinal vascular malformations, the presence of multiple small feeders and failure of the embolic material to hit the draining vein resulted in a low rate of initial success and a higher recurrence rate.[13,22] In a meta-analysis,

Table 1. Patient Characteristics

Case Number	Age	Gender	Feeding Artery	Number of Feeders	Course of Disease (Months)	Clinical Details	Preoperative Embolization	ICG-VAG Findings	Number of ICG Injections	Postdisconnection ICG-VAG	Postoperative DSA	Resurgery
1	84	M	Th6 R	1	24	Hypesthesia L1, paraparesis, ataxia, wheel chair, suprapubic catheter	0	Th6 R	2	Complete	Same as ICG-VAG	
2	69	M	Th12 R	1	12	Hypesthesia lower extremities, paraparesis, ataxia, incontinence	0	Th12 R	3	Complete	Same as ICG-VAG	
3	47	M	Th7 R	1	24	Lumbago, paraparesis, ataxia, wheel chair, incontinence	0	Th7 R	3	Complete	Same as ICG-VAG	
4	53	M	Th4 R	1	24	Dysesthesia lower extremities	0	Th4 R	2	Complete	Same as ICG-VAG	
5	78	F	Th8 L	1	12	Hypesthesia lower extremities, paraparesis, ataxia, incontinence	0	Th8 L	5	Complete	Same as ICG-VAG	
6	71	M	S1 L	1	24	Claudicatio spinalis, incontinence	1	S1 L	2	Complete	Same as ICG-VAG	
7	61	M	Th6 R (2x)	2	2	Hemihypesthesia	0	Th6 R	2	Complete	Not same as ICGVAG	Resurgery
8	74	F	Th7 R	1	3	Hypesthesia lower extremities, paraparesis, ataxia, incontinence	0	Th7 R	2	Complete	Same as ICG-VAG	
9	64	F	Th5 L	1	10	Hypesthesia lower extremities, spastic, paraparesis, ataxia	0	Th5 L	2	Complete	Same as ICG-VAG	
10	68	M	L2 L	1	9	Hypesthesia lower extremities, paraparesis, ataxia	1	L2 R	2	Complete	Same as ICG-VAG	
11	55	M	Th8 L	1	24	Hypesthesia lower extremities, wheel chair, suprapubic catheter	0	Th8 L	2	Complete	Same as ICG-VAG	

DSA, digital subtraction angiography; ICG, indocyanine green; ICG-VAG, indocyanine green video angiography.

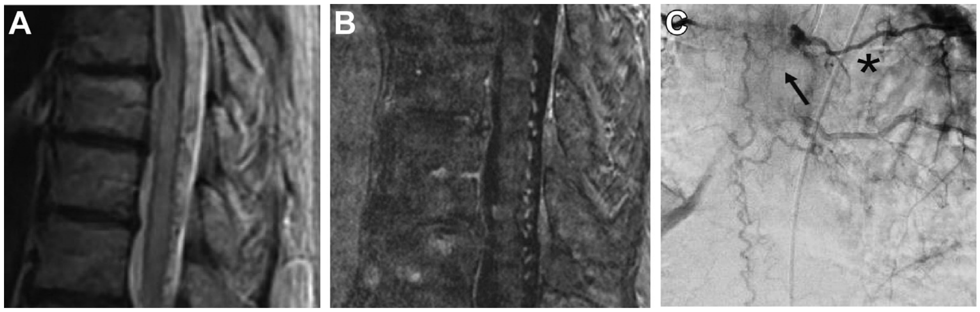

Figure 2. Preoperative magnetic resonance imaging (MRIs) and digital subtraction angiography (DSA) of a patient with a dural arteriovenous fistula from the left radicular artery Th5. The T2-weighted MRI shows edema (**A**), which is caused by a perimedullary venous congestion in ceMRA (**B**). DSA (**C**) shows a fistula that has its feeder from a left radicular artery Th5 (*asterisk*) and the fistulous connection (*arrow*). ceMRA, contrast-enhanced magnetic resonance angiography.

surgery seemed to be superior to endovascular treatment with a complete obliteration rate of 98% compared with 46%.[2,14] In some cases, the presence of multiple feeders led to higher recurrence rates after embolization. Therefore, it is important to evaluate the entire vascular supply of the suspected feeders, because the vessels may also supply the anterior or posterior spinal artery. For a better understanding of the complex angioarchitecture for surgical planning, the application of ICG was reported in recent studies.[9-12,23] The first study using ICG in spinal dAVF with complete obliteration of the fistula was performed in 2011. The restoration of the normal venous flow in the previously arterialized veins was confirmed by ICG-VAG.[24] However, it was discussed that ICG-VAG required a couple of minutes before dissipation of ICG fluorescence, requiring repeated time-consuming studies. Also, intravenous ICG brightened all vessels in the operative field, which made the identification of the arterial and venous phase difficult. Therefore, ICG was applied directly by intra-arterial injection in another study. Multiple short-interval evaluations of hemodynamic changes after obliteration were possible.[24] Also, in spinal AV malformations and perimedullary AV fistulas, ICG-VAG turned out to be a useful technical adjunct, especially when multiple feeders were apparent. The use of ICG-VAG improved the

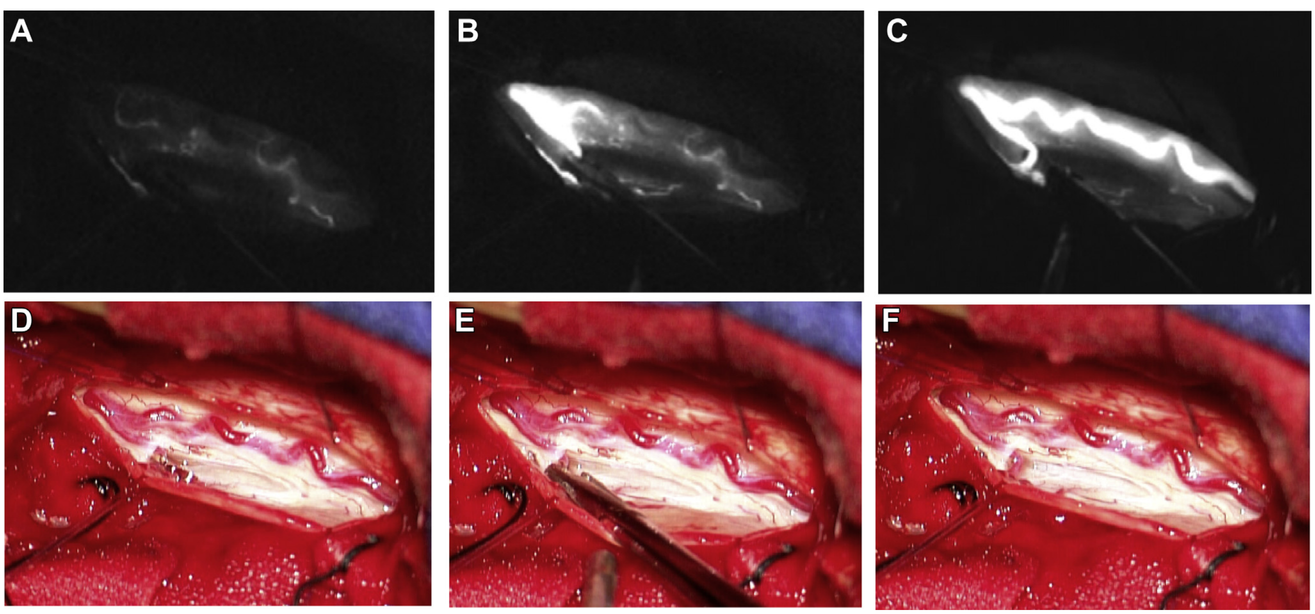

Figure 3. Intraoperative findings with indocyanine green (ICG) video angiography: (**A, D**) the left radicular artery Th5 was identified as a suspicious feeder. (**B, E**) This feeder was clipped and ICG was administered, pooling was awaited, and the clip was removed. (**C, F**) While breathing arrest and intraoperative monitoring, the ICG filling into perimedullary veins was observed.

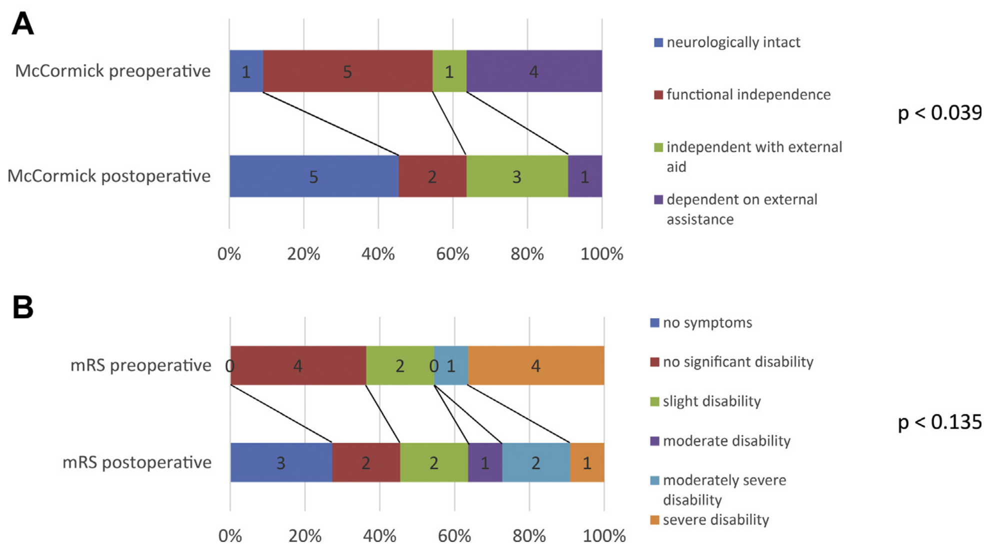

Figure 4. Clinical outcome according to the McCormick and modified Rankin scale (mRS).

visualization of the fistulous points, the nidus, and helped to preserve the normal feeding arteries and draining veins of spinal parenchyma.[11,12,23] Analytical color visualization and semi-quantitative analysis of the ICG-VAG data provided additional perfusion information about flow characteristics of the draining vein. Those recent developments showed additional information for the angioarchitecture, but the implementation of those semi-quantitative analyses in the clinical routine might be time consuming. Therefore, we developed this new protocol to simplify the operation procedure, to reduce the ICG application frequency due to an improved differential image quality. In most cases, the fistulous point could be identified by only 1 ICG injection and the obliteration could be confirmed by another second ICG injection. In our study, complete obliteration was confirmed in 10 of 11 patients by postoperative DSA. In 1 patient, a new feeding artery was observed through the collateral circulation of the spinal cord in the postoperative angiography. This points in the direction that we still consider postoperative angiography as a gold standard that cannot be replaced by ICG-VAG.[23]

CONCLUSIONS

Taken together, ICG-VAG is a useful adjunct in the surgical treatment of spinal dAVF because it is a simple, real-time, noninvasive, radiation-free technique with adequate image resolution. Furthermore, our study presents a new ICG pooling protocol, which overcomes previous ICG-VAG limitations, attributable to low-flow pathologic vessel architecture. Our data analysis reveals a favorable long-term clinical outcome in spinal dAVF.

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Conflict of interest statement: This work was carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans. This study was approved by the institutional review board (project no. 17-821) of the University of Munich, Germany. Informed consent was obtained from all patients. All authors have read and approved submission of the manuscript. JCT served on the advisory board of Roche, MerckSerono, Celldex and received speakers honoraria from Roche, MerckSerono, BrainLab, and Siemens. Except from this, this research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors. None of the authors has any personal, institutional, or financial interest in drugs, materials, or devices described in the manuscript.

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