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Recanalization of the Chronically Occluded Internal Carotid Artery: Review of the Literature

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Key words
- Internal Carotid Artery
- Occlusion
- Recanalization
- Stroke

Abbreviations and Acronyms

COICA: Chronically occluded internal carotid artery
ET: Endovascular technique
HS: Hybrid surgery
ICA: Internal carotid artery
MCA: Middle cerebral artery
MoCA: Montreal Cognitive Assessment
SBP: Systolic blood pressure
TIA: Transient ischemic attack

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■ INTRODUCTION: **We reviewed the literature on interventions for patients with medically refractory chronically occluded internal carotid artery (COICA) to assess the risks and/or benefits after recanalization via an endovascular technique (ET) or hybrid surgery (HS, i.e., ET plus carotid endarterectomy).**

■ METHODS: **A systematic search of the electronic databases was performed. Patients with COICA were classified into 4 different categories according to Hasan et al classification.**

■ RESULTS: **Eighteen studies satisfied the inclusion criteria. Only 6 studies involved an HS procedure. We identified 389 patients with COICA who underwent ET or HS; 91% were males. The overall perioperative complication rate was 10.1% (95% confidence interval [CI]: 7.4%—13.1%). For types A and B, the successful recanalization rate was 95.4% (95% CI: 86.5%—100%), with a 13.7% (95% CI: 2.3%—27.4%) complication rate. For type C, the success rate for ET was 45.7% (95% CI: 17.8%—70.7%), with a complication rate of 46.0% (95% CI: 20.0%—71.4%) for ET and for the HS technique 87.6% (95% CI: 80.9%—94.4%), with a complication rate of 14.0% (95% CI: 7.0%—21.8%). For type D, the success rate of recanalization was 29.8% (95% CI: 7.8%—52.8%), with a 29.8% (95% CI: 6.1%—56.3%) complication rate. Successful recanalization resulted in a symmetrical perfusion between both cerebral hemispheres, resolution of penumbra, normalization of the mean transit time, and improvement in Montreal Cognitive Assessment (MoCA) score (ΔMoCA = 9.80 points; *P* = 0.004).**

■ CONCLUSIONS: **Type A and B occlusions benefit from ET, especially in the presence of a large penumbra. Type C occlusions can benefit from HS. Unfortunately, we did not identify an intervention to help patients with type D occlusions. A phase 2b randomized controlled trial is needed to confirm these findings.**

INTRODUCTION

Patients with medically refractory chronically occluded internal carotid artery (COICA) have an annual stroke risk of 5%—7%.[1-3] In addition, they suffer from cognitive impairment, with a significant decrease in their quality of life and in those that care for them.[4-7] Unfortunately, the cognitive decline goes unnoticed by physicians as it is not considered in the definition of "medically refractory." Furthermore, patients with COICA suffer from refractory hypertension,[8,9] which places them at a higher risk of end-organ damage such as retinopathy, left ventricular hypertrophy and heart failure, myocardial infarction, impaired renal function, and death.[10] Lowering their blood pressure can worsen cerebral hypoperfusion[11] due to loss of autoregulation, a phenomenon known as cerebral misery perfusion.[12] On the other hand, keeping elevated blood pressure goals increases by 50% their chances to experience an adverse cardiovascular event.[13] This emphasizes the importance of identifying candidates who will have more favorable outcomes with surgical intervention, and selecting the most appropriate surgical approach.

To date, there has not been an effective intervention that can fulfill the criteria above. We reviewed the literature on interventions for patients with COICA to assess the risks and/or benefits after recanalization via endovascular techniques (ETs) or hybrid surgery (HS, i.e., ET plus carotid endarterectomy). We evaluated the rate of successful recanalization and the associated changes in cognition, hemodynamic parameters, and control of symptoms.

METHODS

Study Design

Following Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines, we performed a systematic search of the electronic databases Ovid MEDLINE, EMBASE, and the Cochrane Library. Inclusion criteria were: 1) manuscripts published in English language; 2) original research studies (retrospective or prospective); 3) patients with COICA; 4) follow-up of 1 year or greater; and 5) at least 1 arm involved ET or HS. Studies were included if they reported the duration of occlusion, successful recanalization rate, and morbidity and mortality rates. Studies that met the inclusion criteria were reviewed and the following data were extracted: number of patients undergoing intervention, age, duration of occlusion before treatment, complications (minor and major), restenosis/occlusion rate, hemodynamic parameters, and cognitive outcomes.

Classification of Carotid Artery Occlusion

Carotid occlusion was defined as 100% cross-sectional stenosis of the vessel lumen as documented on computed tomography angiography or magnetic resonance angiography and confirmed with digital subtraction angiography. Chronicity was defined as $\geq$1 month of known occlusion of the cervical internal carotid artery (ICA) noted on imaging studies. We have previously suggested a classification of COICA that may be useful in the assessment of risks and/or benefits of endovascular intervention.[8] Briefly, this classification was derived from 100 angiogram images of patients with COICA from 4 institutions and relies on the morphology and location of the occlusion, and the presence (or absence) of reconstitution of the distal ICA. It yielded 4 types of occlusion: type A is a tapered occlusion with supraclinoid reconstitution of the ICA; type B is an abrupt occlusion (presence of a stump) with supraclinoid reconstitution; type C is a completely absent ICA from the bifurcation with supraclinoid reconstitution; and type D is a completely absent ICA from the bifurcation without supraclinoid reconstitution. Thus, in types A and B, the ICA is initially visualized with contrast injection, whereas it is not in types C and D.

Outcomes Assessment

Successful recanalization was defined as a final residual diameter stenosis $\leq$20%. Major complications were defined as periprocedural complications that resulted in significant morbidity or mortality, including symptomatic stroke (hemorrhagic or ischemic), reperfusion injury, or death. Clinically silent strokes were labeled as a minor complication. Bradycardia was defined as an observed drop in heart rate from baseline $\geq$20 beats per minute. Asystole was defined as the absence of a heart beat for greater than 5 seconds. Bradycardia and asystole were analyzed separately but were labeled as major complications if they warranted an intervention or were symptomatic (associated transient ischemic attack [TIA], stroke, or need for placement of a permanent pacemaker).

Statistical Analysis

Data analysis was performed in Python 3.7. A paired *t*-test was performed to evaluate the relationship between age and presence of bradycardia as ages were normally distributed. The assumption that each categorical ICA classification would result in a similar proportion of patients with bradycardia was assessed with chi-square (χ^2) analysis. The χ^2 test was also used to evaluate for any differences in success and complication rates between the types of COICAs. If equal variance or normality failed, we used nonparametric analysis of our data, such as Mann-Whitney U to compare the pre- and postoperative Montreal Cognitive Assessment (MoCA) scores. Significance was defined as a P value $<$0.05. We performed a Bayesian inference assuming a fix-effect model. The 95% highest posterior distribution served as the confidence interval (95% credibility interval [CI]) using the Markov Chain Monte Carlo algorithm in PyMC 3.6 (Python 3.7).

RESULTS

General Findings

Eighteen studies satisfied the inclusion criteria. Only 6 studies involved an HS procedure. The studies were heterogeneous and consisted of retrospective reviews of case reports and case series. Some studies had 1 interventional arm and 1 medical arm. We excluded studies that included bypass for the occluded carotid, regardless of the type of bypass. Table 1 presents the demographics, technical success, and overall complication rates of the studies, both individually and aggregately, and Table 2 presents the Bayesian meta-analysis. We identified 389 patients with COICA who underwent ET or HS. Male represented 91% of the sample. Age ranged from 50 to 82 years. The duration of occlusion ranged from 0.5 to 27.7 months. Follow-up duration ranged from immediate to 15 months after intervention. Reperfusion syndrome occurred in 2.6% of cases (95% CI: 1.2%–4.2%). Ischemic complications and hemorrhagic complications occurred in 3.6% (95% CI: 2.0%–5.5%) and 2.8% (95% CI: 1.3%–4.4%) of patients, respectively. The mortality rate was 2.6% (95% CI: 1.2%–4.2%).

COICA Classification Guides Successful Intervention and Disease Control

The rate of successful recanalization varied from 60% to 100% across the literature, with an overall mean of 95.4% (95% CI: 87%–93%) (Table 2). The overall perioperative complication rate was 10.1% (95% CI: 7.4%–13.1%), with a mean minor complication rate of 3.9% (95% CI: 2.2%–5.7%) and a mean major complication rate of 6.5% (95% CI: 4.0%–8.7%). This heterogeneity in the reported data suggests that specific criteria should be used when stratifying patients with COICA. In fact, a subgroup analysis based on the COICA classification proposed by Hasan et al[8] showed a significant difference in the success rate (P = 0.00028). For types A and B, the successful recanalization rate using ET was 95.4% (95% CI: 86.5%–100%) with a 13.7% (95% CI: 2.3%–27.4%) complication rate (Table 3). For type C, the success rate for ET was 45.7% (95% CI: 17.8%–70.7%), with a complication rate of 46.0% (95% CI: 20.0%–71.4%) for ET; however, for the HS technique that was developed to treat specifically type C patients, the overall success based on the 5 studies[25,29-32] was 87.6% (95% CI: 80.9%–94.4%), with a complication rate of 14.0% (95% CI: 7.0%–21.8%). For type D, the success rate of recanalization was 29.8% (95% CI: 7.8%–52.8%), with a 29.8% (95% CI: 6.1%–56.3%) complication rate.

Successful recanalization led to improvement in the neurological symptoms with control of the recurrent TIAs.

Table 1. Combined Demographics, Technical Success, and Complication Rates

Author (Year)	Patients	Age (Years)	Male	Occlusion Duration (Months)	Successful Recanalization, N (%)	Complications Major	Complications Minor
Ishihara et al (2006)[14]	1	70s	0	0.75	1 (100)	0	0
Thomas et al (2007)[15]	2	65.0 ± 7.0	2	3.5 ± 3.5	2 (100)	0	0
Kao et al (2007)[1]	30	72.1 ± 8	27	NA	22 (73)	1 (3)	0
Lin at el (2008)[16]	54	69.2 ± 9.8	48	7.9 ± 10.9	35 (65)	2 (4)	3 (6)
Bhatt et al (2009)[17]	1	50s	0	9	1 (100)	0	0
Terada et al (2010)[18]	15	66.1 ± 6.4	13	5.1 ± 3.6	14 (93)	1	1
Kim et al (2010)[19]	1	60s	1	NA	1 (100)	0	0
Shojima et al (2010)[20]	8	68 (50—78)*	8	19.4 ± 7.3	7 (88)	0	1 (13)
Yue et al (2011)[21]	17	63.6 ± 9.6	12	1.1 ± 1.0	12 (71)	0	0
Iwata et al (2012)[22]	4	75.5 ± 6.6	4	4 ± 0.8	4 (100)	0	0
Namba et al (2012)[23]	11	63.9 ± 9.5	11	4.3 ± 4.2	8 (77.2)	0	0
Rostambeigi et al (2013)[24]	1	50s	0	1	1 (100)	0	0
Shih et al (2013)[25]	3	63.3	3	NA	3 (100)	0	0
Fan et al (2014)[26]	18	65.2 ± 4.2	16	21 ± 6.7	16 (89)	2 (11)	0
Chen et al (2016)[27]	138	66.7 ± 9.8	115	NA	85 (62)	6 (4)	0
Bigliardi et al (2016)[28]	1	60s	1	3	1 (100)	0	0
Hasan et al (2018)[8]	37	65.8 ± 8.7	26	2.4 ± 3	22 (69)	2 (6)	4 (13)
Liu et al (2018)[29]	21	56	19	NA	15 (71.4)	2 (9.5)	4 (19)
Zhang et al (2019)[30]	30	54.5 ± 7.4	26	0.5—4	30 (100)	1 (3.3)	1 (3.3)
Li et al (2019)[31]	32	65.8 ± 8.0	25	NA	71.9	7 (21.8)	NA
Aggregate	389	67.2 ± 9.3	354 (91)	0.5—27.7	349 (89.4)	24 (6.7)	14 (3.9)

Counts listed as number (percent); continuous variables listed as mean ± standard deviation.
NA, not available.
*Excluded from aggregate statistics for age due to no standard deviation.

The probability of an ischemic event in the recanalized group was 13.4% (95% CI: 5.0%—21.6%) and in the group that failed recanalization 41.3% (14.1%—65.4%), which infers an absolute risk reduction of 27.9%. Thus, if this holds true in a prospective randomized trial, for every 4 patients with type A or B successfully treated, 1 stroke is prevented.

COICA Subgroups Have Different Types of Complications

In addition to the rate of complications, the type of complication depends on the type of COICA. Bradycardia occurred in 62% (36/69) of COICAs treated with ET, and in 0% of HS. There was no statistically significant difference in mean age between patients with and without bradycardia (63.36 years old vs. 67.71 years old, $P = 0.226$). There was a statistically significant difference in the observed proportion of bradycardic patients among COICA classifications: bradycardia occurred in 90% of type A, 80% of type B, 44% of type C, and 44% of type D ($P3 = 0.014$). It suggests that the development of bradycardia is associated with the proximity of the angioplasty to the carotid bifurcation. No events occurred with balloon angioplasty of the mid-distal cervical ICA. Two patients had intraoperative symptomatic bradycardia consistent with hemiparesis with facial droop, and 3 patients had intraoperative asystole. All patients had immediate resolution of their bradycardia and associated symptoms or asystole with immediate deflation of the balloon and treatment with atropine and/or glycopyrrolate with the exception of 1 patient (2.63%, 1/38) who required a permanent pacemaker.

Recanalization Can Reverse Hypertension

Successful recanalization leads to a reversal of the systolic hypertension, which was maintained at follow-up in 23 of 27 (85.7%) patients ($P < 0.001$). All subjects with failed revascularization (10/10) had no significant changes in systolic blood pressure (SBP). There was no significant difference in SBP at baseline between the 2 groups at baseline (successful vs. failed revascularization). However, successful recanalization significantly improved SBP values ($P < 0.001$). Patients who continued to have elevated SBP after

Table 2. Bayesian Meta-Analysis with the Inference of the 95% Credibility Interval

	Mean Probability (%)	95% CI Probability (%)
Overall success	90.6	87.7—93.3
Major complications	6.5	4.0—8.7
Minor complications	3.9	2.2—5.7
Total complications	10.1	7.4—13.1
Mortality	2.6	1.2—4.2
Reperfusion	2.6	1.2—4.2
Postoperative ischemic stroke	3.6	2.0—5.5
Hemorrhagic complication	2.8	1.3—4.4
Dissection	1.5	0.4—2.7
Perforation	1.8	0.7—3.1
Pseudoaneurysm	0.5	0.0—1.2
CCF	0.8	0.1—1.5
Restenosis	1.6	0.5—2.7
Bradycardia	68.4	56.5—79.5

CCF, carotid-cavernous fistula; CI, confidence interval.

Table 3. Outcomes of Intervention in COICA According to Type of Occlusion

	Mean Probability (%)	95% CI Probability (%)
Success for A and B using ET	95.4	86.5—100
Success for C using ET	45.7	17.8—70.7
Success for C using HS	87.6	80.9—94.4
Success for D using HS	29.8	7.8—52.8
Complications for A and B using ET	13.7	2.3—27.4
Complications for C using ET	46.0	20.0—71.4
Complications for C using HS	14.0	7.0—21.8
Complications for D using HS	29.8	6.1—56.3

CI, confidence interval; ET, endovascular therapy; HS, hybrid surgery.

revascularization (SBP > 120 mm Hg after procedure) developed hemorrhagic events within the first 24 hours after procedure (1 with type B, 3 with type C; described above). Thus, uncontrolled blood pressure contributed to 75% of all permanent complications (3/4) and 30% (3/10) of all complications.

Recanalization Improves Cognition

Only 3 papers in the literature have discussed cognitive outcomes in patients with COICA.[26,33,34] Lin et al[33] demonstrated that recanalization leads to improvement in cognitive outcomes, and Fan et al[26] showed an increase of 8 points in MoCA score after ET compared with the medically managed group. Zanaty et al[34] reported on 5 patients (2 males, and 3 females) and 6 COICAs. Large penumbra areas on computed tomography perfusion were associated with worse preoperative MoCA scores. Successful recanalization resulted in a symmetrical perfusion between both cerebral hemispheres, resolution of penumbra, normalization of the middle cerebral artery and improvement in MoCA score (ΔMoCA = 9.80 points; 95% CI: 7.37%—12.38%; P = 0.004) (Figure 1).

DISCUSSION

Although medically refractory COICA has a poorly defined natural history, it is known to result in recurrent strokes/TIAs, dementia, and refractory hypertension.[1-5,8,9] Furthermore, treating hypertension can lead to episodes of hypotension with watershed infarcts in patients with cerebral misery perfusion,[11,12,35,36] whereas keeping it elevated increases their chance of experiencing adverse cardiovascular events, end-organ damage, and even death.[10,13,35,36] We have shown that patients with COICA have different success and complication rates depending on the classification assigned, with types A and B showing higher recanalization and lower complication rates compared with type D. In fact, the majority of type D procedures were aborted. Type C had low success and high complications when treated with ET. However, HS for type C had high success and low complication rates. Visualization of the initial segment of the ICA at the common carotid artery bifurcation, combined with the presence of supraclinoid filling, makes ET suitable for occlusion types A and B. The HS was developed for type C, where an endarterectomy is performed initially to

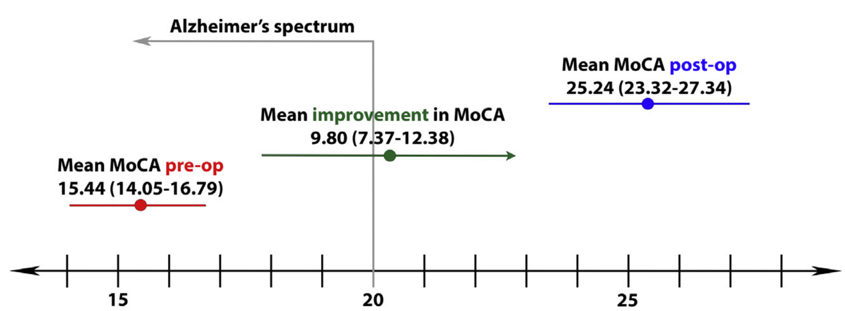

Figure 1. Bayesian inference of preop MoCA, postop MoCA, and improvement (Postop MoCA – Preop MoCA). The mean preop MoCA score was 15.44 (95% CI: 14.05—16.79), whereas the postop MoCA score after recanalization was 25.24 (95% CI: 23.32—27.34). For reference, a normal MoCA score is >25, whereas Alzheimer's mean score is <20. The 95% CI do not intersect as shown in the graph. In addition, the mean improvement score was 9.80 (95% CI: 7.37—12.38). CI, confidence interval; MoCA, Montreal Cognitive Assessment.

create a stump to visualize the initial segment of the ICA (i.e., upgrade the occlusion to a type A or B) followed by ET for definite recanalization. The HS technique is described in detail elsewhere.[32] Type D occlusions have no supraclinoid filling and cannot be upgraded. Types A and B benefited from ET, whereas type D had higher complications and lower success. Thus, we recommend endovascular intervention for A and B, whereas type D should be considered for bypass. The efficacy of HS is yet to be determined given the low number of patients and the different techniques used. Whereas Zanaty et al[34] and Liu et al[29] performed HS on type C occlusions only, Zhang et al[30] performed it on a variety of COICAs. All 3 authors reported good outcomes. Because HS is more aggressive, it is prudent to reserve it for type C. None of the revascularized patients suffered any ischemic events in the short follow-up; however, longer follow-ups are needed to establish a true comparison.

The detrimental effect of COICA management on cognition has not been well studied, as we managed to find only 3 published papers in the literature.[26,33,34] The risk of dementia in patients with COICA increases to 40% with concomitant TIAs and to 70% with stroke.[35,36] We have shown that CT perfusion markers are not only improved but normalized and become symmetric with the nonaffected cortex. Previous attempts to improve cognitive function in this cohort failed using the extracranial to intracranial bypass (RECON trial).[37] The rationale for that is the fact that this technique relied on a small caliber donor artery (superficial temporal artery) to revascularize the entire hemisphere affected. This significantly improved the oxygen extraction in the middle cerebral artery territory affected but failed to normalize it. In addition, this technique reestablished cerebral flow to the majority of the ipsilateral middle cerebral artery territory, but it was not enough to revascularize most of the limbic system structures involved in executive and cognitive functioning supplied by the anterior cerebral artery branches (**Figure 2**). ET and HS restore the caliber of the cervical ICA and therefore the blood flow for all vessels (middle and anterior cerebral artery) with clear evidence on CT perfusion of complete resolution and normalization of mean transient time. This could provide an explanation of the difference of both techniques in improving executive and cognitive function. Revascularization using ET or HS restored cerebral blood flow to the ipsilateral hemisphere of the COICA as demonstrated by the normalization of mean transient time and significant improvement in cognitive

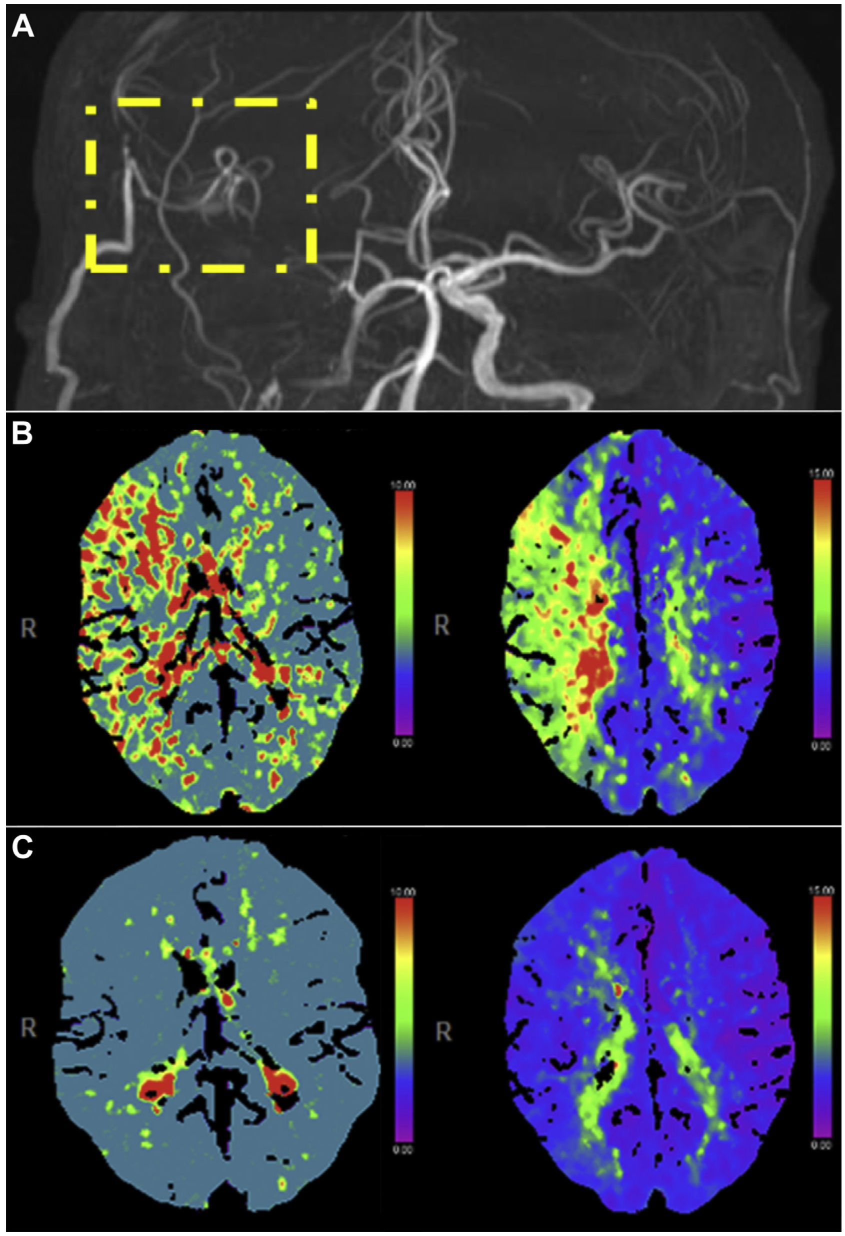

Figure 2. A 66-year-old man with symptomatic R COICA underwent successful revascularization using the STA-MCA bypass procedure. The *yellow dashed box* in (**A**) demonstrates the anastomosis of STA to MCA and improved blood flow in a small region of the MCA territory. (**B**) The marked increase in MTT in the entire R hemisphere on CTP pre-procedure. (**C**) Significant improvement in the MTT compared with pre-op, but it is not normalized when compared to the left hemisphere. COICA, chronically occluded internal carotid artery; CTP, computed tomography perfusion; MCA, middle cerebral artery; MTT, middle cerebral artery; STA, superficial temporal artery.

function. Aggressive medical management of this cohort may be sufficient to reduce the risk of recurrent stroke and TIAs but not enough to improve executive and cognitive function and minimize accelerated risk of dementia and Alzheimer's disease. This creates a clinical gap and a must needed alternative approach to help this cohort.

We have shown that types A and B had significantly higher rates of bradycardia. This is unsurprising as the proximity of the bifurcation to the stenosis is an independent risk factor predictive of bradycardia in ET.[38] However, HS did not trigger a bradycardic response, likely because removal of the obstruction was performed approximately 4 cm distal to the sinus. However, as stated above, HS was performed only in 2 patients. The higher SBPs reported in patients with COICA is likely related to both the perceived low blood pressures by the sinus baroreceptors and the chronically reduced cerebral perfusion. In the majority of our successfully recanalized COICAs, we were able to wean patients off their blood pressure medication. This suggests that recanalization has an important role in normalization of sinus baroreceptor thresholds, cerebral blood flows, and perfusion pressures in the involved hemisphere. Finally, successful recanalization can avoid episodes of blood pressure lability and watershed infarcts from cerebral misery perfusion phenomena.[12]

COICA studies are limited by the low number of patients included. Moreover, because major complications are more likely to be reported in medical charts (whereas transient complications such as TIAs or bradycardia may be under-reported), the retrospective design of these studies increases bias and precludes generalizability of the results. Similarly, endovascular complications related to groin access, for example, may not be always reported. The short follow-up period available (1−1.5 years in most studies) does not allow for an accurate assessment of recurrent TIAs and strokes over time. In the study by Zanaty et al,[34] only 5 patients had pre- and postoperative assessment of MoCA scores. Although all patients in this study had successful recanalization and improvement in their MoCA score, the small number of subjects and the lack of a negative control group (patient with dementia where ET did not help) did not allow for a meaningful comparison. Thus, the statistically significant improvement in MoCA scores observed after intervention could be time-related only. In fact, Fan et al[26] showed an improvement in cognition in the medically treated group, but this improvement was to a lesser extent compared with the intervention group. However, the rapid and drastic improvement in cognition, the control of SBP, the resolution of ischemic symptoms, and the reduction of recurrent TIAs/strokes—at least in the short term—are enough to consider a larger prospective study or randomized trial. Overall, most HS procedures are being performed for type C occlusions. It has similar outcomes despite minor differences in techniques.

CONCLUSIONS

Patients with medically refractory COICA can suffer recurrent ischemic symptoms, refractory hypertension, and cerebral misery perfusion. In addition, COICA may be a cause of reversible dementia. Type A and B occlusions benefit from ET, especially in the presence of a large penumbra. Type C occlusions can benefit from HS. Unfortunately, we did not identify an intervention to help patients with type D occlusions, and thus could be referred for bypass. A phase 2b randomized controlled trial is needed to confirm these findings.

DECLARATION OF COMPETING INTEREST

The authors declare that the article content was composed in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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MZ and JAR contributed to study design, acquisition of data, statistical analysis, and drafting of the manuscript; PMJ and EAS to critical review of the manuscript; and DMH contributed to study design and supervision.

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