Chapter 9
Intracranial atherosclerotic disease: Common, dangerous, and treatable

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INTRODUCTION

The use of endoluminal revascularization has revolutionized many areas of medicine, including cardiology and vascular surgery. More recently, the application of balloons and stents to the intracranial circulation has been made possible by rapid and constant developments in device technology. These advances have fostered the use of stenting for the treatment of various intracranial disorders, including atherosclerosis, aneurysms, and arterial dissections. Angioplasty and stenting for the treatment of intracranial atherosclerotic disease (ICAD) seems to be a natural extension of endovascular medicine. In this chapter, the rationale and indications for endovascular treatment of ICAD are presented. The technical aspects and future directions of endoluminal revascularization for ICAD are discussed.

ICAD: COMMON AND DANGEROUS

Atherosclerotic stenosis of the intracranial arteries is an important cause of the more than 700,000 strokes occurring annually in the United States (2). Although the true incidence is unknown, between 8 and 10% of ischemic strokes are attributed to intracranial atherosclerotic lesions (43, 50). The incidence of ICAD may be even higher, according to a review of 4748 angiograms in which the presence of this disease was identified in 22.6% of cases (18). ICAD is known to have greater prevalence in Asian, Hispanic, and African-American populations (43). Additionally, higher rates of ICAD are found in patients with cortical symptoms or signs (31). Unfortunately, the majority of patients do not present with a transient ischemic event or other warning sign to indicate the presence of ICAD; most come to the clinician's attention with the first-ever symptom of a major stroke (38).

MEDICAL THERAPY

The true natural history of patients with untreated, symptomatic, medically refractory intracranial atherosclerotic stenosis is unknown. For the anterior circulation, prospective data on the risk of stroke comes from the Extracranial-Intracranial Bypass Study (13). In that study, symptomatic middle cerebral artery stenosis incurred a 7.8% per patient-year incidence of ipsilateral stroke incidence among patients randomized to best medical therapy (5) After the Extracranial-Intracranial (EC-IC) bypass study demonstrated a worse clinical outcome for patients with middle cerebral artery stenosis, antithrombotic medications (antiplatelet agents, warfarin, or heparin) were the sole treatment for patients with symptomatic ICAD atherosclerotic disease (13). Even for patients with ICAD receiving antithrombotic therapy, the risk of stroke is significant (47). Despite maximal medical therapy, more than 50% of patients with severe ICAD experience recurrent ischemic symptoms, usually within the first month after the initial event (47). Moreover, the risk of recurrent stroke in these patients may be as high as 15% each year (7, 49).

The Warfarin-Aspirin Symptomatic Intracranial Disease (WASID) study retrospectively examined the benefit of aspirin (325 mg daily) versus warfarin (typically adjusted to maintain an international normalized ratio (INR) of 2.0 to 3.0) in

patients with symptomatic large artery intracranial stenosis (7). The risk of stroke in the territory of the stenotic artery was 10% in the warfarin group at 11 months and 23% in the aspirin group at 19.7 months. The risk of clinically and statistically significant hemorrhage was higher in the warfarin group, partially offsetting the neurological benefit. The results of this retrospective study led to the WASID prospective study in which patients with transient ischemic attack or stroke caused by 50 to 99% stenosis (angiographically documented) of a major intracranial artery were randomized to receive either warfarin (target INR, 2.0–3.0) or aspirin (1,300 mg per day) (8). The primary endpoint for the study was ischemic stroke, brain hemorrhage, or death from vascular causes other than stroke. After 569 patients (of the initial goal of 800) had undergone randomization, enrollment was stopped because of concerns about the safety of patients assigned to receive warfarin. During a mean follow-up period of 1.8 years, the adverse event rates were 9.7% in the warfarin group versus 4.3% in the aspirin group. The rate of death from all vascular causes was higher in the warfarin group as well (5.9% versus 2.3% in the aspirin group). These findings led the study investigators to conclude that medical therapy with warfarin was associated with significantly higher rates of adverse events and provided no benefit over aspirin for symptomatic ICAD. Clearly, an alternative therapeutic approach is needed for this patient population at high risk for stroke.

ENDOLUMINAL REVASCULARIZATION

In extracranial carotid atherosclerotic lesions, embolic ischemic injury is more common than hemodynamic failure. Although embolic events can also occur in patients with intacranial atherosclerotic lesions, reduced regional cerebral blood flow is the principal cause of symptoms in these patients. Therefore, the primary goal of endoluminal revascularization of intracranial atherosclerosis is to enhance blood flow through the affected artery.

Several variations of endoluminal revascularization have been reported for the treatment of ICAD. These include percutaneous transluminal angioplasty alone, conventional stenting (predilation of the lesion followed by stent placement during the same procedure), staged angioplasty and implantation of a balloon-expandable stent (angioplasty followed by stent placement at least 1 month later), and primary stenting (stent placement without preliminary angioplasty) (Fig. 9.1). Recently, the combination of angioplasty and self-expanding stent deployment has been described (19).

Percutaneous transluminal balloon angioplasty is the most simplistic endovascular approach for treating ICAD, even though it is associated with advantages and disadvantages. Angioplasty can be beneficial for some patients with intracranial atherosclerosis who remain symptomatic, despite aggressive antithrombotic therapy. However, complication rates associated with intracranial angioplasty alone have ranged as high as 20% (46). Intracranial angioplasty without stenting can lead to vessel dissection, vasospasm, distal embolization, or acute occlusion (9). Another drawback of this approach is recurrent stenosis, which can result from fibrosis caused by injury to the intima. Mori et al. found that eccentric intracranial atherosclerotic lesions that are 5 to 10 mm in length have a 31% rate of restenosis at 3 months; and lesions that are tortuous, angulated, or longer than 10 mm have a 67% rate of restenosis at 3 months (36). On the other hand, a more recent report suggested that angioplasty alone led to a reduction in the risk of further stroke in symptomatic patients (33). In this retrospective study, 36 patients with 37 symptomatic intracranial atherosclerotic lesions underwent primary balloon angioplasty and were followed for a mean duration of 52.9 months. The periprocedural death and stroke rate was 8.3% (two deaths and one minor stroke). Two patients had strokes in the territory of the angioplasty site at 2 and 37 months after the procedure, respectively. The annual stroke rate in the angioplasty territory was 3.36%.

Intracranial vessels have features that are unique in comparison with coronary or peripheral vessels, making them a challenge for achieving a technically successful result with endoluminal revascularization. These vessels are surrounded by cerebrospinal fluid and have less adventitia, less elastic tissue, and a greater proportion of smooth muscle, which may make them more prone to dissection or rupture (Fig. 9.2). Moreover, the bony confines of the petrous portion of the internal carotid artery make this vessel segment particularly difficult to dilate with an angioplasty balloon. Proximal bony encasement of the internal carotid and vertebral arteries complicates endovascular access to

distal vessel segments because, unlike arteries in other locations, the proximal vessel segments cannot be straightened with stiff wires. The potential serious consequence of occluding perforating vessels represents another unique feature of the intracranial vasculature (15).

Adjunctive stent placement has been shown to increase the safety and effectiveness of angioplasty in cervical carotid artery disease (51). Most of the published experience with angioplasty and stenting for ICAD thus far consists primarily of case reports and retrospective series (1, 12, 14, 17, 20, 35, 39). Most interventionists reserve intracranial angioplasty and stenting for patients with at least 50% stenosis who have symptoms despite antithrombotic therapy. (There may be a role for endoluminal revascularization in asymptomatic patients with documented poor vascular reserve and/or hypoperfusion, but this indication is less defined.) In one study, 10 patients with cerebral ischemic symptoms despite antithrombotic therapy and having intracranial stenosis of at least 60% underwent treatment with balloon-expandable coronary stents (34). The procedures were unsuccessful in two patients because the site of arterial stenosis could not be accessed. Among the eight patients (10 lesions) who underwent angioplasty and stenting, the stenosis severity was reduced from an average of 80% before treatment to 7% after treatment. No complications occurred during or after the procedures. No recurrent stenosis was evident on angiographic follow-up at 3 months, and no neurological ischemic events were observed during an average follow-up of 10 months in duration.

Another study reported stent-assisted angioplasty for the treatment of 34 patients with symptomatic intracranial atherosclerosis or dissections (32). The lesions were located in the anterior circulation (53%) and the vertebrobasilar system (47%) and produced a stenosis of at least 50% (mean 75%). One patient died after the procedure because of reperfusion-related hemorrhagic transformation and another died of a myocardial infarction, for a mortality rate of 6%. The transient procedural morbidity rate was 12%, and the transient neurologic morbidity rate was 6%. Follow-up angiograms obtained in 20 patients within 6 months showed an average stenosis of 18% with no evidence of recurrent stenosis.

In a series of 11 patients treated with stent-assisted vertebrobasilar angioplasty, three periprocedural deaths were reported in addition to one delayed death from a procedure-related brainstem infarction (28). Another patient had a pontine infarction after stenting, with subsequent residual diplopia. The remaining seven patients were symptom-free at an average of 4 months postprocedure. Follow-up angiograms at that time showed improved patency of the stented lesions in five patients (71%), minimal intrastent stenosis in one patient, and a new stenosis proximal to the stent as well as an aneurysm within the stented portion of the basilar artery in another.

In the more recent report of the Stenting of Symptomatic Atherosclerotic Lesions in the Vertebral or Intracranial Arteries (SSYLVIA) study, a new, flexible, stainless-steel stent designed for intracranial placement (Neurolink, Guidant Corporation, Indianapolis, IN) was successfully deployed in vessels in 58 of 61 (95%) symptomatic patients with stenoses in 43 intracranial arteries and 18 extracranial vertebral arteries (44). The stroke rates were 6.6% at 30 days postprocedure and 7.3% between 30 days and 1 year postprocedure. Significant recurrent stenosis (> 50% stenosis) was found in 30% of the patients, 65% of whom were asymptomatic. Vertebral ostial lesion, diabetes, more than 30% residual stenosis, and pretreatment vessel diameter were identified as predictors of postprocedure stenosis. Also recently, a technical success rate of 97.6% was reported in the treatment of 42 symptomatic M1 segment MCA stenoses in 40 patients with balloon-mounted coronary stents (21). None of the 38 patients for whom clinical follow-up was available experienced a stroke or a recurrent transient ischemic attack at 10 months. Angiographic follow-up imaging was performed in eight patients; postprocedure stenosis was identified in one of these.

According to results obtained from the cardiac literature, stenting in small arteries may lead to lower rates of recurrent stenosis than balloon angioplasty alone (23). In coronary arteries, a poor technical result may increase the risk of acute stent thrombosis or restenosis. An important factor associated with restenosis after coronary angioplasty and stenting is the degree of residual stenosis after the procedure (22). Nevertheless, marked improvement of flow in an intracranial vessel can be attained with modest enlargement of the lumen diameter (11). Because flow increases at the fourth power of the radius (Poiseuille's Law), any additional lumen gain may result in resolution of the symptoms. Thus, it may not be necessary to achieve a poststent vessel diameter equivalent to that of the parent vessel lumen. We strongly believe that limited submaximal revascularization with a final residual stenosis under 50% with

angioplasty alone or staged angioplasty and stenting is safer than primary, aggressive stenting (26, 29). Moreover, recanalization of a clinically significant, high-grade (> 50%) intracranial stenosis has been reported to cause a reperfusion hemorrhage (30). At our center, the performance of staged stent-assisted angioplasty for symptomatic intracranial vertebrobasilar stenosis was associated with low neurological morbidity (25). None of the patients treated experienced permanent neurological complications. The rationale of the staged approach is to minimally dilate a high-grade stenosis, thus increasing flow while minimizing the risk of a dissection or embolic shower. In this technique, the lesion is crossed with an undersized angioplasty balloon (rather than a higher profile device, like a balloon-mounted stent), which may lessen the risk of plaque dislodgement. The minimum 1-month interval between the angioplasty and stent procedure allows for the occurrence of a fibrous healing response induced by the angioplasty, which may lessen the risk of embolic shower or snowplowing (plaque forced into perforator ostia by stent struts resulting in perforator occlusion) (25) (Fig. 9.3). Although direct stenting has been shown to be safe in the coronary circulation (4), this technique may result in snowplowing and subsequent perforator occlusion. In addition to staged and direct stenting, conventional stenting (predilation of the lesion followed by stent placement during the same procedure) is also commonly used for intracranial stent deployment.

Two studies have recently reported the novel technique of angioplasty followed by deployment of self-expandable stents. In one of these, 15 patients with symptomatic ICAD were treated with a combination of balloon angioplasty and WingSpan (Smart Therapeutics/Boston Scientific, Natick, MA) self-expanding nitinol stent deployment (19). One case of transient neurological deterioration occurred due to the occlusion of an M2 middle cerebral artery branch during angioplasty. The symptoms of all the study patients had improved or were stable 4 weeks after treatment. The results of the WingSpan Multicenter Study were recently presented (6). Forty-five patients with symptomatic ICAD (stenosis severity > 50%) were treated with a combination of balloon angioplasty and self-expanding stent deployment. The procedure could not be performed in 1 of 45 patients for technical reasons. Of 44 patients treated, 50% of the lesions were in the anterior circulation, with nine located at the middle cerebral artery. The periprocedural incidence of stroke and death was 4.4% (two patients; one stroke, one stroke causing death). The severity of stenosis was 74.9% before treatment and 31.9% after angioplasty and stent deployment. Interestingly, implantation of the self-expanding stent resulted in further lumen gain, with a mean residual stenosis of 28% at the 6-month follow-up review.

PERIPROCEDURE MANAGEMENT AND INTRACRANIAL STENTING TECHNIQUE

Medical management

All endovascular procedures carry some risk of intimal injury with potential for thrombosis and vessel occlusion. Therefore, adequate antiplatelet and anticoagulation therapy should be administered to patients in preparation for tenting. Nevertheless, the selection and dosing of antithrombotic medications should also minimize the risk of hemorrhagic complications. Most information about antithrombotic treatment provided in conjunction with endovascular intracranial interventions has been obtained from the cardiac literature.

For elective angioplasty and stenting procedures for ICAD, patients are placed on aspirin (325 mg daily) and clopidogrel (75 mg daily) for at least 3 days before the procedure. Alternatively, a loading dose of clopidogrel (450 mg) and aspirin (650 mg) can be given early on the day of the procedure, with a minimum interval of 4 hours between drug administration and initiation of the intervention.

Platelet glycoprotein (GP) IIb-IIIa inhibitors can be used as an adjunct in cases where intracranial microdissection is noticed after angioplasty or in cases of intraluminal filling defect after angioplasty or stenting. These agents block the final common pathway of platelet aggregation by preventing the binding of fibrinogen to platelets and are the most potent of the antiplatelet drugs. Three intravenous GP IIb-IIIa inhibitors are abciximab (a monoclonal antibody), eptifibatide (a cyclic heptapeptide), and tirofiban (a nonpeptide mimetic). All three drugs have a rapid onset of antiplatelet activity and have been found to provide similar benefits in the setting of ischemic heart disease (48). However, reversal of platelet inhibition after infusion is more rapid with eptifibatide and tirofiban, and both agents are more specific GP IIb-IIIa receptor antagonists than abciximab (16). Abciximab can be given as an intravenous loading dose of 0.25 mg/kg 10 to 60 minutes before the procedure, followed by a 12-hour infusion at a rate of 10 µg/min. Alternatively, eptifibatide may be administered as an intravenous loading dose of 180 µg/kg before the procedure, followed by a 20 to 24-hour infusion of 2 µg/kg. It is advisable to maintain the activated coagulation time at

approximately 200 seconds when GP IIb-IIIa inhibitors are used along with a heparin infusion. Ideally, computed tomographic imaging should be obtained before starting any GP IIb-IIIa inhibitor infusion to rule out the presence of intracerebral hemorrhage.

For most intracranial stent procedures, an intravenous bolus dose of heparin (70 U/kg) is administered after catheterization of the target vessel. In addition, saline irrigation solutions are prepared with heparin (5 U/ml). An activated coagulation time of approximately 250 seconds is maintained for the duration of the procedure.

After stent placement, heparin therapy is usually discontinued, but not actively reversed. In some situations, such as when an angiographically visible dissection or thrombosis is present, the heparin infusion is continued to maintain the activated prothrombin time 1.5 to 2 times the baseline value. Aspirin (325 mg daily) and clopidogrel (75 mg daily) are administered for at least 4 weeks after the procedure (40, 41). When implanting drug-eluting stents, we prescribe this dual antiplatelet regimen for longer periods of time, varying from 3 to 9 months postprocedure, depending on the stent used.

Procedural technique

The technique of angioplasty and stent placement varies slightly for each case, depending on the clinical situation. The following is a general outline of the technique used for endoluminal revascularization in cases of ICAD at our center: The procedure is performed in an angiography suite with biplane digital subtraction imaging and fluoroscopic imaging capabilities. Sedative and analgesic agents are administered (rather than general anesthesia) to permit continuous neurological assessment while the patient is in an awake state. A 6-French sheath is inserted into the femoral artery. A 5-French catheter is advanced over a 0.035-inch hydrophilic wire into the aortic arch. The intracranial artery of interest is catheterized, proximal to the lesion. The sheath and catheter are then removed, with the wire left in place. A 6-French guide catheter is placed in the vessel. An angiogram is obtained, and road-mapping technique is used.

At this point, the most appropriate stent available for the case is selected. We cannot overemphasize the need to undersize balloons and stents for treatment of ICAD. Given the unique characteristics of intracranial vessels described above, the use of such devices drastically reduces the risk of complications. Two different techniques can be used to navigate the stent intracranially. One is to perform an exchange maneuver. In this technique, a microcatheter and a 0.014-inch microwire are used to cross the lesion, with the catheter and wire system being advanced a sufficient distance beyond the portion of the artery to be stented to provide enough scaffolding to support deployment of the stent, particularly if the vessel is tortuous. The microwire is removed; and a stiffer 300-cm, 0.014-inch exchange wire is placed through the microcatheter. This system is then advanced across the lesion. The microcatheter is withdrawn and a balloon-mounted, over-the-wire stent is navigated across the stenotic region and then deployed.

The second technique is direct stent navigation, in which a balloon-mounted or self-expanding stent is guided with the operator's wire of choice primarily into the target vessel. This technique has become more commonplace with the advent of more flexible, navigable stents. Direct stent navigation avoids the inherent risks associated with exchange maneuvers in the intracranial circulation and decreases the overall duration of the procedure. Stenting for intracranial atherosclerosis calls for a low-profile stent with a high degree of trackability to permit passage of the stent past narrow, potentially friable lesions.

Traditionally, with concepts applied from cardiology, the stent for such lesions should have a relatively high outward radial force to stabilize the plaque (i.e., to prevent the embolization of plaque fragments) and prevent vessel recoil. Currently, we use cobalt-chromium stents for this application. When deploying balloon-expandable coronary balloons, we tend to perform slow inflations, meanwhile watching for full expansion of the stent. In most cases, we are able to keep the deployment pressure below the nominal pressure for the device in use. Once again, our routine is to perform staged angioplasty followed by stenting at least 4 weeks after angioplasty. Stent placement is reserved for cases in which severe stenosis (> 50%) is apparent on the follow-up angiogram or in the event of persistence of symptoms.

THE ISSUE OF RESTENOSIS

As mentioned, high rates of recurrent stenosis have been reported in the early experience of stent-assisted angioplasty in the intracranial circulation. The recent success reported in clinical trials of drug-eluting stents for the treatment of coronary atherosclerosis has created expectations for intracranial atherosclerosis treatment (3, 10, 27, 37, 45). Sirolimus (rapamycin), an antifungal agent, and paclitaxel, a microtubule inhibitor, have been shown to prevent neointimal proliferation and restenosis in the coronary vessels (when compared with bare metal stents) (10, 42). In the Randomized Study with the Sirolimus-Eluting Bx Velocity Balloon-Expandable Stent (RAVEL), sirolimus-eluting stents prevented neointimal proliferation, regardless of vessel diameter (42). Neointimal formation and restenosis (at 6 months) were reduced in a prospective, randomized, multicenter trial involving the placement of paclitaxel-eluting stents in 536 patients (10).

These clinical results provided the impetus for experimental investigations of the effects of heparin-coated and sirolimus-eluting stent implantation in canine basilar arteries. The use of heparin-coated stents resulted in an average 12% luminal stenosis 12 weeks after implantation, compared with 22% in the bare metal stent group (24). Sirolimus-eluting stents (compared with bare metal stents) tended to reduce smooth muscle proliferation without impairment of endothelialization (27). No toxicity to the surrounding vessel wall or brainstem was found. These investigations have shown promising results. Further evaluation of the potential benefits of drug-eluting stents in the intracranial circulation is needed, and clinical studies are warranted.

The novel combination of angioplasty and self-expanding stent implantation provides a different perspective on intracranial vessels restenosis. The recently presented WingSpan Study showed a surprisingly low incidence of in-stent stenosis (10%, 4 of 40 cases with follow-up), with three cases being asymptomatic and only one symptomatic (6). Even though the follow-up period was brief (6 months in duration) and a small number of cases were treated, these results suggest that this approach, consisting of balloons and stents with a lower radial force, may result in a lower incidence of in-stent stenosis.

CONCLUSION

Intracranial atherosclerosis is a common disease and poses a high risk of stroke. Refinements in techniques and better comprehension of the disease process for optimal patient selection should improve the overall treatment results and will likely place endoluminal revascularization as the first-line treatment for ICAD. Strategies and devices specifically designed for the intracranial circulation are needed. Of paramount importance, future device development should consider the unique characteristics of the intracranial vessels. Validation of the concept of angioplasty and self-expanding stenting for the treatment of ICAD and upcoming clinical trials comparing medical treatment and endoluminal revascularization will benefit this population at high risk for stroke.

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Fig. 9.1 Case illustrating staged angioplasty and stenting: This 71-year-old woman presented with the sudden onset of left-upper extremity paresis. A magnetic resonance angiogram demonstrated severe stenosis in the M1 segment of the right middle cerebral artery (MCA) (A). Digital subtraction angiography confirmed the presence of the lesion (B). The patient initially underwent angioplasty of the lesion with a good revascularization result (C). Eight weeks after treatment, a follow-up angiogram was performed and demonstrated recurrent stenosis (D and E). Notice the normal vessel lumen at the right posterior communicating artery (PComA) with a fetal pattern. At this time, the MCA lesion was successfully stented using a 2.5-mm diameter stent (F). Three months later, the patient presented with transient

ischemic events referable to the right MCA distribution. A cerebral angiogram demonstrated in-stent stenosis (G), which was successfully treated with angioplasty (H). An angiogram 6 months later demonstrated good patency of the stented segment. Amazingly, the patient developed a new stenotic lesion at the origin of the right PComA (I), which was successfully treated with angioplasty alone (J). Fourteen months later, the patient is asymptomatic with no significant stenosis of the right MCA or PComA.

Fig. 9.2 Case illustrating the importance of undersizing devices to prevent catastrophic events: This 79-year-old woman was treated on separate occasions with limited submaximal angioplasty (stage 1 of planned 2-stage angioplasty/stenting) for symptomatic stenosis of the midbasilar artery and carotid angioplasty with stenting for asymptomatic but severe stenosis of the right carotid artery. Five months after the basilar angioplasty and 3 months after the carotid procedure, the patient (now asymptomatic) underwent a follow-up angiogram. This study revealed the presence of severe residual stenosis at the midbasilar artery (A). The decision was made to stent this lesion per our protocol because of the severity of stenosis and the poor natural history of this condition. A 4- × 13-mm Vision stent (Guidant) was selected, based on measurements obtained of non-diseased distal and proximal basilar artery segments of 3.3 mm and 3.8 mm, respectively. The stent was positioned (B) then deployed. Once the balloon inflation reached three atmospheres, the patient started complaining of a headache and eventually lost consciousness. A cerebral angiogram demonstrated contrast extravasation that was compatible with basilar artery rupture (C). The balloon was promptly reinflated to tamponade the bleeding. After multiple tamponade inflations of the balloon, the bleeding was controlled (D). Unfortunately, the patient did not tolerate the event and died 24 hours later.

Fig. 9.3 Case illustrating the snowplowing effect: This 77-year-old man presented with symptomatic stenosis of the basilar artery. Anteroposterior (A) and lateral (B) digital subtraction angiograms demonstrating 75% stenosis of the midbasilar artery. Digital subtraction angiograms (C and D) demonstrated endoluminal revascularization of the basilar artery following direct stent placement (Neurolink stent, Guidant). Two hours after stent deployment, the patient became densely quadriparetic and dysarthric. A computed tomographic scan of the head did not show any intracranial hemorrhage. Cerebral angiography demonstrated good patency of the stented vessel. Long TR-weighted axial magnetic resonance imaging demonstrated acute infarction of the pons after direct stenting of the basilar artery, resulting in dense quadriparesis (E), probably as a result of the occlusion of multiple perforators after stent deployment.