Intracranial Atheromatosis Disease (ICAD) and Stent Supported Angioplasty. A Long-Term Follow-up

Doença Ateromatosa Intracraniana (DAIC) e angioplastia com stent. Um seguimento a longo prazo

Guilherme Cabral de Andrade MD¹,²,³, Mirti Nelso Prandini PhD², Helvercio F. Poisagque Alves³, Eduardo Rafael Pereira¹, Walter M. Climaco¹, Roberto Parente Jr¹, Carmine P. Salvarani MD³, René Anxionnat MD¹, Luc Picard PhD¹, Serge Bracard PhD¹

1 - Service of Neuroradiology, CHU - Nancy / France.
2 - UNIFESP/EPM - São Paulo / SP / Brazil.
3 - CININ- Centro Integrado de Neurologia e Neurocirurgia - Maringá / PR / Brazil.

RESUMO
Objetivos: A doença ateromatosa intracraniana sintomática possui prognóstico desfavorável. A indicação do tratamento endovascular com angioplastia transluminal percutânea (ATP) assistida com stent deve ser realizada de acordo com: a eficácia, segurança, complicações e o risco de re-estenose a longo prazo. Material e Métodos: Estudo realizado entre 1996 e 2008, inclui 28 pacientes com estenoses localizadas na artéria carótida interna (11), artéria basilar (14) e artéria vertebral (5). Todos sintomáticos mesmo sob tratamento anticoagulante e stenose >60% (média de 83,5%). Resultados: Houve uma redução significativa do grau de estenose (inferior a 50%), com estenose média residual de 36,8%. Ocorreram duas complicações, com hematomas de reperfusão (6,6%). No seguimento a longo prazo, encontrou-se um único caso de reestenose e nenhum paciente apresentou acidente vascular cerebral isquêmico transitório ou definitivo. Conclusão: O tratamento das estenoses intracranianas com angioplastia assistida com stent é eficiente, com baixo índice de complicação e de reestenose nesta série.

Palavras Chave: Estenose intracraniana, angioplastia, AVC-i, Stent.

ABSTRACT
Objectives: The symptomatic intracranial atheromatous disease has unfavorable prognosis. The endovascular treatment with percutaneous transluminal angioplasty (PTA) assisted with stent must be held in accordance with the efficacy, safety, complications and the risk of restenosis in the long term. Materials and methods: A study conducted between 1996 and 2008 includes 28 patients with stenosis located in the internal carotid artery (11), basilar artery (14) and vertebral artery (5). All cases were symptomatic even under anticoagulation treatment and stenosis>60% (average 83.5%). Results: There was a significant reduction in the degree of stenosis (less than 50%) with average residual stenosis of 36.8%. There were two complications, with reperfusion hematoma (6.6%). In the longterm follow-up, a single case of reestenosis was found and no patient had a transient or permanent ischemic stroke. Conclusion: The treatment of intracranial stenosis with stent-assisted angioplasty is effective, with low complication and stenosis rate in this series.

Key words: intracranial stenosis, angioplasty, ischemic stroke, Stent.
INTRODUCTION

Intracranial atheromatous disease (ICAD) may evolve with a chronic hypoperfusion condition, emboli and arterial occlusion. It constitutes an important cause of ischemic strokes, especially in the black, hispanic and asian population corresponding to about 10% of all cerebral ischemic events in US, totaling between 70,000 to 90,000 ischemic strokes / year. In patients with stenosis greater than 50%, the annual risk of recurrent stroke can reach 15% and in cases of stenosis between 70% and 99% the risk of death ranges from 2% to 4 % per year. Intracranial stenosis is associated with several risk factors such as hypertension, diabetes mellitus, smoking, dyslipidemia, and no Caucasian race. Most studies define this type of lesion as radiologically significant when it presents stenosis greater than 50% of the normal artery caliber, combined with infarction in the region of the affected artery in the absence of sources of embolism7.

The evolution to an ischemic event can occur in different ways as perfusion failure with a compensation disability of collateral circulation, local thrombosis, arterio-arterial embolization and occlusion of perforating vessels. In a systematic review of retrospective studies of the circle of Willis arteries, analyzed separately, the internal carotid artery is the most affected, in about 50% of cases, with annual risk of ipsilateral ischemic stroke ranging from 3.1 to 8.1 % for ICA, up to 7.8% for MCA and up to 8.7% in the vertebral basilar system. The location of the arterial lesion has a direct influence on the annual death rate for stroke, with an annual average of 6.8% in the MCA stenosis, 11.6% in the vertebral basilar stenosis and 12.4% in the ICA stenosis, with a potentially variable risk represented by stenosis in different intracranial arteries7. A prospective multicenter study, GESICA2, showed that 60.7% of patients with significant hemodynamically stenosis had recurrent stroke or transient ischemia, in an average follow-up of 23.4 months, even with medical treatment and the combination of anticoagulation and antiplatelet at maximum doses. In a critical analysis of the natural history of intracranial atheromatous disease, a high rate for positive results with the endovascular treatment for severe stenosis was found.

MATERIALS AND METHODS

Between November 1996 and August 2008, 28 patients with 30 diseased vessels (Fig. 1), aged between 41 and 82 years old, average of 63.8 years, with symptomatic intracranial atheromatous disease, were treated with endovascular treatment with stent angioplasty, in the Service of Neuroradiologique du Centre Hospitalier et Universitaire (CHU) of l’Université Henri Poincaré Nancy-France and CINN Maringá, Brazil; 25 were male patients, aged from 41 to 82 years old and average of 62.8 years and three females, aged 44 to 76 years old, average of 68 years. The gender rate was 8M/1F.

Inclusion criteria were: (1) older than 18 and younger than 82 years old, (2) incidence of recurrent transient ischemic attack or ischemic stroke in maximum anticoagulant and antiplatelet therapy (100-325 mg of aspirin daily, 250mg per day of ticlopidine or clopidogrel 75 mg per day), (3) atheromatous stenosis greater than or equal to 60% and less than 99% diagnosed by digital subtraction angiography method WASID5, (4) stenosis affecting the major intracranial artery - the internal carotid artery (including the petrous and cavernous segment), basilar artery and vertebral artery (V4 segment), (5) having at least two vascular risk factors: hypertension, diabetes, hypercholesterolemia, smoking, history of coronary artery disease, peripheral arterial disease, preexisting atheromatous stenosis in another location or presence of plaques in the aorta, (6) absence of intraluminal thrombus, (7) NIHSS less than 15 at enrollment, (8) absence of permanent neurological deficit.

The vast majority of cases had stenosis greater than or equal to 60%, and in three cases (8.1%), symptomatic lesions amenable to treatment were found in more than one artery(Fig. 1, 2 and 3).

Figure 1. A,B,C and D: AB stenosis 95%, ASD lateral (black arrow) (A) ; DSA 3D (B) ; angioplasty procedure and stenting undersized (black arrow) (B) ; DSA PA control showing a 20% residual stenosis (black arrow) (C) ; and tomographic reconstruction of the stent showing the modification of the mesh by calcified plaque (D).

Figure 2. A,B,C and D: Right VA stenosis Mori B Type in 70%, DSA 3D (A) ; angioplasty immediately after balloon angioplasty and undersized stenting, in DSA 3D with residual stenosis 10% (C) ; and tomographic reconstruction of the stent showing the modification of the mesh by calcified plaque (D).

Figure 3. A,B,C and D: Mori A Type stenosis of the left ICA. DSA PA showing 85% stenosis (A) ; and lateral (B) ; and an anticipation of the time pressure of the superficial temporal artery (black arrows) in relation to MCA. Control by DSA PA (C) and lateral (D) after angioplasty followed by stenting with a 100% reperfusion and an major intracranial perfusion improvement with the return of the intracranial circulation of the MCA (white arrow) in anticipation of the superficial temporal as well as the perfusion of the ACA (white arrow).

Andrade GC, Pindá MN, Alvès HFR Pereira ER, Climaco VM, Jr RR, Salvareni CR, Anxionnat R, Picard L, Bracard S - Intracranial Atheromatosis Disease (ICAD) and Stent Supported Angioplasty. A Long-Term Follow-up.

**Therapeutic Interventional Procedure**

All patients were previously treated with antiplatelets, starting three days before the procedure, at a dose of 75 mg Clopidogrel (Plavix®, Sanofi, Inc) and aspirin 325 mg. After the procedure, they remained in the intensive care unit for 24 hours. The GP IIb/IIIa (Abximab - ReoPro®) inhibitor was available for an eventual necessity.

The procedure was performed under general anesthesia. During the procedure, 5000U heparin was intravenously infused in bolus, followed by 40IU/kg/h after femoral catheterization. A selective diagnostic angiography via femoral artery with 4F or 5F vertebral catheter, held in the carotid and vertebrobasilar systems. In the case of ICA stenosis, a common carotid injection was performed, to assess the difference in extra and intracranial arterial time. Then, selective catheterization of the internal carotid artery or vertebral artery in its V3 segment with a 6F guide catheter (6F Guider Boston) and 0.035 mm hydrophilic guide was performed, keeping continuously infused under pressure. Following the acquisition of 3D images, the diameter of the vessel in its normal segment, as well as the diameter of the stenotic segment, are analyzed by the software AW3D ANALYSIS GE MS (General Electric Medical Systems) on a Butterfly biplanar device or captorplan monoplanar Innova GE MS (General Electric Medical Systems). The stenosis grade is calculated by the equation: stenosis percent = [(1 - (Dstenosis / Dnormal)] x 100.

**Angioplasty and Stenting**

The endovascular treatment strategy varied according to lesion location and type of injury, according to the Mori classification type A, B or C. In Mori type C stenosis cases, > 95%, angioplasty procedure was performed initially, independent of the choice of the stent, with MAVERICK balloon (Boston Scientifc - Galway - Ireland). The techniques used were percutaneous transluminal angioplasty (PTA) followed by stent deployment, with coronary stent NeuroLink® (Guidan Corporation - Indianapolis, IN).

Using the negative images of the arterial system, “road mapping”, a GT Terumo microguide 0.016”/90° (Terumo – Tokyo - Japan) and a Rapid Transit™ microcatheter (Cordis - AA Roden - The Netherlands) or a GT Terumo microguide 0.012”/90° (Terumo - Tokyo - Japan) and an Excel 14 microcatheter (Boston Scientific - Galway - Ireland) were used for surpassing the stenosis. After placing the microcatheter distal to the injury, the microguide is replaced by a 0.014 CHOICE microguide of 300cm (Boston Scientifc - Galway - Ireland) left distal to the stenosis. The microcatheter is removed and, in a coaxial way, the MAVERICK angioplasty balloon (Boston Scinetific - Galway - Ireland) undersized at least 0.5 mm smaller than the adjacent normal vessel diameter and with a variable length from 10mm to 20mm depending on the extent of the injury, is placed in the stenosed segment, always with the concept of slow and progressive enlargement, but never reaching the nominal pressure of the balloon. If the existence of angiographic vasospasm is verified, a continuous infusion of 300 mg of papaverine through the 6F catheter is used.

A coronary stent NeuroLink® (Guidan Corporation - Indianapolis, IN) is positioned coaxially in the stenosed segment and released after a slow and gradual expansion of the balloon. The choice of stent dimensions always obeyed the evaluation of plaque extent, as well as the degree of stenosis, with the use of an undersized stent in the possibility of calcified plaque.

**Results**

Using the Kruskal-Wallis test, the degree of stenosis correlated with the location, did not reach significant value with p = 0.074. The basilar artery the basilar artery showed more severe stenosis and internal carotid showed less severe ones. Correlating the degree of stenosis with MORI classification, the result was significant with p=0.0001. The posterior circulation stenosis, vertebral artery and basilar artery, were more severe with most MORI B and C grades (Fig.4). The degree of residual stenosis after the procedure was not significant with p=0.43. The relative difference in the degree of residual stenosis, correlating with MORI classification, was not significant with p = 0.96. Mann-Witney test evaluated technology and grade of stenosis, with non-significant results p=0.78. The average residual stenosis as well as the relative difference in residual stenosis showed no significant result with p = 0.12.

The results show a degree of stenosis before the procedure ranged from 60% to 95% with an average of 83.5%. After the procedure it ranged from 0% to 50% with an average of 33.3%.

The degree of residual stenosis in the basilar artery was between 40% to 50% in half the cases. In one third of cases, it was between 30% to 40%. In the remaining cases the residual stenosis was 0% to 30%. In 25% of cases of carotid stenosis, residual stenosis was between 40-50%. In the remaining 75% of cases, residual stenosis rate was 30% or less. In the remaining cases, residual stenosis was less than or equal to 30%. In the AV stenosis, 25% had a residual stenosis between
40% to 50%, in 20% the residual stenosis it was 30% to 40% and in 55% the residual stenosis it was between 10% to 30%. The basilar artery showed the largest percentage of residual borderline stenosis between 40% to 50%, followed by ICA and AV (Fig.5).

Two complications (6.6%) occurred in a period of up to 30 days after treatment, with two late reperfusion hemorrhage and permanent neurological deficit. The first case of hemorrhage after stent occurred in a VA stenosis greater than 95% and the other in a stenosis of 95% AB. In two cases of ICA stenosis (5%) there was a technical failure. During clinical follow-up and with imaging exams, at least six months after the procedure, with an average of 18.7 months, only one case showed restenosis greater than 50% (3.3%). All patients had clinical and radiological follow-up with digital or AngioRM angiography from six months, up to 12 to 15 months, with patients who have up to 120 months of follow-up.

**Distribution for Mori Type and Artery**

Figure 4. Distribution of the stenosis, according to the Mori classification with Mori C type stenosis, most severe in the posterior circulation.

**Residual Stenosis After Stenting**

Figure 5. Residual stenosis after angioplasty / stenting, with higher amounts of stenosis between 40-50% in BA and VA.

**DISCUSSION**

The clinical treatment of symptomatic intracranial atheromatous disease must be exhausted before any indication for endovascular treatment. Currently it involves the combined use of aspirin, dipyridamole, statins, ticlopidine, clopidogrel, warfarin, and angiotensin-converting enzyme inhibitors. The WA-SID showed that the annual risk of stroke in patients treated with aspirin was 10.4% per year, while with warfarin it was 3.6% but with a significant hemorrhage rate4.

The ICA is the most common place of stenosis, reaching about 50% of cases. The first published series showed an annual risk of stroke of 11.6%. The intracranial ICA stenoses greater than 50% are directly related to an increased risk of ischemic stroke. In stenosis of the vertebral basilar system, the stroke rate may reach 14.3% annually and highly morbimortality reaching up to 50%.3 The functional anatomical area related to vertebral basilar system (brainstem) and ICA which involves large amount of brain tissue, is related to a higher rate of morbimortality in cases of extensive infarction17. The multicenter study GESI-CA23, with 21 participating centers, evaluated in a prospective way in a period of four years, 102 patients with stenosis of the middle cerebral artery, internal carotid, vertebral and basilar, noting a risk of recurrent ischemic events of 38.2 % in the stenosed artery territory in two years.

According to Poiseuille’s Law, flow is directly proportional to the fourth power of the radius artery in a laminar flow system: Flow= ΔΡr4/8, which means a significant increase in blood flow caused by a small increase in luminal diameter9. Another important principle observed was that intracranial arteries are less resistant to expansion when compared to coronary and extracranial arteries, because they lack the external elastic lamina as well as the extensive adventitial layer6.

GESICA23 multicenter study, in prospective evaluation of symptomatic stenosis equal to or grater than 50%, still showed high morbimortality, with 14.2%, morby-mortality of 14.2%, limiting its indication as first choice treatment of intracranial stenosis to medically refractory treatment cases.

A Latin American experience, where six centers treated a total of 33 injuries with stent mounted in balloon, all with stenosis greater than 50%, with an average of 68%, the complication rate was 6.2%, directly related to smaller diameter arteries, a stenosis of the MCA and M1 posterior cerebral. The mortality rate was 9.4%11.

The effectiveness of the endovascular treatment for intracranial atheromatous disease remains controversial, however, the use of angioplasty alone is not effective, with failure in 12.9% of the cases and the need for stenting in the same act22.
Complications of the method such as dissections, arterial perforations, thrombus formation during the procedure, as well as the formation of pseudoaneurysms were reduced after the systematization of a series of technical measures such as: general anesthesia, systemic anticoagulation with the use of heparin, subsequent therapy with platelet antiaggregation decreasing the deposition of fibrin and platelets on the endothelium altered by angioplasty, as well as the limitation of time dilation of the angioplasty balloon.

Other complications described in stent use are: subarachnoid haemorrhage, stent migration, occlusion of perforating arteries with segmental ischemic stroke and death. The presence of perforating arteries in the arterial segment compromised by the plaque as in the basilar artery, increases the risk of occlusion of these perforators, the “snow plow” effect, when the plaque is pushed against the ostium during stent implantation. However, submaximal dilation can reduce this complication.

Another uncommon complication, the hyperperfusion syndrome, which occurs due to loss of arterial pressure regulation, characterized by unilateral headache, facial and eye pain, convulsions and / or focal neurological deficit, preceding a hematoma or cerebral edema, occurs between 1 to 2% of the cases. The injury of the vertebrobasilar system (>90%) have a high risk of complications and may reach 28%, when added transient ischemia, permanent ischemic stroke and death. The risk of restenosis may vary from 0% to 25% in the vertebrobasilar system, reaching 36% of angioplasties in the anterior circulation in most patients, 61% asymptomatic at six month follow-up.

In our series, there were two cases of hyperperfusion: one in a right VA stenosis greater than 95%, with absence of the contralateral VA and the other in a 95% stenosis of the basilar artery, both cases with permanent neurologic deficit. The 6.6% morbidity rate was lower than presented in the literature, which may be related to a series of cases that include the indication with MRA or cerebral angiography. The injury of the vertebrobasilar system (>90%) have a high risk of complications and may reach 28%, when added transient ischemia, permanent ischemic stroke and death. The risk of restenosis may vary from 0% to 25% in the vertebrobasilar system, reaching 36% of angioplasties in the anterior circulation in most patients, 61% asymptomatic at six month follow-up.

In our series, there were two cases of hyperperfusion: one in a right VA stenosis greater than 95%, with absence of the contralateral VA and the other in a 95% stenosis of the basilar artery, both cases with permanent neurologic deficit. The 6.6% morbidity rate was lower than presented in the literature, which may be related to a series of cases that include the indication with MRA or cerebral angiography. The injury of the vertebrobasilar system (>90%) have a high risk of complications and may reach 28%, when added transient ischemia, permanent ischemic stroke and death. The risk of restenosis may vary from 0% to 25% in the vertebrobasilar system, reaching 36% of angioplasties in the anterior circulation in most patients, 61% asymptomatic at six month follow-up.

In the evaluation of stenting versus angioplasty, the post-pro-
in the Asian population, with follow-up of 3 years, noted that the functional assessment and the risk of late ischemic event was more favorable in patients treated with stenting. However there is an increased risk in cases of stenosis in arterial segments with perforating arteries such as middle cerebral artery and basilar artery which can be prevented with the option of the use of self-expandable stent.

## CONCLUSION

The intracranial atheromatous disease (ICAD) has significant risk of stroke even under medical treatment. Percutaneous transluminal angioplasty with stenting has been increasingly used at increasingly smaller risks due to technical and material evolution. Studies comparing the complications of conservative treatment and endovascular has been drawn. The risk of late restenosis has shown to be increasingly smaller when stent is used compared to the use of angioplasty alone. However, both the long-term patency and the risk of recurrent stroke in patients treated with stenting remain uncertain.

The analysis of the studied series indicate that symptomatic intracranial atherosclerotic arterial stenosis that initially may have endovascular treatment with stenting indication are those above 60% and located in the main arterial trunks (basilar artery, vertebral artery and ICA), with a resultant low (6.6%) complication rate. The experience shows a very low restenosis rate in this series (1/30), reducing the risk of stroke during a long-term follow-up. The multidisciplinary assessment should always be considered before any therapeutic approach in patients with intracranial atheromatous disease. In the absence of data to support endovascular treatment for intracranial atheromatous disease (ICAD), assisted angioplasty with stent remains a treatment option for patients at high risk of stroke even under drug treatment.

## REFERENCES


