JACC: CARDIOVASCULAR INTERVENTIONS
VOL. 7, NO. 11, 2014

ISSN 1936-8798/$36.00
PUBLISHED BY ELSEVIER INC.
http://dx.doi.org/10.1016/j.jcin.2014.05.021

Predictors of Carotid Occlusion Intolerance During Proximal Protected Carotid Artery Stenting

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ABSTRACT

OBJECTIVES The aim of this study was to identify predictors of occlusion intolerance (OI) developing during proximal protected carotid artery stenting (CAS).

BACKGROUND The use of proximal embolic protection devices, such as endovascular occlusion, during CAS has been demonstrated to be particularly safe and effective. However, endovascular occlusion can expose the ipsilateral hemisphere to hypoperfusion and produce transient neurological symptoms (OI).

METHODS From March 2010 to March 2012, 605 consecutive patients underwent proximal protected CAS at our institution. To identify independent predictors of OI, a multivariate logistic regression model was developed that included all patients' clinical/angiographic and procedural characteristics.

RESULTS OI developed in a total of 184 patients (30.4%). Compared with patients in whom OI did not develop, those who experienced OI had lower occlusion pressure (OP) (42.3 ± 12.7 mm Hg vs. 61.9 ± 15.4 mm Hg, $p < 0.001$). Receiver-operating characteristic curve analysis demonstrated that OP was the most consistent predictor of OI with a C-statistic of 0.85 (95% confidence interval [CI]: 0.82 to 0.88) with best cutoff being ≤40 mm Hg (sensitivity, 68.5%; specificity, 93.3%). By logistic regression analysis, the most powerful independent predictor of OI developing was an OP ≤40 mm Hg (odds ratio: 33.2, 95% CI: 19.1 to 57.7) and the most powerful clinical predictor of such OP was the presence of contralateral internal carotid artery occlusion (odds ratio: 3.1, 95% CI: 1.5 to 6.2).

CONCLUSIONS OI may occur in as many as one-third of the patients undergoing proximal protected CAS. This event is more common in those patients with an OP ≤40 mm Hg. Patients presenting with concomitant occlusion of the contralateral internal carotid artery more frequently have an OP ≤40 mm Hg. (J Am Coll Cardiol Intv 2014;7:1237–44)

Current guidelines recommend use of an embolic protection device (EPD) during carotid artery stenting (CAS) (1). Among the EPDs that are in clinical use, proximal EPDs have the advantage to provide cerebral embolic protection during all phases of the endovascular intervention (2). The use of endovascular occlusion, a proximal EPD, during CAS has been demonstrated to be particularly safe and effective in large registries and clinical trials (3,4). Moreover, the use of a proximal EPD has been associated with a reduced amount of cerebral embolization signals compared with distal protection devices (5).

Proximal EPDs act through the occlusion of the common carotid artery (CCA) and expose the ipsilateral cerebral hemisphere to the risk of hypoperfusion

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Manuscript received March 8, 2014; accepted May 8, 2014.

ABBREVIATIONS AND ACRONYMS

ACT = activated clotting time
CAS = carotid artery stenting
CCA = common carotid artery
CI = confidence interval
ECA = external carotid artery
EPD = embolic protection device
ICA = internal carotid artery
MACE = major adverse cardiac event(s)
OI = occlusion intolerance
OP = occlusion pressure
OR = odds ratio

with consequent transient neurological symptoms (occlusion intolerance [OI]) (2,4).

The ability to predict in advance the risk of OI, which is relatively frequent (3,4), might help the operators to be ready to deal with this event.

Thus, the aim of the present study was to identify the predictors of developing carotid OI during proximal protected CAS.

METHODS

STUDY POPULATION. From January 2010 to March 2012, 605 consecutive patients underwent CAS using endovascular occlusion with a proximal EPD at our institution. Inclusion criteria were the degree of internal carotid artery (ICA) stenosis, determined by angiography according to the North American Symptomatic Carotid Endarterectomy Trial Criteria (3): 1) asymptomatic stenosis ≥80% and 2) symptomatic stenosis ≥50%. Symptomatic was defined a carotid stenosis occurring within 6 months before the intervention, with amaurosis fugax, ipsilateral hemispheric transient ischemic attack, or ipsilateral ischemic stroke not resulting in a major residual neurological deficit (stroke scales: Barthel score ≤60; National Institutes of Health Stroke Scale score ≥15, or Rankin Scale score >3).

Patients with the following criteria were excluded: 1) presence of a critical stenosis of the ipsilateral CCA; occlusion of the ipsilateral external carotid artery (ECA); 3) contraindication to thienopyridines; and 4) refused to provide informed consent before enrollment.

CLINICAL ASSESSMENT. In each patient, clinical history and risk factors were assessed. Smokers included current and former smokers. Hypertension was diagnosed if the systolic arterial pressure was >140 mm Hg and/or diastolic arterial pressure was >90 mm Hg on repeated measurements or if the patient used antihypertensive drugs. Hypercholesterolemia was diagnosed if plasma total cholesterol was >200 mg/dl, plasma low-density lipoprotein cholesterol was >130 mg/dl, or if the patient used lipid-lowering drugs because of a history of hypercholesterolemia. Diabetes mellitus was diagnosed if plasma fasting glucose was >126 mg/dl or if the patient used hypoglycemic agents. Hospital records documented previous cardiovascular events or other comorbid conditions.

TECHNIQUE OF THE CAS PROCEDURE. All procedures were performed percutaneously with the patient under local anesthesia. At the procedure start, an 8- to 9-F, 25-cm long introducer sheath (Terumo, Tokyo, Japan) was inserted in the infrarenal aorta via the common femoral artery. After aortic arch angiography, selective bilateral carotid artery catheterization was performed using a 5-F JR4 diagnostic catheter advanced over a 0.035-inch soft hydrophilic wire (Standard Glidewire, Terumo). Once diagnostic angiography was completed, the wire was advanced into 1 of the ECA distal branches, the diagnostic catheter was advanced in the distal ECA, and then the hydrophilic wire was exchanged for a 300-cm, 0.035-inch stiff wire (Hi-Torque Supracore, Abbott Vascular, Abbott Park, Illinois). The endovascular occlusion device (Mo.Ma system, Medtronic Inc., Santa Rosa, California) was guided over the stiff wire until the radiopaque marker of the distal balloon was located in the ECA, at ~1 cm beyond bifurcation and in proximity to or at the superior thyroid artery (6). Then the distal balloon was inflated in the ECA and the proximal balloon in the CCA, thus blocking the antegrade and the retrograde flow across the target vessel. A 0.014-inch wire was then navigated through the ICA stenosis. Lesion pre-dilation was left to the operator's discretion, and self-expanding carotid stents were deployed (Carotid Wallstent, Boston Scientific, Natick, Massachusetts; X-Act, Abbott Vascular; Precise, Cordis, Miami Lakes, Florida; Acculink, Abbott Vascular; Cristallo Ideale, Medtronic). After post-dilation, at least 60 ml of blood was aspirated and filtered through sieves, checking for visible plaque debris. Blood flow was restored only after 3 consecutive aspirations free of debris, deflating first the distal balloon and then the proximal balloon. The final angiography included ipsilateral biplane carotid and intracranial views (3).

CONCOMITANT THERAPY. All patients received aspirin (75 to 160 mg/day) and should have been on ticlopidine (250 mg twice daily) for at least 7 days. Alternatively, patients received clopidogrel preload (300 mg) 24 h before the procedure. After the procedure, thienopyridines were continued for at least 3 months, whereas aspirin was continued for life. For anticoagulation, 70 to 100 IU/kg of heparin was administered before wiring the ECA, with the intention to achieve an activated clotting time (ACT) >250 s. Additional heparin was administered at the operator's discretion according to ACT values (7).

POST-PROCEDURAL PATIENT MANAGEMENT. Femoral sheaths were removed when the ACT was <150 s. Access site hemostasis was achieved by manual compression in all patients. If clinical signs of limb

ischemia occurred on the side of femoral access, sheaths were removed independently of post-procedural time and ACT values. A complete blood count was obtained before the CAS procedure and before hospital discharge. An independent neurologist assessed all patients (3).

DEFINITIONS AND ENDPOINTS. *OI* was defined as any transient neurological deficit observed during occlusion time, but showing a complete recovery within 20 min after restoring antegrade flow (4). *Occlusion time (time of flow blockage)* was defined as the time from the inflation to the deflation of the proximal balloon in the CCA (3).

Device success was defined as the ability to position, deploy, and retrieve the intact Mo.Ma device during the index procedure (3). *Protection success* was defined as complete blockade of antegrade blood flow in the ICA throughout the entire procedure (3). *Technical success* was defined as device success and the ability to successfully implant a carotid stent with a residual ICA stenosis <30% (3). *Procedural success* was defined as technical success without the occurrence of any major adverse cardiac or cerebrovascular event or unresolved OI during the index procedure.

The primary endpoint of the study was to evaluate the incidence of OI and the predictors of OI development.

The secondary endpoint of the study was to evaluate the incidence of major adverse cardiovascular events (MACE), including death, myocardial infarction, and any stroke in-hospital and at 30 days between patients in whom OI developed and those who did not have this procedural complication.

Neurological complications were classified as one of the following: 1) minor stroke defined as a new neurological deficit that either resolves completely within 30 days or an increase in the National Institutes of Health Stroke Scale score of ≤3; and 2) major stroke defined as a new neurological deficit that persists for >30 days and increase in the National Institutes of Health Stroke Scale score of ≥4 (8).

Patients were considered at high surgical risk if presenting with at least ≥1 high-risk criteria in either medical comorbidities (80 years of age or older, Canadian Cardiovascular Society angina class III or IV or unstable angina, congestive heart failure class III or IV, left ventricular ejection fraction <30%, left main and/or 2-vessel coronary disease, urgent [<30 days] heart surgery, recent myocardial infarction [<30 days], severe chronic lung disease, severe renal disease) or anatomic criteria (high cervical lesion, lesion below the clavicle, previous radical neck surgery or radiation, carotid endarterectomy restenosis, contralateral carotid occlusion, tracheostomy, contralateral laryngeal nerve palsy) (1).

FOLLOW-UP. All patients received a follow-up clinical assessment at 1 month. Clinical examination assessed overall general conditions, neurological signs and symptoms, medications, hospitalizations, or any type of complication that occurred after the procedure.

STATISTICAL ANALYSIS. Statistical analyses were performed using SPSS version 16.0 (IBM, Chicago, Illinois). Variables were expressed as absolute numbers and percentages or mean ± SD. Comparisons were made with the *t* test for unpaired samples or the chi-square test as appropriate. To identify the occlusion pressure (OP), occlusion time, and arterial pressure delta threshold levels that provided the best cutoff for OI prediction, we chose the values in which the sum of the specificity and sensitivity was the highest. This value was obtained by receiver-operating characteristic curve analysis. The C-statistic was used to assess the ability to classify risk.

TABLE 1 Baseline Characteristics of the Study Population (N = 605)

Age, yrs	70.8 ± 8.0
Age ≥80 yrs	88 (14.5)
Males	421 (69.6)
High surgical risk	289 (47.8)
Risk factors	
Smoking	437 (72.2)
Hypertension	546 (90.2)
Hypercholesterolemia	482 (79.7)
Diabetes mellitus	204 (33.7)
Comorbidity	
CAD	321 (53.1)
Symptomatic CVD	111 (18.3)
COPD	62 (10.2)
Medications	
Antiplatelet agents	605 (100.0)
Beta-blockers	272 (45.0)
RAS inhibitors	448 (74.0)
Statins	428 (70.7)
Carotid features	
Right ICA stenosis %	55.3 (37.4)
Left ICA stenosis %	53.2 (38.0)
ICA stenosis ≥90%	184 (30.4)
Ipsilateral ECA stenosis >75%	22 (3.6)
Contralateral ICA stenosis 75%–100%	91 (15.1)
Contralateral ICA stenosis 75%–99%	55 (9.1)
Contralateral occlusion	36 (6.0)

Values are mean ± SD or n (%).

CAD = coronary artery disease; CVD = cerebrovascular disease; COPD = chronic obstructive pulmonary disease; ECA = external carotid artery; ICA = internal carotid artery; RAS = renin-angiotensin system.

A multivariate logistic regression analysis was performed to identify predictors of OI. The first model was built using the occurrence of OI as a logistic binary variable and all the following variables as the predictors: ≥80 years of age or older; male sex; smoking history; hypertension; diabetes; hypercholesterolemia; chronic obstructive pulmonary disease; coronary artery disease; symptomatic status; the presence of string sign; the presence of ICA stenosis >90%; the presence of ipsilateral ECA stenosis; the presence of contralateral critical ICA stenosis (75% to 99%) and occlusion; and OP ≤40 mm Hg. A second model was then built using OP ≤40 mm Hg as logistic binary variable and all the following variables as the predictors: ≥80 years of age or older; male sex; smoking history; hypertension; diabetes; hypercholesterolemia; chronic obstructive pulmonary disease; coronary artery disease; symptomatic status; the presence of the string sign; the presence of ICA stenosis >90%; the presence of ipsilateral ECA stenosis; the presence of contralateral critical ICA stenosis (75% to 99%); and occlusion.

All statistical tests were 2-sided. For all tests, a p value <0.05 was considered statistically significant.

TABLE 2 Characteristics of the Patients According to the Occurrence of Occlusion Intolerance

	Intolerance (n = 184)	Tolerance (n = 421)	p Value
Age, yrs	71.5 ± 7.6	70.6 ± 8.2	0.192
Age ≥80 yrs	26 (14.1)	62 (14.7)	0.848
Males	124 (67.4)	297 (70.5)	0.438
High surgical risk	92 (50.0)	197 (46.8)	0.468
Risk factors			
Smoking	126 (68.5)	311 (73.9)	0.173
Hypertension	175 (95.1)	371 (88.1)	0.008
Hypercholesterolemia	154 (83.7)	328 (77.9)	0.104
Diabetes mellitus	69 (37.5)	135 (32.1)	0.193
Comorbidity			
CAD	111 (60.3)	210 (49.9)	0.018
Symptomatic CVD	34 (18.5)	77 (18.3)	0.956
COPD	19 (10.3)	43 (10.2)	0.967
Medications			
Antiplatelet agents	184 (100)	421 (100)	
Beta-blockers	91 (49.5)	181 (43.0)	0.141
RAS inhibitors	142 (77.2)	306 (72.7)	0.246
Statins	129 (70.1)	299 (71.0)	0.820
Carotid features			
ICA stenosis ≥90%	43 (23.4)	141 (33.5)	0.013
Ipsilateral ECA stenosis >75%	4 (2.2)	18 (4.3)	0.204
Contralateral ICA stenosis 75%–100%	39 (21.2)	52 (12.4)	0.005
Contralateral ICA stenosis 75%–99%	20 (10.9)	35 (8.3)	0.314
Contralateral occlusion	19 (10.3)	17 (4.0)	0.003
Procedure features			
Occlusion pressure, mm Hg	42.3 ± 12.7	61.9 ± 15.4	<0.001
Occlusion time, s	288.7 ± 107.7	291.7 ± 127.0	0.782
Arterial pressure delta, mm Hg	31.2 ± 28.7	25.9 ± 21.9	0.015

Values are n (%) or mean ± SD.
Abbreviations as in Table 1.

RESULTS

Table 1 shows the baseline characteristics of the study population. The patient population enrolled in this study exhibited a robust prevalence of cardiovascular risk factors. OI was observed in 181 patients (29.9%); nevertheless, in all cases, CAS could be concluded under cerebral protection. In most of these cases, symptoms started after stent post-dilation, during blood aspiration, and the procedure could be concluded under proximal protection. Only 6 patients (1.0%) showed immediate intolerance to balloon occlusion. In these patients, we decided to deflate the proximal balloon and use the Mo.Ma system as a guiding catheter. Briefly, the Mo.Ma was left in place with only the distal balloon inflated, and a filter was advanced in the ICA through the Mo.Ma working channel. Once the filter device was correctly placed distally to the lesion, stenting was completed under distal protection.

Device and technical success was achieved in all the patients. Protection success was achieved in all but those 6 patients (98.9%) who experienced immediate intolerance.

No patients died during the hospital stay, but 3 patients had a minor stroke and 2 patients had a major nonfatal stroke. The cumulative in-hospital incidence of death and stroke was 0.8%; consequently, procedural success was achieved in 99.2% of the cases. During the 30-day follow-up, no additional MACE occurred. Stroke incidence was not significantly different between patients in whom OI developed (1.6%) and those in whom it did not develop (0.5%; p = 0.149). All patients received a complete clinical assessment at 30 days.

Table 2 reports clinical and procedural characteristics of the study population according to the occurrence of OI. Notably, patients with OI were more likely to be affected by hypertension and showed a lower prevalence of subocclusive ICA stenosis (Table 2). Not surprisingly, the presence of significant pathology of the contralateral ICA was associated with higher rate of intolerance occurrence (Table 2). No differences between the 2 groups were observed with respect to other cardiovascular risk factors, age, and the presence of comorbidities (Table 2). Regarding procedural characteristics, patients in whom OI developed had a significantly lower OP and post-procedural blood pressure decrease (Table 2).

TABLE 3 Characteristics of the Patients in Whom Immediate Occlusion Intolerance Developed Versus Those in Whom Occlusion Intolerance Developed Later During the Procedure

	Immediate (n = 6)	Late (n = 178)	p Value
Age, yrs	79.5 ± 8.6	71.2 ± 7.6	0.010
Age ≥80 yrs	3 (50.0)	23 (12.9)	0.010
Males	4 (66.7)	120 (67.4)	0.969
High surgical risk	3 (50.0)	89 (50.0)	1.000
Risk factors			
Smoking	5 (83.3)	121 (68.0)	0.426
Hypertension	5 (83.3)	170 (95.5)	0.174
Hypercholesterolemia	3 (50.0)	151 (84.8)	0.023
Diabetes mellitus	3 (50.0)	66 (37.1)	0.520
Comorbidity			
CAD	5 (83.3)	106 (59.6)	0.242
Symptomatic CVD	2 (33.3)	32 (18.0)	0.340
COPD	1 (16.7)	18 (10.1)	0.604
Medications			
Antiplatelet agents	6 (100)	178 (100)	1.000
Beta-blockers	2 (33.3)	89 (50.0)	0.422
RAS inhibitors	3 (50.0)	139 (78.1)	0.107
Statins	1 (16.7)	128 (71.9)	0.004
Anatomic features			
ICA stenosis ≥90%	1 (16.7)	42 (23.6)	0.693
Ipsilateral ECA stenosis >75%	0	4 (2.2)	0.710
Contralateral ICA stenosis 75%–100%	3 (50.0)	36 (20.2)	0.079
Contralateral ICA stenosis 75%–99%	2 (33.3)	18 (10.1)	0.072
Contralateral occlusion	1 (16.7)	18 (10.1)	0.604
Procedure features			
Occlusion pressure, mm Hg	22.0 ± 4.9	43.0 ± 12.4	<0.001
Occlusion time, s	155.8 ± 116.7	293.2 ± 104.8	0.002
Arterial pressure delta, mm Hg	10.0 ± 10.9	31.9 ± 28.8	0.066

Values are mean ± SD or n (%).
Abbreviations as in Table 1.

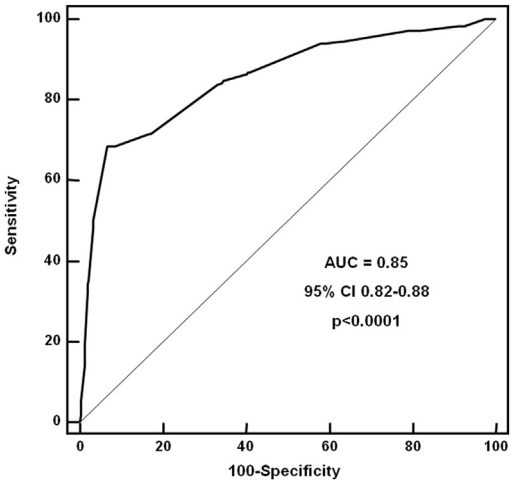

FIGURE 1 Occlusion Pressure Receiver-Operating Characteristic Curve

Receiver-operating characteristic curve showing sensitivity and specificity of occlusion pressure in predicting occlusion intolerance. AUC = area under the curve; CI = confidence interval.

Table 3 shows clinical and procedural characteristics of patients in whom OI developed immediately versus those in whom OI developed later during the procedure. Interestingly, patients in whom OI developed immediately were older those in whom it developed later during the procedure. Of note, OP and, obviously, occlusion time were significantly lower in immediate OI group.

PREDICTORS OF OI. Figure 1 displays the receiver-operating characteristic curve for OP in relation to the occurrence of OI. The OP cutoff value that provided the maximal sum of the specificity and sensitivity in predicting the intolerance was ≤40 mm Hg. The C-statistic (area under the curve) for OP was 0.85 (95% confidence interval [CI]: 0.82 to 0.88, p < 0.0001). In contrast, the C-statistics for occlusion time and arterial pressure delta were low and not significant (0.54, 95% CI: 0.49 to 0.57, p = 0.157 and 0.54, 95% CI: 0.49 to 0.57, p = 0.179, respectively).

The multivariate logistic regression analysis showing the predictors of OI is shown in Figure 2. The most powerful independent predictor was an OP ≤40 mm Hg (odds ratio [OR]: 33.2, 95% confidence interval: 19.1 to 57.7). Also, hypertensive status conferred a significantly higher risk of the development of OI (OR: 3.9, 95% CI: 1.5 to 10.3).

Figure 3 shows the clinical predictors of an OP ≤40 mm Hg. The clinical predictors of OP were the presence of contralateral ICA occlusion (OR: 3.1, 95% CI: 1.5 to 6.2) and, to a lesser extent, the presence of hypercholesterolemia (OR: 1.8, 95% CI: 1.1 to 3.1).

Figures 4 and 5 show the influence of arterial pressure delta and occlusion time on patients with and without an OP ≤40 mm Hg. Of note, whereas in patients with an OP ≤40 mm Hg, neither arterial pressure delta nor occlusion time interferes with intolerance occurrence, higher arterial pressure delta (≥50 mm Hg) and occlusion time (≥300 s) in those with an OP >40 mm Hg increase the chances of having OI.

DISCUSSION

Our study demonstrates the following. 1) The occurrence of OI is a frequent complication of proximal protected CAS, occurring in as many as one-third of

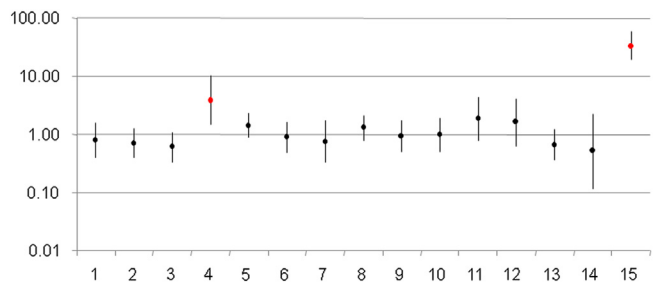

FIGURE 2 Predictors of Occlusion Intolerance

Multivariate logistic regression analysis showing predictors of occlusion intolerance. x-axis: 1 = age ≥80 years; 2 = male sex; 3 = smoking; 4 = hypertension; 5 = diabetes mellitus; 6 = hypercholesterolemia; 7 = chronic obstructive pulmonary disease; 8 = coronary artery disease; 9 = symptomatic stenosis; 10 = string sign; 11 = contralateral stenosis (75% to 99%); 12 = contralateral occlusion; 13 = stenosis >90%; 14 = external carotid artery stenosis; 15 = occlusion pressure ≤40 mm Hg. y-axis: odds ratio. **Black circles** = p = NS; **red circles** = $p < 0.05$.

the patients and is not associated with an increased risk of post-procedural MACE. 2) An OP ≤40 mm Hg is the most powerful independent predictor of OI. 3) An OP ≤40 mm Hg occurs more frequently in those patients with concomitant contralateral ICA occlusion. 4) In those patients with an OP >40 mm Hg, an occlusion time >300 s or a post-procedural arterial systolic blood pressure decrease of ≥50 mm Hg increases the chances of OI.

It is accepted that EPDs lower the stroke risk with CAS. In theory, a proximal EPD may afford better neuroprotection for 2 important reasons. First, a proximal EPD affords neuroprotection throughout all phases of the procedure, including initial lesion crossing, whereas distal EPDs must cross the lesion before neuroprotection can be afforded. Proximal EPDs are able to capture particulate debris with high efficiency (2), and a direct in vitro comparative study between proximal and distal EPDs demonstrated better capture efficiency of large particles for proximal EPDs (2). Clinical studies using transcranial Doppler and/or diffusion-weighted magnetic resonance imaging have suggested that CAS-related microembolizations are effectively reduced with the use of EPDs (5,9,10). A recent meta-analysis demonstrated that the use of proximal EPDs for neuroprotection in patients undergoing CAS is associated with a minimal incidence of total stroke (1.71%) and composite MACE (2.25%) at 30 days (11).

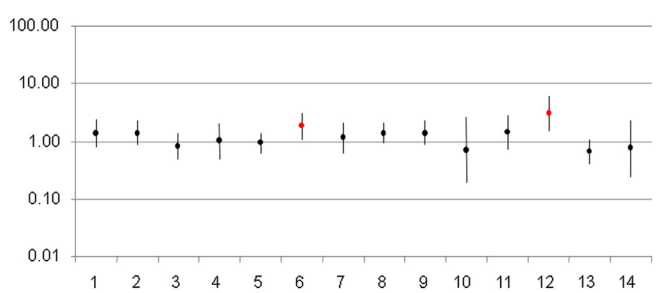

FIGURE 3 Predictors of Occlusion Pressure ≤40 mm Hg

Multivariate logistic regression analysis showing predictors of OP ≤ 40 mm Hg. x-axis: 1 = age ≥80 years; 2 = male sex; 3 = smoking; 4 = hypertension; 5 = diabetes mellitus; 6 = hypercholesterolemia; 7 = chronic obstructive pulmonary disease; 8 = coronary artery disease; 9 = symptomatic stenosis; 10 = string sign; 11 = contralateral stenosis (75% to 99%); 12 = contralateral occlusion; 13 = stenosis >90%; 14 = external carotid artery stenosis; 15 = occlusion pressure ≤40 mm Hg. Y axis: odds ratio. **Black circles** = p = NS; **red circles** = $p < 0.05$.

Proximal occlusion devices stop or reverse flow by occluding the carotid artery, much in the same way that a carotid endarterectomy accomplishes neuroprotection. An OP ≤40 mm Hg after occlusion of the CCA has been suggested to be a predictor of OI (12,13) during proximal protected CAS, and our study provides the definitive proof of this hypothesis. Measuring blood pressure (stump pressure) in the distal ICA during occlusion of the ICA is reported to be a reliable safety index to predict ischemia after permanent occlusion of the ICA (carotid sacrifice) performed for the management of complex cerebral aneurysms (14). Of note, the OP threshold of 40 mm Hg that we found associated with the development of OI corresponds to the literature regarding balloon test occlusion for carotid sacrifice used by cerebral angiographers (14). Even if other studies demonstrated in a different clinical setting that such low pressure is associated with the development of neurological symptoms, this is the first study to confirm this finding in the setting of proximal protected CAS. Careful monitoring of the distal OP on occlusion is therefore advised when proximal EPDs are used.

Moreover, our study demonstrates that those patients presenting a concomitant contralateral ICA occlusion are at increased risk of having an OP ≤40 mm Hg. With endarterectomy, a shunt is used to provide antegrade perfusion to reduce the risk of cerebral ischemia when a contralateral occlusion is present, as this condition represents an established high-risk feature and this is due to compromise of the patient's primary collateral pathway. Similarly, in our study, the most powerful clinical predictor of developing OI was contralateral carotid occlusion because in patients with this condition, the most important collateral pathway is lacking. During CAS, no shunt is possible, so the

presence of a contralateral occlusion could determine a poor tolerance of the device. During a proximal protected CAS, however, the duration of arterial occlusion is limited (3), and there are often other avenues for collateralization from the posterior circulation, and the device can be well tolerated, even in the presence of a contralateral occlusion. In a recent meta-analysis (11) on the use of proximal EPDs during CAS, a contralateral occlusion was present in 4.65% of the study population, yet OI requiring interruption of use or a change to an alternate protection method occurred in <1% of the patients. Furthermore, the presence of a contralateral occlusion did not predict a higher incidence of MACE. In high-volume centers with substantial experience with proximal neuroprotection, application of flow reversal embolic protection in patients with contralateral ICA occlusion has been done without an increase in adverse events.

Of note, in our study, the occurrence of OI was more frequent in hypertensive patients, and arterial hypertension remains significantly associated with a higher risk of the development of OI also on multivariate analysis, maybe because hypertensive patients are used to higher cerebral perfusion pressures. Patients with hypertension likely harbor an incompetent circle of Willis on cerebral angiography, and in the absence of large intracranial vascular collaterals, in these patients, pial collaterals and increased systemic hypertension are relied on to maintain their cerebral perfusion. In addition, pial collaterals are more likely to fail with endovascular occlusion.

Another important finding is that the presence of a tight stenosis of the target vessel was more frequent in those patients who did not experience OI, probably because the vascular bed fed by the treated artery is already adapted to hypoperfusion, whereas in patients with reduced stenosis severity, the ipsilateral hemisphere relies more on the target artery for perfusion, and their collaterals have not been clinically challenged before the procedure. Thus, a comprehensive evaluation of intracranial angiography and collateral pathways may be the best way to predict the development of OI before commitment of the patient to MO.MA device, but the findings of our study may be of great interest and utility because they suggest the clinical predictors of poor tolerance to this device, which can be evaluated before the procedure is performed.

Finally, our study suggests that the operator must pay a lot of attention to any procedural details. If the OP is ≤40 mm Hg, the chance of having OI is relatively high, and it will mostly occur during the phase of blood aspiration; therefore, the operator should be aware of this possibility to be ready to manage the patient's symptoms. On the other hand, if the OP is >40 mm Hg, the operator, to avoid the risk of OI, should complete the procedure within 300 s, and the systolic blood pressure should be monitored to avoid a decrease of ≥50 mm Hg, which can occur after stent deployment or post-dilation. In this regard, it is important to note that, in our study, the vast majority of patients experienced OI late in the procedure after stent post-dilation. This may be due to 2 important reasons: 1) as endovascular

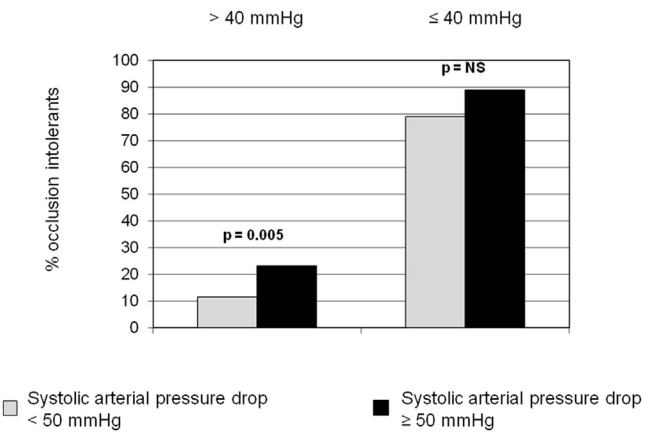

FIGURE 4 Occurrence of Occlusion Intolerance According to Occlusion Pressure and Systolic Arterial Pressure Drop

Bar graph showing the rate of occurrence of occlusion intolerance according to occlusion pressure and systolic arterial pressure decrease at procedure end.

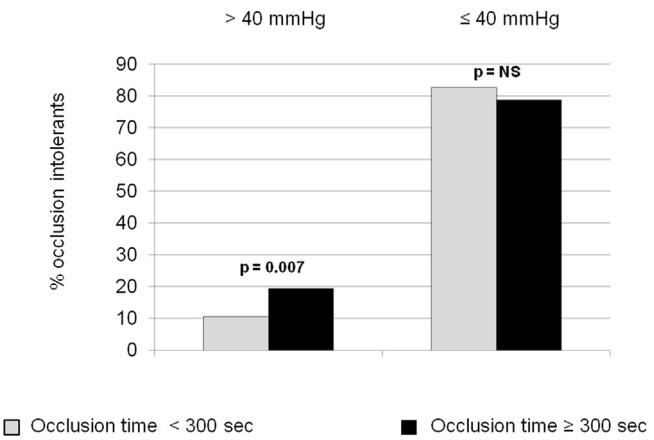

FIGURE 5 Occurrence of Occlusion Intolerance According to Occlusion Pressure and Occlusion Time

Bar graph showing the rate of occurrence of occlusion intolerance according to occlusion pressure and occlusion time

occlusion proceeds, there is a natural fatiguing of collateral patterns over time and 2) stent post-dilation often induces systemic hypotension due to a vagal response induced by carotid sinus manipulation, even if in almost all cases atropine was used to minimize this effect.

STUDY LIMITATIONS. This is a single center experience from a high volume institution with a robust experience on the use of proximal protection for CAS. The study's finding should be confirmed in a multicenter registry before being adopted in the clinical practice.

CONCLUSIONS

Our study provides relevant information to identify those patients who can experience OI during a proximal protected CAS, an event that can be easily managed if the operator is prepared to handle it.

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KEY WORDS carotid artery stenting, endovascular occlusion, occlusion intolerance