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PREDICTORS OF OUTCOME IN CAROTID ENDARTERECTOMY WITH REGIONAL ANESTHESIA

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FACULDADE DE MEDICINA
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PREDICTORS OF OUTCOME IN CAROTID ENDARTERECTOMY WITH REGIONAL ANESTHESIA

JOÃO MANUEL PALMEIRA DA ROCHA NEVES
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João Rocha Neves

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PREDITORES DE RESULTADO NA ENDARTERECTOMIA CAROTÍDEA SOB ANESTESIA REGIONAL

Thesis to obtain the degree of Doctor
from the Faculty of Medicine of the University of Porto

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DECLARAÇÃO

Tese de candidatura ao grau de Doutor pelo programa Doutoral em Ciências Cardiovasculares, submetida à Faculdade de Medicina da Universidade do Porto e elaborada no acordo com os Critérios Curriculares desta faculdade para Recrutamento na Carreira Académica e Admissão e Classificação a Provas Académicas, em vigor a partir de 21 de julho de 2021, nomeadamente no vertido no ponto III.2 – a respeito dos Critérios de Exigência Mínima para Submissão de Pedido de Admissão a Provas da Tese de Doutoramento.
Decorrendo do predito enquadramento, apresenta-se uma tese estruturada pela compilação de trabalhos de investigação, na forma de artigos científicos completos originais, em que o candidato é primeiro autor e que foram publicados em revista indexada com factor de impacto.

O trabalho "Onset of Neurological Deficit During Carotid Clamping With Carotid Endarterectomy Under Regional Anesthesia Is Not a Predictor of Carotid Restenosis. Ann Vasc Surg. 2019;61:193-202.doi:10.1016/j.avsg.2019.05.025" foi utilizado na obtenção de grau de Mestre pela Faculdade de Medicina da Universidade do Porto em maio de 2019.
Mais se declara que os restantes 4 trabalhos aqui compreendidos não foram submetidos para obtenção ou reconhecimento de outro grau nesta ou noutra instituição de ensino superior, encontrando-se reproduzidos na integra no corpo da tese.

Ademais, dentro do Doutoramento e durante a execução do plano de trabalho, o candidato também foi autor de várias apresentações na forma de comunicações orais e resumos de congresso. Embora estes produtos científicos não façam parte da estrutura central da tese, são também derivados do plano de trabalho realizado e têm assegurado a divulgação dos resultados em múltiplas frentes nacionais e internacionais. Uma lista abrangente destes trabalhos científicos adicionais é apresentada no currículo do candidato.

A presente tese cumpre os pressupostos do artigo 8.º do decreto-lei número 388/1970.

Exmo. Senhor

Mestre João Manuel Palmeira da Rocha Neves

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Provas de Doutoramento

Informo V. Exª. que, por meu despacho de 2022.12.07, proferido no âmbito de delegação reitoral, nomeei o júri proposto para as provas de doutoramento em Ciências Cardiovasculares, requeridas por V. Exª., com a seguinte constituição:

Presidente: Doutora Isaura Ferreira Tavares, Professora Catedrática da Faculdade de Medicina da Universidade do Porto

Vogais:

- Doutor Piotr Myrcha, Professor Associado da Medical University of Warsaw, Polónia;

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- Doutor Pedro Miguel Araújo Campos Castro, Professor Auxiliar Convidado da Faculdade de Medicina da Universidade do Porto;

- Doutora Marina Felicidade Dias Neto, Professora Auxiliar Convidada da Faculdade de Medicina da Universidade do Porto.

Com os melhores cumprimentos,

A Vice-Reitora,

(Profª. Doutora Fátima Vieira)

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CONTENTS

ABBREVIATION LIST

AMI — acute myocardial infarction
aOR — adjusted odds ratio
AUC — area under the curve
BMI — body mass index (kg/m2)
CACC — carotid cross-clamping
CAD — coronary artery disease
CBC — complete blood count
cCEA — conventional carotid endarterectomy
CEA — carotid endarterectomy
CHUSJ — Centro Hospitalar Universitário de São João, E.P.E.
CI — confidence interval
CLTI — chronic limb-threatening ischemia
CKD — chronic kidney disease
CS — carotid stenosis
CV — cardiovascular
DM — diabetes mellitus
DUS — Doppler ultrasound
eCEA — eversion carotid endarterectomy
GA — general anesthesia
GALA — cost-effectiveness analysis of general anaesthesia versus local anaesthesia for carotid surgery
ICA — internal carotid artery
ICH — intracerebral hemorrhage
IND — intraoperative neurologic deficits manifested during carotid clamping
MCA — middle cerebral artery
NIRS — near-infrared spectroscopy cerebral oximetry
NLR — neutrophil-to-lymphocyte ratio
OR — odds ratio
PAD — peripheral artery disease
PLR — platelet-to-lymphocyte ratio
PSM — propensity score matching
RA — regional anesthesia
RBC — red blood cell
RCT — randomized controlled trial
RDW — red blood cell distribution width
RDW-CV — red blood cell distribution width – coefficient of variation
ROC — receiver operating characteristic
rSO2 — regional cerebral oxygen saturation
SD — standard deviation

ABSTRACT

INTRODUCTION

Stroke is the first leading cause of mortality in Portugal, and the second one in Europe, following ischemic heart disease. Carotid endarterectomy (CEA) has been established as the recommended treatment for symptomatic internal carotid stenosis (CS) and for all asymptomatic patients with a CS degree of 60-99%, that were classified as representing a potential high risk of a further stroke event. In addition, CEA, when performed under regional anesthesia (RA), transports the risk of developing intraoperative or postoperative neurologic alterations induced by inherent carotid cross-clamping (CACC), due to secondary cerebral hypoperfusion, which may be responsible for hemodynamic imbalance or embolic events.
Previous guidelines advocated tighter Doppler ultrasound (DUS) surveillance in patients presenting CACC associated intraoperative neurologic deficits (IND), due to higher likelihood of hemodynamic stroke in the long-term, although evidence is lacking regarding its benefit. The assumption that IND patients have a higher risk of developing a hemodinamic stroke if the ipsilateral carotid artery becomes stenosed or occluded, justified the recomendation for the need of further surveillance over the risk of restenosis after endarterectomy.

AIMS

The two major aims of the study consist to: a) evaluate preoperative clinical and hematological parameters predictive of IND; b) assess whether patients who demonstrate signs of insufficient cerebral perfusion by the onset of neurological deficits during CACC in CEA with RA are more prone to developing perioperative and long-term events.

METHODS

To accomplish the first aim, a sample of patients from a tertiary referral center (Centro Hospitalar Universitário de São João), that were submitted to CEA under RA with a diagnosis of IND, were prospectively and consecutively included. For the inclusion in the control group, the next subsequent patient that was submitted to the same surgical intervention, but without IND, was selected in a 1:1 ratio. Postoperative complications such as stroke, myocardial infarction, all-cause mortality, and Clavien–Dindo classification were assessed after the procedure. Follow-up was implemented in the outpatient clinic with DUS and clinical examination.

RESULTS

A total of 180 patients were included, with 90 (50%) presenting IND associated to arterial clamping. The clinical variables presenting statistical significance after multivariable analysis comprised: age (adjusted odds ratio (aOR): 1.04 5-95% confidence interval [CI], [1.003-1.078], p = 0.034), obesity (aOR: 3.537 [1.445 – 8.658], p=0.006), lower ipsilateral CS degree (aOR: 0.725 [0.525 -0.997], p = 0.049) and higher contralateral CS degree (aOR: 1.266 [1.057-1.516], p = 0.010). Additionally red cell distribution width coefficient of variation (RDW-CV) demonstrated statistical significance independently of predicting IND, with an aOR of 1.394 [1.076-1.805] , p = 0.012.
The 30-day stroke rate was significantly higher in the IND group, with an aOR of 5.13 [CI 1.058 – 24.87], p = 0.042 after propensity-score match (PSM). Postoperative complications (Clavien-Dindo ≥ 2) were also associated with IND (after PSM aOR of 2.748 [CI, 0.976 – 7.741], p = 0.051).
The incidence of restenosis within 2 years did not differ significantly between groups (p=0.856). Patients with IND did not have a higher incidence of long-term stroke (90.6% SD: 3.5% ND: 91.1% SD:3.6% p=0.869), major adverse cardiovascular events (ND: 69.2%SD: 5.5% control 73.6 SD: 5.2%, p=0.377) or all-cause mortality (ND: 90.6%SD: 3.5% control 91.1 SD: 3.6%, p=0.981) than controls.

CONCLUSION

Increased RDW-CV, age, obesity, a lower degree of ipsilateral CS and a higher degree of contralateral CS have demonstrated relevance to predict IND. On the other hand, IND was an independent risk factor for 30-day stroke and postoperative complications with a Clavien-Dindo ≥ 2.

The present study does not support the assumption that patients that presented IND during internal carotid test clamping sustain a higher risk of developing late stroke. Moreover, this group of patients did not present a higher incidence of restenosis. For these reasons, tighter DUS surveillance in this group seems disputable.

RESUMO

INTRODUÇÃO

Os acidentes vasculares cerebrais (AVC) são a principal causa de mortalidade em Portugal e a segunda na Europa, após a doença coronária. A endarterectomia carotídea (CEA) é o tratamento de eleição para a estenose carotídea (CS) sintomática e para todos os pacientes assintomáticos com grau de CS de 60-99%, que foram classificados como apresentando um risco potencial elevado de um AVC de novo. Além disso, a CEA quando realizada sob anestesia regional (RA), aumenta o risco de desenvolver alterações neurológicas intra- ou pós-operatórias induzidas pela clampagem carotídea (CACC), devido à hipoperfusão cerebral secundária que origina um desequilíbrio hemodinâmico ou por eventos embólicos.
As diretrizes anteriores defendiam uma vigilância mais rigorosa com ecografia Doppler (DUS) em pacientes com défices neurológicos intraoperatórios (IND) associados à CACC, especulando-se existir uma maior probabilidade de AVC a longo prazo devido à maior sensibilidade a alterações hemodinâmicas. A hipótese de que os pacientes com IND possuem maior risco de desenvolver um AVC hemodinâmico se a artéria carótida ipsilateral se tornar restenosada ou ocluída justificaria a necessidade de vigilância adicional com DUS sobre o risco de reestenose após endarterectomia.

OBJETIVOS

Os principais objetivos desta tese são: a) avaliar os parâmetros clínicos e hematológicos pré-operatórios preditivos de IND; b) Avaliar se os pacientes que demonstram sinais de perfusão cerebral insuficiente pelo aparecimento de défices neurológicos durante CACC em CEA com RA têm maior predisposição a desenvolver eventos perioperatórios e a longo prazo.

MÉTODOS

Para atingir o primeiro objetivo, uma amostra de pacientes de um centro terciário de referência, que foram submetidos à CEA em RA com diagnóstico de déficit neurológico intraoperatório, foram incluídos de forma prospectiva e consecutiva. Para inclusão no grupo controlo, o paciente subsequente que foi submetido à mesma intervenção cirúrgica, não manifestando IND, foi selecionado na proporção de 1:1. As complicações pós-operatórias como AVC, enfarte do miocárdio, mortalidade por todas as causas e complicações pós-operatórias utilizando a classificação de Clavien-Dindo foram avaliadas após a cirurgia. O plano de seguimento foi realizado em ambulatório com ecografia Doppler e avaliação clínica.

RESULTADOS

Foram incluídos 180 pacientes, dos quais 90 (50%) apresentavam IND associada a CACC. As variáveis clínicas que apresentaram significância estatística após análise multivariada foram: idade (*odds ratio* ajustado (aOR): 1,04 (intervalo de confiança de 5-95% [CI]) [1,003-1,078], p = 0,034), obesidade (aOR: 3,537 [1,445 – 8,658], p=0,006), grau de CS ipsilateral inferior (aOR: 0,725 [0,525 -0,997], P = 0,049) e grau de CS contralateral superior (aOR: 1,266 [1,057-1,516], p = 0,010). Além disso, o coeficiente de variação do índice de anisocitose dos eritrócitos (RDW-CV) demonstrou significância estatística após a previsão de IND, com aOR de 1,394 [1,076-1,805], p = 0,012.
A taxa de AVC em 30 dias foi significativamente maior no grupo IND, com aOR de 5,13 [IC 1,058 – 24,87], P = 0,042 após a correspondência do *score* de propensão (PSM). Complicações pós-operatórias (Clavien-Dindo ≥ 2) também foram associadas à IND (após PSM aOR de 2,748 [CI, 0,976 – 7,741], P = 0,051).
A incidência de reestenose em 2 anos não diferiu significativamente entre os grupos (p=0,856). No seguimento a

longo prazo os pacientes com IND não tiveram maior incidência de AVC (90,6% DP: 3,5% ND: 91,1% DP:3,6% p=0,869), eventos cardiovasculares adversos (ND: 69,2% DP: 5,5% controle 73,6 DP : 5,2%, p=0,377) ou mortalidade por todas as causas (ND: 90,6%SD: 3,5% controlo 91,1 SD: 3,6%, p=0,981) do que os controlos.

CONCLUSÃO

O aumento do RDW-CV, a idade, a obesidade, o menor grau de CS ipsilateral e o maior grau de CS contralateral demonstraram ter relevância para a predição de IND. Por outro lado, a presença de IND foi um fator de risco independente para AVC em 30 dias e complicações pós-operatórias com Clavien-Dindo ≥ 2.
O presente estudo não suporta a tese de que pacientes que apresentaram IND durante a clampagem da carótida interna apresentam maior risco de desenvolver AVC tardio (<31 dias). Além disso, esse grupo de pacientes não apresentou maior incidência de reestenose. Por essas razões, a vigilância rigorosa utilizando a DUS neste grupo é discutível.

INTRODUCTION

Epidemiology of Carotid Stenosis (CS)

Cerebrovascular and cardiovascular (CV) events originated from atherosclerotic processes are the leading basis for the majority of registered deaths registered in developed countries (1). Stroke is the second leading cause of death in Europe whereas Portugal has one of the highest stroke mortality rates compared to other European countries (2). Around 80% of cerebral vascular accidents are ischemic, and the foremost ethiologies comprehend internal carotid artery (ICA) or middle cerebral artery (MCA) embolization (25%), small intracranial vessel disease (25%), cardio-embolization (20%), and others (30%) (3). In total, 10-15% of those events are directly triggered by an atherosclerotic plaque narrowing and blocking the intimal layer of the ICA wall or an embolus at the common carotid artery bifurcation (4, 5).
The prevalence of moderate (>50%) or severe (>70%) asymptomatic CS in the general population has been described in other populations has ranging from 0.3% to 4.5% in women and 0.5% to 5.7% in men, below 50 and above 80 years old , respectively (6). The annual risk of stroke for patients with severe asymptomatic CS is approximately 2 to 5% (7-9).

Pathophysiology of carotid stenosis

Understanding CS pathophysiology, progression and its crosstalk with sustained low-grade inflammation remain significant in identifying new disease predictors (10-14). Unstable or vulnerable atherosclerotic plaques are characterized by extensive inflammation and accumulation of macrophages. Unstable plaques are more prone to rupture, leading to thrombotic and/or embolic events (15). Unstable plaques are characterized by a thin fibrous capsule, less smooth muscle cells, more inflammatory cells enclosing a vast lipid and necrotic core (14, 15). Hemodynamic stroke, in which the blood flow to the brain is temporarily suspended and then restored due to hemodynamic fluctuation, is a rare event (16, 17).
Several markers have been reported, including hematological parameters observed in the complete blood count (CBC). It must be remembered that platelets play a crucial role in the development and progression of atherosclerotic disease by secreting proinflammatory cytokines (18, 19). Likewise, neutrophils promote plaque destabilization and subsequent rupture while stimulating thrombogenesis and increasing platelet aggregation (20, 21). Lymphopenia is also associated with physiologic stress, immunodeficiency, cardiovascular complications and increased mortality (22, 23). Therefore, it is not surprising that some ratios displayed in CBC are demonstrating an increasing relevance as they are easily available and may have prognostic value (24). Additionally, these ratios may also assist in the monitoring of patients with expected risk of adverse outcomes, tailoring patient management or to aid on preoperative status improvement, and possibly in the development of targeted anti-atherosclerotic therapy (25, 26). Such is the case of the neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR), that are able to predict outcomes in tumors, systemic lupus erythematosus, sepsis, and cardiovascular disease (23, 24, 27-33). Moreover, in the vascular field, these parameters were associated with increased risk of death within two years of major vascular surgery (34), greater risk for progression or de novo chronic limb-threatening ischemia (CLTI) (35), and amputation rates in patients with CLTI (36-38), poorer limb survival after embolectomy for acute limb ischemia (39), higher risk of complications following surgical abdominal aortic aneurysm repair (40) and worse prognosis after acute mesenteric ischemia (41, 42). However, the clinical relevance of these hematological ratios in patients with CS is scarcely described in the literature and rarely used in real-world settings.
The underlying utility of another hematological marker, the red blood cell distribution width (RDW) in atherosclerotic cardiovascular disease (CV), is also not thoroughly studied. RDW-coefficient of variation (RDW-CV) reflects the heterogeneity of red blood cell (RBC) volume (anisocytosis), and it is defined by the ratio between RBC standard deviation (SD) and the mean corpuscular volume, multiplied by 100, with values below the reference limit being infrequent and clinically meaningless (43). Inflammation and oxidative stress, critical in atherosclerosis (44), have an inhibitory effect on erythropoiesis, leading to increased RBC volume variation

(45). Treatments for atherosclerosis targeting inflammatory pathways still have low-quality scientific evidence, mainly based on either observational or small interventional studies (46). Increased RDW was initially known as a marker of iron deficiency (47). However, several additional potential mechanisms increased RDW, such as nutritional deficiency (e.g. vitamin B12, folic acid), bone marrow depression, or inflammation as a homeostatic adaptation leading to RBC lifespan extension (48, 49). Inflammatory conditions, such as diabetes mellitus (DM), due to multiple pathophysiological mechanisms, also leads to the increase of RDW (50). Therefore, several studies explored the potential role of this biomarker as a prognostic tool in several conditions. Thus, increased RDW is associated with a worse prognosis in gastrointestinal, urological, and respiratory malignancies (51-53) and in patients with sepsis (54). RDW is also strongly associated with stroke and acute myocardial infarction (AMI) incidence (55). Furthermore, it seems to be a reliable and independent predictor of mortality in coronary artery disease (CAD) and ischemic stroke (56, 57).

Patient selection criteria for carotid endarterectomy

Although CEA effectively reduces stroke and mortality rates in patients with CS, it has been increasingly questioned the suitability of this invasive procedure in treating patients, especially the asymptomatic ones (58-60). CEA is associated with postoperative complications, such as neuropathy, hematoma, bleeding and infection. Besides, there is a risk of stroke, AMI, and death in the perioperative period, as exposed in several prior investigations (59, 61, 62). CS is also a good marker of systemic atherosclerosis, and CEA is insufficient to control its diffuse attainment (61, 63, 64). Patients with carotid disease usually have concomitant CAD, chronic kidney disease (CKD), peripheral artery disease (PAD). Literature shows that 25% of stroke patients have a coexisting arterial disease affecting one territory, 40% on various vascular systems, and nearly 95% of them have one or more additional comorbidities, being at high risk of having a related adverse CV event (5, 65-67).
Therefore, medical treatment is favored for asymptomatic patients with CS > 60%, and for asymptomatic patients with CS > 60%, invasive treatment is recommended (67-69). According to the European Society of Cardiology / European Society of Vascular Surgery guidelines, the periprocedural major stroke/death rate reported should be inferior to 6% for symptomatic patients and inferior to 3% for asymptomatic patients (69). Real-world data disclose a stroke incidence and a death rate of 2.0%-2.5% postoperatively in all patients undergoing CEA (3, 70, 71). Selected patients on best medical therapy, with clinical and imaging features classifying them as having a higher probability of suffering a stroke, might benefit from surgical procedures. Moreover, patients treated with the best medical therapy that do not benefit from surgical procedure might take profit from regular imagiological follow-up (72).

Anesthesia in carotid endarterectomy

CEA may be performed under regional anesthesia (RA) or general anesthesia (GA) without significant differences regarding mortality or stroke rates (73). The General Anaesthesia versus Local Anaesthesia (GALA) trial (3526 patients) is the largest randomized controlled trial (RCT) to date and has reported no significant difference regarding perioperative death, stroke, or AMI between GA (4.8%) and RA (4.5%) (73). In a recent meta-analysis with thirty-one studies comprising 152376 patients, RA was associated with shorter surgical time and minor probability stroke, cardiac complications, and in-hospital mortality. However, when including only the RCTs, this latter effect was non-significant (74).
From a physiological point of view, the intraoperative cerebral autoregulation is preserved during RA surgery with a physiological rise in systemic blood pressure and cerebral oxygenation after the carotid clamping but lost in a proportion of patients during CEA performed under GA (75). Therefore, the preservation of cerebral autoregulation may contribute to reducing ischemic episodes (76). Cerebral blood flow is more reduced than the cerebral metabolic rate of oxygen under GA, resulting in an increased ratio of metabolism to blood flow (77).

Monitoring is necessary to ensure adequate brain perfusion, especially during carotid clamping and shunting. Cerebral monitoring techniques include electroencephalography, somatosensory evoked potentials, transcranial Doppler sonography, carotid artery stump pressure, or evaluation of the continuous cerebral oxygenation using noninvasive cerebral oximetry (78). The monitoring of neurologic status in an awake patient is currently considered the gold standard method for detecting critical cerebral ischemia during CEA with RA. Still, other noninvasive cerebral perfusion measurements should be considered since clinical neurological deterioration might go unnoticed after carotid cross-clamping (CACC) due to missed diagnosis of minor deficits, particularly in the non-dominant hemisphere (usually the right), and these measurements can be applied under GA when necessary (79).

RA allows the direct monitoring of the neurological status of the patient during the surgical procedure. It is the most accurate, cost-effective, and straightforward method for diagnosing critical cerebral perfusion due to low-flow or embolic phenomena (80). Indeed, neurological examination is the accepted most accurate strategy for cerebral monitoring during CEA (81-83). IND manifested during carotid clamping is a risk factor for perioperative stroke, presenting higher predictive value over the remaining methods for adverse events (84-86). IND occurs in 7 – 30% of patients submitted to CEA under RA, and these patients are most prone to adverse events (84-87). Accordingly, RA will be highly effective in preventing stroke resulting from hemodynamic failure. However, one cannot expect RA to prevent strokes secondary to embolization of intraluminal thrombus following clamp release, intracerebral hemorrhage (ICH) following postoperative surges in blood pressure, or stroke following postoperative carotid thrombosis. As hemodynamic strokes constitute a relative minority of all perioperative strokes embolism (88), it is perhaps not surprising that the GALA trial has failed to demonstrate that CEA under RA conferred significant reductions in the overall 30-day rate of death or stroke (89).

RA is associated with less resort to shunt (73, 83), shorter surgical time (90), and lower risk of coronary events (91). Resort to shunting during CEA has been recommended after the occurrence of IND associated with CACC (92). Described predictive factors for shunting include female gender and age superior to 75 years (93), contralateral carotid occlusion (93-95) and moderate ipsilateral ICA stenosis (94, 95), symptomatic presentation (94), arterial hypertension (93) and need for shunting in the first procedure (96). Contralateral common artery blood flow >619 mL/min and history of contralateral carotid surgery were considered protective for cerebral ischemia (93).

Near-infrared spectroscopy cerebral oximetry (NIRS) is applicable in all patients, and it is a noninvasive and real-time method of regional cerebral oxygen saturation (rSO2) measurement reflecting changes in cerebral blood flow during CEA (8). Moreover, NIRS is easily used and interpreted by both the anesthesiologist and the surgeon (9). The cutoff for rSO2 might vary depending upon the type of equipment used (75, 97). This limitation is important as each device may require a previous calibration and be tested individually to establish the critical rSO2 limits (75, 97). Consequently, distinct devices may show some variability in different optimal cutoff values (98). Kamenskaya et al. reported that a reduction of at least 20% in rSO2 on the ipsilateral side of the surgery is strongly associated with a 10-fold increased risk of stroke and an 8-fold amplified risk of cognitive disorders (24). The variation of rSO2 value is also affected by the hematocrit, skin phototype, gender, and brain volume (81). Nevertheless, as these factors are individually stable, the relative changes of rSO2 can be used. Due to the disproportional effect in the cerebral metabolic rate of oxygen and CBF, GA increases the sensitivity of INVOs comparatively to RA since ischemic areas will further present dissociation of this index (77, 99).

Intraoperative Shunt

CACC reduces blood flow to the brain leading to hypoperfusion which is aggravated if the collateral circulation is compromised (94, 100, 101). Carotid shunting is the only proven method that might reduce the risk of perioperative stroke due to hypoperfusion (102, 103). Surgeons tend to be classified as “routine,” “selective,” or “non-shunters”, usually based on their surgical training (92). Resorting to shunt after the occurrence of focal deficits during CACC is widely advised as some intraoperative strokes are triggered by the temporary interruption

of cerebral blood flow in patients in the absence of adequate collateralization (92). Therefore, carotid shunting has been a strategy commonly recommended in patients presenting IND as it might reduce the risk of persistent ischemic lesions due to the temporary interruption of cerebral blood flow (102). Other surgeons that do not resort to shunting or are rather more selective in its use, claim that shunt by itself might lead to distal embolization and stroke, due to dissection, embolization or poor technical execution (104-106). However, the low incidence of IND in RA might lead to decreased technical proficiency when resorting to shunt (107-109). In a pragmatic surgical approach, shunt-related complications might cancel the benefits of selective shunting.
A Cochrane systematic review of six RCTs (including 1270 CEAs) concluded, although based on poor quality data, that no meaningful recommendations could be made regarding routine, selective, or never shunting. Chongruksut et al. did not find significant results in 30-day stroke or death after CEA comparing shunting to non-shunting or selective shunting (92). Recommendations do not advocate the use of routine shunting, as evidence supports shunting only for severe persistent ischemia (110, 111). Literature has conflicting results with reports of beneficial (95), detrimental (91, 112), or no effect (113, 114) of selective shunting. Thus, the routine non-use of shunts is advised based on the assumption that cerebral ischemia is a relatively uncommon cause of intraoperative stroke (88). Considering the current evidence, it is concluded that routine or selective shunt or no shunt is still controversial (2).

Surgical technique

The efficacy of surgical therapy for carotid stenosis depends on continued efforts to minimize perioperative, operative, and late complications. Morbidity related to CEA, including perioperative stroke, asymptomatic carotid occlusion, and recurrent stenosis, may result from technical defects. It was suggested that intraoperative detection and correction of technical errors are crucial means of decreasing the risk of postoperative stroke (115).
Eversion (eCEA) and conventional carotid endarterectomy (cCEA) are the most standard techniques for performing CEA. Arteriotomy closure following cCEA is achieved by either direct closure or by patch angioplasty (pCEA). The main advantage of eCEA is that no prosthetic material is used. However, eCEA is limited by an inability to insert a shunt until the plaque has been removed and by a significantly higher incidence of post-CEA hypertension (116).
A meta-analysis of 10 RCTs (including 2157 CEAs), comparing routine patch angioplasty with routine direct suture CEA, observed that patch closure significantly reduced the combined risk of perioperative stroke and later stroke during long-term follow-up. Patching also reduced the risks of perioperative arterial occlusion and recurrent stenosis during long-term follow-up (117). Late prosthetic patch infection occurs in about 1% of patients (118).
A meta-analysis with 25 eligible studies (5 RCTs, 20 observational studies) involving 49,500 CEAs (16,249 eCEAs; 33,251 cCEAs) demonstrated that, compared with cCEA, eCEA did not confer significant reductions in 30-day stroke, death, death/stroke, death/stroke/MI, or neck hematoma, provided the arteriotomy was patched (119).

Carotid Restenosis

One long term complication which hinders the effectiveness of CEA is the recurrence of carotid stenosis (120). Carotid restenosis is defined as partial or total reocclusion of the ICA after surgical correction of the original stenosis by either CEA or carotid stenting. It is classified as early if developing from 2 months to 2 years following procedure or late if detected after this period (121). Based on peak flow velocities quantified using DUS imaging, carotid restenosis is designated as mild, moderate, or severe (122).
Early restenosis occurs in the presence of internal (endovascular) or external (surgical) injury, and the three arterial layers are involved in neointimal hyperplasia. Several tissues are involved (perivascular, vessel wall, and blood) and as well as numerous cell lineages with multiple molecular signaling networks.

At the site of surgical intervention, endothelial cells are injured, and the subendothelial matrix is exposed to the flowing blood. Platelets and fibrinogen immediately adhere to the surface of the injured vessel. A multistep cascade of platelet and leukocyte adhesion and activation promotes the secretion of inflammatory signaling molecules and growth factors that promote smooth muscle cells migration from the media layer to the intima (123). The smooth muscle cells which proliferate in the intima deposit extracellular matrix, release degrading enzymes with basement membrane destruction, and then transmigrate into the extraluminal tissue, causing stenosis (123).
Restenosis rates, despite variable, remain relatively low among studies, with a prevalence of 5.8% after a mean follow-up of 47 months (124-126). Evidence is lacking regarding whether cerebral ischemic events detected during long-term follow-up are causally associated with arterial reocclusion or whether restenosis is benign. Indeed, a review of recent RCTs suggests that the proportion of strokes following CEA attributable to restenosis is too low to justify the necessity and costs of routine surveillance, and most late strokes occurring in patients without restenosis (126). Despite this, tighter DUS surveillance is suggested by the European Society of Vascular Surgery guidelines for all patients who undergo a relevant decrease in intraprocedural cerebral blood flow following ICA clamping (127). After developing IND, the decision to speed up the surgery may also be made despite not being reported in the literature and further contribute to sub-optimal results. The inexperienced use of shunts can also contribute to technical errors and subsequent higher restenosis rate (109).
Several studies have attempted to ascertain whether restenosis is associated with an increased risk of ipsilateral stroke that might warrant routine DUS surveillance after the procedure (128). Several observational studies have further made an effort to determine which factors might result in increased risk for restenosis. The most commonly associated factors were female gender, dyslipidemia, smoking, arterial hypertension, dialysis dependence, direct suture, high-grade contralateral ICA stenosis, and high-fasting glycemia in the context of metabolic syndrome or non-insulin-dependent DM. The latter two are most notably associated with severe (>70%) restenosis (128-130). The effect of age on the risk of restenosis is conflicting between studies, with some authors reporting a higher incidence in patients with increasing age (129) and others in patients younger than 65 years (131). Systemic inflammation, evaluated with lectin-2 genotype, preoperative C-reactive protein, serum homocysteine, apolipoprotein J, vitamin C serum levels correlate with unfavorable outcomes (132, 133). eCEA and pCEA with bovine pericardium or dacron is associated with a lower incidence in both short-term and late undesired outcomes following CEA and seems to represent the best choice compared with other carotid closure techniques, including direct suture (134).

THESIS OVERVIEW

Specific Aims

The neurologic examination of the awake patient is considered the best reliable method to assess IND. The reasoning for the present thesis is the assumption that patients developing IND during CACC have a higher risk of developing a complete stroke. Assessment of the perioperative prognostic value of CACC-associated IND was paramount for the relevance of this work.

This thesis also sought to:

1 Evaluate reasonable preoperative clinical and hematological parameters predictive of IND;

• Rocha-Neves J, Pereira-Macedo J, Ferreira A, Dias-Neto M, Andrade J, Mansilha A. Impact of intraoperative neurologic deficits in carotid endarterectomy under regional anesthesia. Scand Cardiovasc J. 2021;55(3):180-6. doi:10.1080/14017431.2021.1874509 Q4, IF: 1.992

• Pereira-Neves A, Rocha-Neves J, Fragao-Marques M, Duarte-Gamas L, Jacome F, Coelho A, Cerqueira A, Andrade J, Mansilha A. Red blood cell distribution width is associated with hypoperfusion in carotid endarterectomy under regional anesthesia. Surgery. 2021;169(6):1536-43. doi:10.1016/j.surg.2021.01.004 Q1, IF: 4.348

2 Evaluate the diagnostic and discriminative value of the NIRS cerebral oximeter in detecting cerebral hypoperfusion and determining high-risk of neurologic deterioration;

• Rocha-Neves J, Pereira-Macedo J, Moreira A, Oliveira-Pinto J, Afonso G, Mourao J, Andrade J, Vaz R, Mansilha A. Efficacy of near-infrared spectroscopy cerebral oximetry on detection of critical cerebral perfusion during carotid endarterectomy under regional anesthesia. Vasa. 2020;49(5):367-74.doi:10.1024/0301-1526/a000879 Q4, IF: 1.961

3 Characterize and compare technical approaches - selective shunting or routine non-shunting - in regards to adverse events rates in patients with IND under regional anesthesia;

• Rocha-Neves J, Pereira-Macedo J, Dias-Neto M, Andrade J, Mansilha A. Benefit of selective shunt use during carotid endarterectomy under regional anesthesia. Vascular. 2020;28(5):505-12. doi:10.1177/1708538120922098 Q4, IF: 1.285

4 Assess whether patients who demonstrate signs of insufficient cerebral perfusion by the onset of neurological deficits during CACC in CEA with RA are more prone to developing post-CEA restenosis;

5 Address the occurrence of adverse CV events, including stroke during the postoperative period and the long term follow-up of the patients who had manifested IND. In this subset of patients, the progression of the stenosis could be more likely to be associated with major hemodynamic stroke.

• Vieira-Andrade J, Rocha-Neves J, Macedo J, Dias-Neto M. Onset of Neurological Deficit During Carotid Clamping With Carotid Endarterectomy Under Regional Anesthesia Is Not a Predictor of Carotid Restenosis. Ann Vasc Surg. 2019;61:193-202.doi:10.1016/j.avsg.2019.05.025 Q4, IF: 1.125

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ORIGINAL ARTICLE

Impact of intraoperative neurologic deficits in carotid endarterectomy under regional anesthesia

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ABSTRACT

Objective: Patients undergoing carotid endarterectomy (CEA) may experiment neurologic deficits during the carotid cross-clamping due to secondary cerebral hypoperfusion. An associated risk of postoperative stroke incidence is also well established. This work aimed to assess the postoperative adverse events related to neurologic deficits in the awake test after clamping and to determine its predictive factors. *Methods.* From January 2012 to January 2018, 79 patients from a referral hospital that underwent CEA with regional anesthesia for carotid stenosis and manifested neurologic deficits were gathered. Consecutively selected controls ($n = 85$) were submitted to the same procedure without developing neurological changes. Postoperative complications such as stroke, myocardial infarction, all-cause death, and Clavien–Dindo classification were assessed 30 days after the procedure. Univariate and binary logistic regressions were performed for data assessment. *Results.* Patients with clamping associated neurologic deficits were significantly more obese than the control group (aOR = 9.30; 95% CI: 2.57–33.69; $p = .01$). Lower degree of ipsilateral stenosis and higher degree of contralateral stenosis were independently related to clamping intolerance (aOR = 0.70; 95% CI: 0.49–0.99; $p = .047$ and aOR = 1.30; 95% CI: 1.06–1.50; $p = .009$, respectively). Neurologic deficits were a main 30-day stroke predictor (aOR = 4.30; 95% CI: 1.10–16.71; $p = .035$). *Conclusions.* Neurologic deficits during carotid clamping are a predictor of perioperative stroke. Body mass index $> 30\,kg/m^2$, a lower degree of ipsilateral stenosis, and a higher degree of contralateral stenosis are independent predictors of neurologic deficits and, therefore, might play a role in the prevention of procedure-related stroke.

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Carotid endarterectomy; carotid stenosis; neurologic deficits; perioperative stroke; regional anesthesia

Introduction

Carotid endarterectomy (CEA) is the recommended treatment for symptomatic carotid stenosis [1]. The procedure implies carotid cross-clamping (CACC), which might lead to the intraoperative manifestation of neurologic deficits (IND) due to the hypoperfusion caused by the former and also exposes the patient to further embolism [2]. Prolonged CACC time was demonstrated to augment the risk of 30-day stroke and death, with an OR 1.1 for each 10-minute increase [3]. It may also affect hemodynamic stability, and both hypertension and hypotension were associated with stroke postoperatively [4]. CACC reduces blood flow to the brain leading to hypoperfusion, which can be aggravated if collateral circulation is compromised [2,5–7]. Preoperative dual anti-aggregation has significantly reduced the incidence of postoperative embolic stroke [2]. Regarding hemodynamic stroke, recommendations have been made to avoid hypotension and adjust blood pressure into high mean arterial pressure values during CEA [4,8].

CEA can be performed under general or regional anesthesia (RA), without significant differences regarding mortality or stroke rates [9]. However, RA is associated with less resort to shunt [10,11], shorter surgical time [12], and lower risk of coronary events [3]. A neurological examination is the most accurate strategy for cerebral monitoring during CEA [10,13,14]. Post-clamping IND are associated with higher ischemic event rates [6,15]. Resort to shunting during CEA has been recommended after the occurrence of IND associated to CACC [16]. Described predictive factors for shunting include female gender and age superior to 75 years [17], contralateral carotid occlusion [7,17,18] and moderate ipsilateral internal carotid artery stenosis [7,18], symptomatic presentation [7], arterial hypertension [17] and need for shunting in first procedure [19]. Contralateral common artery blood flow >619 mL/min and history of contralateral carotid surgery were reported as protective for cerebral ischemia [17].

Cerebral perfusion is preserved during RA surgery by a physiological rise in systemic blood pressure and cerebral

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oxygenation after the carotid clamping. However, during general anesthesia, autoregulation is compromised in some patients. Therefore, the preservation of cerebral autoregulation might contribute to the further reduction of ischemic episodes [20].

Most of the current literature focuses on IND in the setting of general anesthesia. Still, the neurologic examination of the awake patient is considered the best reliable method to assess IND. This study sought to evaluate reasonable predictors of perioperative neurologic implications of CACC during CEA performed under RA. Additionally, potential adverse events associated with IND were also assessed.

Materials and methods

Study population

From January 2012 to January 2018, all patients from a tertiary referral center who underwent CEA under RA for carotid stenosis were reviewed. Analysis of all patients ($n = 79$) who presented alterations in the neurologic examination after internal carotid artery clamping during CEA was performed. Control patients, who were submitted to the same procedure without presenting neurologic alterations, were consecutively selected. Additionally, the center exclusion criteria for RA were synchronous cardiac surgery and patients *a priori* unwilling to stay awake during the procedure, resulting in the use of RA in 97% of cases.

Demographics and comorbidities of the selected patients along with 30-day post procedure adverse events were recorded. The study protocol was approved by the local Ethics Committee (Protocol 248-18) and respected the Declaration of Helsinki. Patient informed consent was waived by the same committee. The study's database is registered and available on https://www.researchregistry.com. Unique identifying number – Research Registry4929.

Perioperative setting

All patients were subjected to preoperative Doppler ultrasound (US) or angio-CT to define the topography and severity according to velocimetric criteria (50–70%; 70–90%; 90–99%), as well as to evaluate the other vessels involved in cerebral vascularization [21]. Patients were evaluated by a vascular surgeon and an anesthesiologist before the surgery, and were under single antiplatelet therapy (>95% acetylsalicylic acid 100 mg) and a statin for at least two days before surgery. Anticoagulation was managed according to present clinical guidelines [22]. None of the patients were submitted to thrombolysis or mechanical thrombectomy prior to surgery.

RA by cervical block was performed with the patient in the supine position, and head turned opposingly to the surgery side. A 22-gauge insulated needle was perpendicularly inserted under US guidance in most cases. After that, 4–5 mL of ropivacaine 0.5% was administered per spinal level (C2–C4) in a total of 12–15 mL (deep cervical blockade) and/or 5 mL of ropivacaine 0.5% at the posterior border of the midportion of the sternocleidomastoid muscle (superficial cervical blockade) were injected [23].

Intraoperative monitoring consisted of consecutive brief awake neurological examinations and continuous anesthetic surveillance during the procedure and arterial clamping, respectively [11]. Cerebral oximeter (INVOS^{TM}) was additionally placed in all cases after 2013, nonetheless, neurological examination always prevailed in the decision [24,25]. According to these criteria, the rate of IND during CEA in this center is 8%/year.

Mean arterial pressure was routinely measured using a 20-gauge catheter placed in the radial artery. Until the carotid artery was declamped, mean arterial pressure was stabilized between baseline values to 20% above. If required, vasoactive medication was administered: ephedrine 5–10 mg bolus for hypotension and atropine 1 mg bolus for bradycardia. All patients underwent surgery with 2 L/min of oxygen by nasal cannula, and a peripheral HbO2 saturation of at least 95% was aimed. Concerning patients who developed critical hypotension, unworkable agitation, or neurologic deficits were converted to general anesthesia with propofol.

Surgical technique and postoperative surveillance

Surgery consisted of CEA followed by patch angioplasty, direct suture or eversion. Shunt technique was applied based on the surgeons' experience. The Javid shunt was used in the period 2012–2015 and changed to the Pruitt-Inahara® 2015–2018 due to logistic options [26]. Findings regarding the selective or non-use of shunt are described elsewhere [26]. Once the surgery was performed, patients were subjected to continuous monitoring for 24 h in a post-anesthetic care unit. A brain CT was then performed if any neurologic alteration was diagnosed.

The result of the surgery was assessed in the subsequent 30–90 days by clinical examination and Doppler US. Additionally, the vascular surgery team has a stroke rate in CEA of 1.8% and a stroke/mortality rate of 1.8% in symptomatic patients [27,28].

Statistical analysis

The required sample for a two-sided test for non-superiority was calculated resorting to WinPepi® V11.65 [29], aiming for statistical power (β) of 90% and an $\alpha < 0.05$. The described neurologic event rate in shunted patients/cerebral malperfusion patients is 4%, and an event rate of 1.8% for the controls was assumed [16,28,30]. A prevalence of 50% of INDs in the sample with a ratio of case to controls of 1.1:1 was considered. An event rate difference of 20% between groups was established, resulting in an estimated minimum sample of 72 patients.

Statistics were performed with SPSS 25.0 (IBM Corp., release 2017; IBM SPSS Statistics for Windows, version 25.0, Armonk, NY). Continuous and categorical data were subject to univariate analysis through Student's t-test, χ^2 or Fisher's test, respectively. Mann–Whitney's U test was used to assess ordinal skewed variables and was presented as median and

5–95% confidence intervals (CIs). Categorical and continuous variables are presented as percentages and as mean ± standard deviation, respectively. The significance level was set to p value <.05 and adjusted odds ratio (aOR) together with 95% CI were calculated.

Multivariable analysis was performed using binary logistic regression by the dimension reduction method. Variables with clinical relevance included in the multivariable analysis were those associated with the group with post-clamping neurologic changes in univariate analysis (variables with p<.15 were included).

Definitions

Symptomatic carotid stenosis was defined according to the clinical practice guidelines of the European Society for Vascular Surgery [31]. Post-clamping deficits were defined as any persistent alteration at neurologic examination during the CACC and resistant to hemodynamic adjustment [4]. All the postoperative neurologic events were confirmed and evaluated by an experienced neurologist.

Postprocedural stroke was defined as an episode of acute neurological dysfunction presumed to be caused by ischemia or hemorrhage, persisting at least 24 h or until death [32]. Surgical hematoma was defined as a significant cervical blood collection associated to respiratory airway compression with the need for surgical intervention.

Clavien–Dindo classification was used for grading adverse events that occur as a result of surgical procedures, and its main characteristic is that the severity of a complication is graded based on the type of therapy required to treat it [33]. In the present study, adverse events were composed of the 30-day rate of stroke, hyperperfusion syndrome, postprocedure hypotension with the need for adrenergic support, and surgical hematoma. No 30-day death or myocardial infarction events were recorded in this cohort.

Posterior circulation disease was defined as the presence of vertebral artery stenosis with hemodynamic significance on US or superior to 50% in the angio-CT in either side of vertebrobasilar circulation [34].

Results

Demographic and clinical data

The study population included 131 men (80%) and 33 women (20%) with a mean age of 69 ± 9.30 years (range 45–89). No significant differences between the post-clamping deficit group and the controls regarding gender was found (24% vs. 16%, p = .226). Mean age of cases was significantly higher than in the control group (71 ± 9.30 years vs. 68 ± 9.0 years, p = .042), although not confirmed by multivariable analysis. Of the total sample, 34% of patients aged >75 years, of which 61% presented clamping associated IND (p = .021) (Table 1).

Cardiovascular risk-factors were discriminated for both groups, demonstrating homogeneity across proportions except for body mass index > 30 kg/m^2, which was significantly more frequent in the group with IND (24% vs. 5%; p = .0001) (Table 1). Concerning the use of anti-hypertensive agents as chronic therapy, only the use of calcium channel blockers reported significant association with IND (p = .019).

American Society of Anesthesia physical status classification (ASA) demonstrated higher grades for the group with IND (2.96 ± 0.406 vs. 2.79 ± 0.514, p = .017). Both groups

Table 1. Population demographics and comorbidities.

Variables	Control n = 85 (%)	IND n = 79 (%)	p Value	Multivariable
Sex (female)	14 (16)	19 (24)	.226	
Age (mean ± SD)	68 ± 9.0	71 ± 9.30	.042	NC
Age ≥ 75	22 (26)	34 (4.0)	.021	
Cardiovascular risk factors				
Hypertension	73 (86)	73 (92)	.182	
Diabetes	33 (39)	37 (47)	.300	
Dyslipidemia	73 (86)	67 (86)	.998	
Smoking	40 (47)	44 (56)	.269	
BMI > 30 kg/m^2	4 (5)	19 (24)	.0001	aOR: 9.30 95% CI: 2.57–33.69; p=.001
CKD	9 (11)	9 (11)	.869	
COPD	7 (8)	9 (11)	.496	
CAD	30 (35)	35 (44)	.239	
PAD	23 (27)	20 (25)	.800	
CHF	12 (14)	14 (18)	.549	
Anti-hypertensive agents (n) (mean ± SD)	2 ± 1.28	2 ± 1.05	.347	
Anti-hypertensive agents				
ACEI	62 (75)	61 (77)	.708	
Beta-blocker	26 (31)	26 (33)	.829	
CCB	25 (30)	38 (48)	.019	NC
Thiazide diuretics	36 (43)	31 (39)	.593	
Nitrate	4 (5)	9 (11)	.124	NC
Hb (g/dL) (mean ± SD)	12.8 ± 2.08	13.2 ± 1.8	.219	
ASA (I–V) (mean ± SD)	2.79 ± 0.514	2.96 ± 0.406	.017	NC

ACEI: angiotensin-converting enzyme inhibitor; aOR: adjusted odds ratio; ASA: American Society of Anesthesiologists Physical Status Classification System; CAD: coronary artery disease; CCB: calcium channel blocker; CHF: chronic heart failure; 95% CI: confidence interval 5–95%; CKD: chronic kidney disease (creatinine = 1.5 mg/dL); COPD: chronic obstructive pulmonary disease; Hb: hemoglobin; PAD: peripheral artery disease; BMI: body mass index; NC: not confirmed on multivariable analysis; IND: alterations on the neurologic examination during carotid clamping.

Table 2. Intraoperative and neurovascular predictors.

Variables	Control $n = 85$ (%)	IND $n = 79$ (%)	p Value	Multivariable
Asymptomatic	46 (54)	47 (60)		
Symptomatic	39 (46)	32 (40.5)	.488	
TIA	11 (13)	6 (87.6)		
Stroke	28 (33)	26 (33)		
Time to revascularization (days) (median) (IQR)	17.5 [10.25–57.75]	13.5 [10–39.25]	.795	
NIHSS ($n = 39$) (mean ± SD)	6 ± 5.891	8 ± 6.134	.493	
NIHSS > 10	4 (10)	6 (19)	.426	
Side (left)	41 (48)	49 (6.0)	.076	NC
Stenosis degree (mean ± SD)	86 ± 9.54	82.5 ± 10.78	.031	aOR: 0.70, 95% CI: 0.49–0.99; p=.047
Contralateral stenosis (mean ± SD)	61.7 ± 17.02	68.9 ± 22.9	.026	aOR: 1.30, 95% CI: 1.06–1.50; p=.009
Vertebrobasilar disease	13 (16)	17 (22)	.353	
Surgery time (min) (mean ± SD)	117 ± 55.2	111 ± 28.0	.408	
Clamping time (min) (mean ± SD)	48 ± 23.106	37 ± 21.508	.007	

aOR: adjusted odds ratio; 95% CI: confidence interval 5–95%; IQR: interquartile range; NIHSS: National Institute of Health Stroke Scale; NC: not confirmed on multivariable analysis; IND: alterations on the neurologic examination during carotid clamping; SD: standard deviation; TIA: transient ischemic attack; time to revascularization: time to revascularization from index event.

Table 3. 30-Day postoperative adverse events following carotid intervention.

Variables 30 days	Control $N = 85$ (%)	IND $n = 79$ (%)	p Value	Multivariable
Stroke	3 (3)	11 (14)	.017	aOR: 4.30; 95% CI: 1.10–16.71; p=.035
Clavien–Dindo ≥ 2	9 (11)	20 (25)	.014	aOR: 2.86; 95% CI: 1.21–6.75; p=.016
CNI	10 (12)	7 (9)	.542	

aOR: adjusted odds ratio; 95% CI: confidence interval 5–95%; CNI: cranial nerve injury; IND: alterations on the neurologic examination during carotid clamping; Clavien–Dindo ≥ 2: stroke, surgical hematoma, hyperperfusion syndrome, postoperative hypotension demanding adrenergic support.

were comparable in terms of preoperatory hemoglobin (g/dL) ($p = .219$) (Table 1).

Neurovascular symptoms and intraoperative features

Regarding the onset of IND, 68 patients (86%) manifested symptoms in the first 5 min after CACC, with a second late incidence peak at 10 min. Concerning the CS, 43% of the patients were symptomatic (33% stroke and 10% transient ischemic attack, with no difference between groups, $p = .488$). The median time between the event and the surgery was 17.5 days (interquartile range (IQR) 10.25–57.75) for the control group and 13.5 days (IQR 10–39.25) for the group with IND ($p = .795$) (Table 2). Similarly, no significant results were found concerning 30-day stroke ($p = .152$) or postoperative complications ($p = .152$).

Regarding the degree of stenosis, ipsilateral stenosis was significantly less marked in the IND group (82.5%±10.78% vs. 86.0%±9.54%, $p = .031$). On the other side, the degree of contralateral stenosis was significantly superior in patients who presented clamping associated IND (68.9%±22.90% vs. 61.7%±17.02%, $p = .026$). Both groups were comparable in terms of surgery time (110 ± 38.00 vs. 117 ± 55.20 min, $p = .408$), but significantly differed for clamping time (48 ± 23.106 vs. 37 ± 21.508, $p = .007$) (Table 2).

Multivariable analysis and confounding

After multivariable analysis, the variables maintaining association with IND were BMI > 30 kg/m^2 (aOR = 9.30; 95% CI: 2.57–33.69; $p = .01$), lower ipsilateral stenosis (aOR = 0.70; 95% CI: 0.49–0.99; $p = .047$) and higher contralateral stenosis (aOR = 1.30; 95% CI: 1.06–1.50; $p = .009$) ($R^2 = 0.21$; and likelihood: 186.4). Clavien–Dindo classification ≥ 2 and 30-day stroke were confirmed associations with IND as above-mentioned. Furthermore, significant results on univariate analysis for the variables age, age > 75, ASA, calcium channel blockers, conversion to general anesthesia and cranial nerve injury (CNI) were not confirmed after adjustment for confounding.

Post-clamping deficits outcomes

A significant relation between post-clamping deficits and 30-day stroke was found. Of the patients with 30-day stroke event, all with ischemic etiology, 79% manifested neurologic changes during CACC, resulting in a superior 30-day stroke rate in this group (14% vs. 3.1%, $p = .017$). IND was confirmed as a major stroke predictor by multivariable analysis (aOR = 4.30; 95% CI: 1.10–16.71; $p = .035$). Likewise, concerning patients classified with a resulting Clavien–Dindo ≥ 2, a higher incidence was also found in the group with post-clamping deficits (25% vs. 11%, $p = .014$), posteriorly confirmed when adjusted for confounding (aOR = 2.86; 95% CI: 1.215–6.75; $p = .016$). For CNI, IND did not show any significant association (9% vs. 12, $p = .542$) (Table 3) (Figure 1).

Shunt was performed in 25 patients (36%) with IND and selective-shunting did not reach significative difference regarding above-mentioned outcomes [26].

All cases of conversion to general anesthesia were due to IND (IND 10 (12.6%) vs. control 0, $p = .001$). Among IND patients, conversion to general anesthesia was not associated to 30-day stroke ($p = .579$).

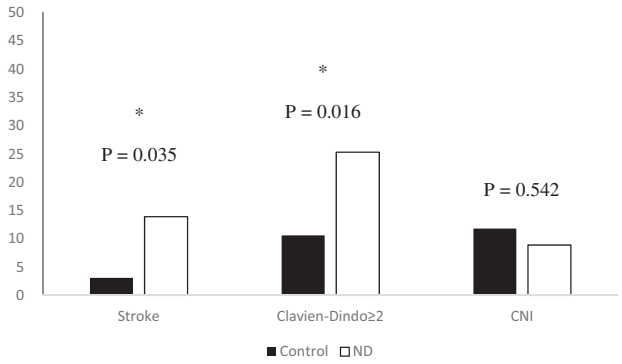

Figure 1. 30 day postoperative adverse events. ND: alterations on the neurologic examination during carotid clamping. *Confirmed by multivariable analysis.

Discussion

The reasoning for the present study is the assumption that patients developing IND during CACC are manifesting some degree of cerebral ischemia, thus having a higher risk of developing a perioperative stroke. In fact, in the present cohort, a fourfold increased risk of developing 30-day stroke in patients with IND was identified. In a study with 385 patients, Piffaretti et al. found a significant association between IND and subsequent postoperative ischemic events, denoting an aOR of 6.60 (95% CI: 1.65–26.36), $p = .008$ [35]. Some ischemic lesions are associated with injury to the ischemic penumbra surrounding recent infarction, in addition to the traditional association between procedure-related embolization and intra- and postoperative stroke [2]. The surgery itself might predispose to remaining flow turbulence and impairment of carotid baroreflex, which has been previously associated with further embolism and stroke in the short-term [36,37].

In the present study, inferior degrees of ipsilateral stenosis were associated with higher rates of post-clamping deficits. It is important to highlight that a stenosis greater than 90% allows for a minimal continuous brain blood flow and consequently decreases the susceptibility to low flow periods [38], allowing better CACC tolerance. In stroke patients with unilateral carotid stenosis, contralateral carotid flow displays a crucial role in compensating cerebral hypoperfusion, whereas posterior circulation becomes fundamental when stenosis is bilateral [17,39]. In fact, patients with severe stenosis have reduced risk of transient ischemic attack/stroke, due to the presence of collateral pathways [38]. A positive association was found between contralateral internal carotid stenosis and increased incidence of IND. A similar trend was found in the General Anesthesia vs. Local Anesthesia for Carotid Surgery (GALA) trial ($p = .098$) [11], and the association of contralateral stenosis with perioperative stroke is frequent in the literature [40,41]. Therefore, the degree of stenosis of both sides must be taken into account during surgery planning as contralateral anatomy might influence different strategies and outcomes.

Concerning the surgery itself, CACC time was significantly lower in the group with IND. However, this finding is a consequence of neurologic deficits detection leading to quicken procedures and, therefore, it must not be interpreted as a potential risk factor. In addition to this, a report has shown clamping tolerance in patients with 40–50 min of CACC, which might explain and supports clamping times in these series [42].

Age was preliminarily found to increase the risk of IND, although when adjusted for confounding, the effect was not confirmed. Actually, older patients might as well endure other comorbidities that potentially affect the results. Nonetheless, higher stroke and mortality rates among octogenarians remain acceptable and should not be labeled as "non-eligible" for surgery according to the actual evidence [43].

Obese patients had a significantly ninefold higher risk of IND during CEA. It was previously reported that BMI $> 30\ kg/m^2$ is associated with increased surgical time and complications [44,45]. Due to the quantity of adipose tissue present in these patients, the surgical technique might display more difficulties leading to higher extensive dissection or additional manipulation and thus generating a predisposition to embolic incidents. Furthermore, these patients could present higher intolerance to the surgery or a lower threshold for dyspnea associated with a shorter neck. Kardassis et al. found an increased plaque area and thickness in common carotid artery and bulb of obese patients, suggesting higher susceptibility to inflammatory stimuli and further hemodynamic stress [46], leading to an increased risk of postoperative stroke in these patients.

It was also verified that the use of calcium channel blockers was associated with an increased incidence of IND, although not confirmed by multivariable analysis. The triggered systemic vasodilation might accentuate hypotension and further cerebral hypoperfusion in addition to the CACC [47]. Furthermore, these agents are associated with cerebral vasodilation after CEA, which might be detrimental for patients with reestablished/higher cerebral perfusion and higher impairment of autoregulation [47]. These changes in blood flow could play a role predisposing higher stroke rates after surgery.

ASA was not comparable between controls and the group with clamping related IND, whereas it has shown significantly higher levels in the latter. This finding is supported by another report that suggests severe forms of atherosclerotic plaques in these patients. These plaques might explain the higher instability and, subsequently, the presence of more intraoperative deficits [48].

While RA was not associated with better outcomes than general anesthesia, there are differences in hemodynamic stability and neurological monitoring ease [23]. Only a few patients in this cohort were converted to general anesthesia ensuring the tolerability of the anesthetic method. Conversion to general anesthesia was always associated with IND in this cohort, although its prognostic implications cannot be definitely assured.

This series describes one of the most extensive series of CEA under RA with post-CACC associated neurologic deficits. The low rate of patients with IND (8%) made the prospective registry and case recruitment a hard task. Patient

selection criteria did not change significantly during the follow-up, although due to the long time frame, some bias could be present. This study was performed in a large academic teaching institution (>100 CEAs per year), which might affect the external validity of the results to community hospitals that perform a large proportion of CEA. In addition, the comorbidities were comparable among groups, which weakens the chance of confounding factors. The option to shunt after the diagnosis of IND was left to the surgeon discretion, which might lead to some interference with the results, although the stroke rate was still elevated comparing to controls [26].

Neurologic deficits associated to CACC was confirmed as a relevant risk factor for major postoperative adverse events. Such patients could benefit from postoperative intensive care surveillance and preoperative patient selection. BMI > 30 kg/m^2, lower ipsilateral stenosis, and higher contralateral stenosis were significantly associated with a higher incidence of IND. Therefore, its management could play a critical role in the prevention of procedure-related stroke.

Future studies should focus on strategies to prevent or reduce IND after CACC. Further steps are necessary to develop a consistent score for patient selection or prompt prophylactic shunt placement among high-risk patients, reducing the exposure to symptomatic cerebral ischemia and the possibility of lifelong lesions.

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Data availability statement

This study database is available in *Clinical registry*: https://www.researchregistry.com. *Identifying number*: researchregistry4929. Hyperlink to the registration: https://www.researchregistry.com/register-now#home/registrationdetails/5cf4721053761c000cc1c25a/

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Red blood cell distribution width is associated with hypoperfusion in carotid endarterectomy under regional anesthesia

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ABSTRACT

Background: A subset of patients submitted to carotid endarterectomy under regional anesthesia develop intraoperative neurologic deficit during carotid artery crossclamping related to critical cerebral perfusion, which may be owing to low flow or embolic phenomena. This subgroup is deemed prone to worse outcomes, which highlights its clinical relevance. The main aim of this study was to identify clinical and hematological predictors for intraoperative neurologic deficit. The secondary aim was to evaluate the perioperative prognostic value of postcarotid artery crossclamping manifestations of cerebral ischemia.
Methods: Between January 2012 to January 2020, patients submitted to carotid endarterectomy under regional anesthesia in a tertiary referral center who presented intraoperative neurologic deficit were prospectively and consecutively included. This group constituted 8% of the total carotid endarterectomy performed in the center during this timeframe. The control group of patients was the subsequent patient submitted to carotid endarterectomy without intraoperative neurologic deficit in a 1:1 ratio. Blood samples were collected before surgery (<2 weeks). Propensity score matching was used to identify well-matched pairs of patients.
Results: A total of 180 patients were included, with 90 (50% of the cohort and 8% of total carotid endarterectomies) presenting intraoperative neurologic deficit associated to clamping. Mean age was 71.4 ± 9.27 years in the study group and 68.8 ± 8.36 years in the control group. The clinical variables presenting significance after multivariate analysis include: age (adjusted odds ratio: 1.04, 5-95% confidence interval, [1.003−1.078]; $P = .034$), obesity (adjusted odds ratio: 3.537 [1.445−8.658]; $P = .006$), lower ipsilateral carotid stenosis grade (adjusted odds ratio: 0.725 [0.525−0.997]; $P = .049$), and higher contralateral carotid stenosis grade (adjusted odds ratio: 1.266 [1.057−1.516]; $P = .010$). Red cell distribution width coefficient of variation demonstrated statistical significance in predicting intraoperative neurologic deficit with an adjusted odds ratio of 1.394 (1.076−1.805); $P = .012$.
The 30-day stroke rate was significantly higher in the intraoperative neurologic deficit group, with an adjusted odds ratio of 5.13 (5−95% confidence interval [1.058−24.87]; $P = .042$) after propensity score matching. Postoperative complications (Clavien-Dindo ≥2) were also associated with intraoperative neurologic deficit (after propensity score matching adjusted odds ratio of 2.748 [5−95% confidence interval, 0.976−7.741]; $P = .051$).

António Pereira-Neves and João P. Rocha-Neves contributed equally to this paper.

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Conclusion: In this study, increased red cell distribution width coefficient of variation demonstrated value to predict intraoperative neurologic deficit. Additionally, age, obesity, a lower degree of ipsilateral carotid stenosis, and a higher degree of contralateral carotid stenosis also demonstrated ability to predict intraoperative neurologic deficit. Moreover, intraoperative neurologic deficit was an independent risk factor for 30-day stroke and postoperative complications Clavien-Dindo ≥2.

Introduction

State of the art still highlights carotid endarterectomy (CEA) as the gold standard for patients with both symptomatic and asymptomatic carotid stenosis (CS), reducing transfemoral carotid artery stenting (CAS) for selected cases owing to a higher risk of procedural (30-day) stroke in CAS versus CEA.[1]

Regional anesthesia (RA) allows the direct monitoring of the neurological status of the patient during CEA, being the most accurate, simple, and cost-effective method for diagnosing critical cerebral perfusion that may be owing to low flow or embolic phenomena.[2] Intraoperative neurological deficit (IND) manifested during carotid clamping has been repeatedly described as a risk factor for perioperative stroke.[3–5] It occurs in 7% to 30%[4] of patients submitted to CEA under RA, and these patients are most prone to adverse events.[3–6] Hence, the importance of predicting IND is evident as it relates to major postoperative events. Moreover, it has been advanced that this subpopulation could have an increased susceptibility to carotid restenosis consequences, requiring closer surveillance during follow-up.[1,7]

The hematological parameters in the standard complete blood cell count have been emerging as potential biomarkers in a broad spectrum of medical areas owing to their wide availability. Their clinical utility has been studied from isolated parameters such as the hemoglobin level,[8] red blood cell distribution width (RDW),[9] and mean platelet count[10] to more complex ratios, such as neutrophil-to-lymphocyte ratio.[11] Red cell distribution width coefficient of variation (RDW-CV) is a hematological parameter that reflects the heterogeneity of red blood cell (RBC) volume (anisocytosis), and it is defined by the ratio between RBC standard deviation and the mean corpuscular volume, multiplied by 100, with values below the reference limit being infrequent and clinically meaningless.[12] On the other hand, increased RDW-CV was related to erythrocyte homeostasis deregulation, including impaired erythropoiesis and abnormal erythrocyte metabolism and survival. Numerous factors can contribute to the increase of RDW-CV, such as oxidative stress, inflammation, erythrocyte fragmentation, poor nutritional status, hypertension, dyslipidemia, and erythropoietin dysfunction, which represent prognostic factors for severe cardiovascular morbidity and mortality.[12,13] Anemia associated with increased RDW may be owing to iron deficiency, hemolysis, vitamin B12 deficiency, folate deficiency, among other etiologies.[12] Remarkably, increased RDW has revealed prognostic ability for worse outcomes without being necessarily associated with hemoglobin levels.[14,15] This predictive ability has covered a wide range of pathologies, such as cancer,[16] coronary artery disease,[17] and peripheral artery disease.[18]

The main aim of this study was to evaluate the predictive ability of different clinical and hematological parameters for IND. The secondary aim was to evaluate the perioperative prognostic value of postcarotid artery crossclamping manifestations of cerebral ischemia.

Methods

Study population

Between January 2012 to January 2020, patients submitted to CEA under RA in a tertiary referral center presenting with IND during CEA were prospectively and consecutively included. The control group was the immediately consecutive patient submitted to CEA under RA without the development of IND with a 1:1 ratio.

Patients were evaluated before surgery by a vascular surgeon and an anesthesiologist. In symptomatic stenosis, patients were also assessed by a neurologist. Participants were followed in the postoperative period in the outpatient clinic, and clinical examination and Doppler ultrasound were performed at 30 to 90 days after discharge and 1 year of follow-up. All the patients were under single antiplatelet (172 patients) or dual antiplatelet therapy (7 patients).

Blood samples were collected up to 2 weeks before surgery, and a blood cell count was performed using a Sysmex XE-2100 analyzer (Sysmex Corporation, Kobe, Japan). Hematological variables were quantified using the sodium lauryl sulfate method for hemoglobin or impedance and optical methods for the remaining parameters. When several samples per patient met inclusion criteria (<2 weeks before CEA), hematological data used for study purposes was the closest sample previous to the surgery.

This study was reported according to the Strengthening the Reporting of Observational studies in Epidemiology guidelines.[19] The study protocol (number 248-18) was approved by the local Ethics Committee and respected the Helsinki Declaration. This trial is registered on the ClinicalTrial.gov public website with the identifier NCT04347785.

Definitions

Neurologic deficits were defined as any symptom alteration or sign at neurologic examination (speech, motor function, and consciousness) during carotid artery crossclamping (CACC) present after hemodynamic adjustment.[20] Event adjudication was performed by the anesthesia-surgical team.

CS was considered symptomatic or asymptomatic according to the clinical practice guidelines of the European Society of Vascular Surgery.[1] CS was measured through either Doppler ultrasound according to velocimetric criteria or computed tomography angiography using the North American Symptomatic Carotid Endarterectomy criteria.[7,21] Postoperative major adverse events were defined as the postoperative complications with a Clavien-Dindo grade ≥2 (30-day stroke rate, hyperperfusion syndrome, hypotension with the need for adrenergic support, and reintervention for neck hematoma).[22]

Obesity was defined as a body mass index >30 kg/m.^{2} A patient was defined as a smoker if there was a current smoking status or a history of smoking (>100 smoked cigarettes in his/her lifetime). Chronic kidney disease was defined as an established diagnosis of chronic kidney disease or a basal creatinine ≥1.5mg/dL.

Surgical technique

The surgical technique consisted of CEA followed by direct suture, patch angioplasty, or eversion technique and was left to the surgeon's decision. The surgeon also decided on the use of a shunt. When faced with IND routine, nonshunters who usually used eversion proceeded with the same approach. Routine nonshunters who used patch frequently resorted to direct suture in favor of reducing clamping time. More than 98% of the CEAs are performed under RA in this referral center. The center has a reported stroke rate in CEA of 2% and a combined stroke/death rate of 2% (>100 procedures per year).[23] The exclusion criteria for RA are synchronous cardiac surgery and patients a priori unwillingness to stay awake during the intervention.

Intraoperative monitoring consisted of consecutive brief awake neurological examinations and surveillance every 3 minutes during CACC. The neurological examinations prevailed in the definition of IND events.[24] Data of the cerebral oximeter (INVOS; Medtronic, Dublin, Ireland) was additionally collected.

Statistical analysis

Statistical analysis was made with SPSS Statistics for Windows, version 26.0 (IBM Corp, Armonk, NY). Comparisons in univariate analysis were performed using $\chi 2$ or Fisher exact tests for categorical variables and Student's *t* test for continuous variables. A *P* value of less than .05 was considered significant.

The necessary sample for a 2-sided test for nonsuperiority was calculated, resorting to WinPepi V11.65,[25] aiming for statistical power (β) of 90% and an $\alpha < .05$. The described neurologic event rate in patients suffering IND is 12%, and an event rate of 1.8% for the control patients was assumed.[26,27] For an event rate difference of 10% between groups, the estimated sample was 68 patients.

Because the 2 subgroups differed significantly concerning many clinical characteristics (Table I), a propensity score matching (PSM) analysis using the preoperative CEA parameters was additionally used to reduce confounding factors between categories. In this procedure, pairs of patients were established using 1:1 nearest-neighbor matching with a ±0.05 caliper and without replacement. A standardized mean difference higher than 0.1 was considered as an imbalance.

The regressive predictive model was created, resorting to regression analysis and dimension reduction by the method of backward feature elimination. Variables with clinical relevance included in the multivariate analysis were associated with the group with IND in the univariate analysis with statistical significance $P < .1$. Based on clinical and hematological predictors with statistical significance for symptomatic intraoperative cerebral hypoperfusion, 2 formulas were created and evaluated: a clinical predictive model and a clinical plus hematological predictive model. A receiver operating characteristic (ROC) curve was applied for the comparison of both models.

Results

Baseline demographics

A total of 180 patients were included, with 90 (50%) presenting IND associated with clamping (case-control study on a 1:1 ratio), representing 8% of the total number of patients who underwent carotid surgery at this center during the timeframe of this study. Mean age was 71.4 ± 9.27 years in the study group and 68.8 ± 8.36 years in the control group, demonstrating statistical significance in univariate analysis and sustaining it on the multivariable review (adjusted odds ratio [aOR] 1.04 [5—95% confidence interval (CI): 1.003—1.078]; $P = .034$). Male sex was predominant in both groups, representing 74.4% and 85.6% in the IND group and control group ($P = .062$, respectively, although not confirmed on multivariable analysis). Concerning patients' comorbidities in the IND and control group, only obesity displayed predictive value for IND ($P = .002$) with an aOR of 3.537 [1.445—8.658]; $P = .006$.

Laterality and the CS symptomatic status were not predictors of IND. On the other hand, both ipsilateral and contralateral CS were predictors. For ipsilateral CS, lower stenosis grade was a risk factor for IND (aOR of 0.725 [0.525—0.997]; $P = .049$), even though it was just an approximate absolute 3% difference, while >70% contralateral CS, higher stenosis grade increased IND risk (aOR of 1.266 [1.057—1.516]; $P = .010$) (Table I).

Hematological parameters and intraoperative neurologic deficit

Of the several hematological predictors tested, including absolute counts of blood cells and hematological ratios, only RDW-CV demonstrated statistical significance for predicting IND with an aOR of 1.380 (5-95% CI: 1.018—1.871); $P = .034$ after PSM (Table II).

Predictive models for intraoperative neurologic deficit

Assuming the clinical characteristics and hematological parameter (RDW-CV), which proved statistically significance in predicting IND, a new predictive model, including RDW-CV, was created.

The clinical plus hematological predictive model performed better (versus clinical predictive model alone) with an area under the ROC of 0.716 (0.640—0.791) and 0.686 (0.608—0.764), respectively (R2 = 0.216 vs R2 = 0.170, respectively) (Fig 1).

30-day postoperative outcomes

The 30-day stroke rate was significantly higher in the IND group, even after PSM adjustment, with a multivariable aOR of 5.13 (5—95% CI, 1.058—24.87; $P = .042$). The postoperative complications Clavien-Dindo ≥ 2 were also significantly more common among the IND group and confirmed with PSM: aOR of 2.748 (5—95% CI, 0.986—7.741), $P = .051$. Thirty-day cranial nerve injury did not vary significantly between groups ($P = .342$) (Table III).

None of the tested hematological predictors revealed predictive value for postoperative 30-day stroke, postoperative adverse events, or cranial nerve injury, independently from the development of IND.

Discussion

The main finding of this study was the ability of RDW-CV to predict IND. Additionally, both age and obesity were clinical characteristics increasing the risk for IND. That susceptibility was also augmented with higher degrees of contralateral CS and lower degrees of ipsilateral CS. A role of IND in predicting 30-day postoperative complications was also established.

It is remarkable that RDW-CV demonstrated further predictive power concerning IND when comparing the 2 predictive models created. Additionally, this study underlines the prognostic significance of intraoperative awake tests, predicting 30-day postoperative complications and stroke, thus underscoring the importance of defining new risk factors and predictive models for IND.

To the best of the authors' knowledge, this is the first study to report a statistically significant association between increased RDW-CV and susceptibility for IND. Recently, RDW values have been positively correlated with carotid intima-media

Table I
Demographics and comorbidities of the patients

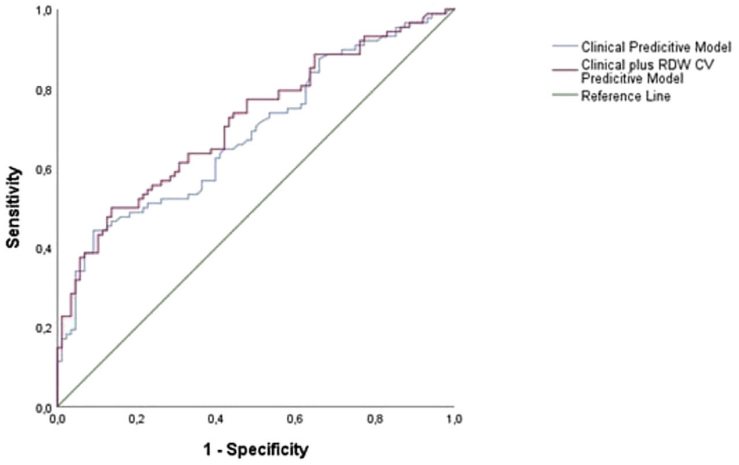
	Study population				After propensity matching		
	Control *n* (%) 90 (50)	IND *n* (%) 90 (50)	*P* value	Multivariable aOR CI 5–95	Control *n* (%) 59 (50)	IND *n* (%) 59 (50)	*P* value
Age (y)	68.76 ± 8.360	71.42 ± 9.271	**.044**	1.04 (1.003–1.078) (0.034)	69.03 ± 8.39	69.78 ± 9.30	.648
Side (right)	50 (56.6)	40 (44.4)	.136		30 (50.8)	30 (50.8)	1.000
Sex (male)	77 (85.6)	67 (74.4)	.062	NC	48 (81.4)	49 (83.1)	.810
Hypertension	79 (87.8)	78 (86.7)	.823		50 (84.7)	48 (81.4)	.624
Smoking history	51 (56.7)	40 (44.4)	.101		28 (47.5)	31 (52.5)	.581
Diabetes	37 (41.1)	41 (45.6)	.547		23 (39)	25 (42.4)	.708
Dyslipidemia	78 (86.7)	77 (85.6)	.829		50 (84.7)	51 (86.4)	.793
Cholesterol	182.0 ± 46.10	180.5 ± 45.56	.841		188.2 ± 50.77	180.5 ± 45.56	.431
HDL	44.2 ± 14.98	42.4 ± 12.86	.416		46.0 ± 12.65	42.4 ± 12.86	.177
LDL	108.5 ± 36.50	127.7 ± 148.1	.265		114.1 ± 40.18	127.7 ± 148.09	.605
Triglycerides	150.6 ± 70.9	139.1 ± 47.4	.232		148.6 ± 80.77	139.1 ± 47.38	.438
CKD	13 (14.4)	12 (13.3)	.829		7 (11.9)	9 (15.3)	.591
BMI >30 kg /m2	8 (8.9)	24 (26.7)	**.002**	3.537 (1.445–8.658) (0.006)	7 (11.9)	8 (13.6)	.782
PAD	22 (24.4)	20 (22.2)	.724		14 (23.7)	14 (23.7)	1.000
CAD	28 (31.1)	33 (36.7)	.431		21 (35.6)	19 (32.2)	.697
COPD	13 (14.4)	10 (11.1)	.503		4 (6.8)	8 (13.6)	.223
CHF	11 (12.2)	11 (12.2)	1.000		8 (13.6)	6 (10.2)	.569
ASA	13 (15.7)	13 (15.5)			12 (21.1)	9 (15.8)	.424
	65 (78.3)	64 (76.2)	.846		43 (75.4)	43 (75.4)	
	5 (6)	7 (8.3)			2 (3.5)	5 (8.8)	
Asymptomatic	50 (55.6)	50 (55.6)			31 (52.5)	36 (61)	.643
Symptomatic	40 (44.4)	40 (44.4)	.963		28 (47.5)	23 (39)	
TIA	9 (10)	8 (8.9)			8 (13.6)	7 (11.9)	
Stroke	31 (34.4)	32 (35.6)			20 (33.9)	16 (27.1)	
Time to revascularization, median (CI 25%–75%)	14 (10–30.5)	12 (8–29)	.379		16.5 (10–38.25)	12 (6.75–62.25)	.390
Ipsilateral stenosis degree	84.7 ± 9.55	81.8 ± 11.07	.071	0.725 (0.525–0.997) (0.049)	84.2 ± 10.04	84.1 ± 0.931	.924
Contralateral stenosis degree	60.1 ± 15.34	66.6 ± 21.17	**.021**	1.266 (1.057–1.516) (0.010) *	61.9 ± 17.27	62.4 ± 17.05	.872
Contralateral stenosis							
(>50%)	41 (45.6)	50 (55.6)	.180		29 (49.2)	32 (54.2)	.58
(>70%)	13 (14.4)	23 (25.6)	**.046**		10 (16.9)	11 (18.6)	.81

Bold–statistically significant values.
aOR CI 5-95, adjusted odds ratio confidence interval 5-95; *ASA*, American Society of Anesthesiologists physical status classification system; *BMI*, body mass index; *CAD*, coronary artery disease; *CHF*, cardiac heart failure; *CI*, confidence interval; *CKD*, chronic kidney disease (creatinine = 1.5 mg/dL); *COPD*, chronic obstructive pulmonary disease; *HDL*, high-density lipoprotein; *IND*, alterations on the neurologic examination during carotid clamping; *LDL*, low-density lipoprotein; *PAD*, peripheral artery disease; *Obesity*, body mass index >30kg/m2; *NC*, not confirmed on multivariable analysis; *TIA*, transient ischemic attack.
* Collinearity with "contralateral stenosis degree."

Table II
Hematologic parameters

	Study population				After propensity matching			
	Control *n* = 59 (%)	IND *n* = 59 (%)	*P* value	Multivariable aOR CI 5–95	Control *n* = 59 (%)	IND *n* =59 (%)	*P* value	Multivariable aOR CI 5–95
Hemoglobin (g/dL)	13.09 ± 1.985	13.14 ± 1.735	.857		12.93 ± 1.95	13.23 ± 1.79	.389	
MCHC (g/dL)	33.930 ± 1.094	33.611 ± 1.207	.065	NC	33.82 ± 1.03	33.71 ± 1.16	.569	
RDW-CV (%)	13.292 ± 1.009	13.722 ± 1.590	.032	1.394 (1.076 –1.805) (0.012)	13.21 ± 0.97	13.76 ± 1.68	.029	1.380 (1.018–1.871) (0.034)
RDW-SD (fL)	43.843 ± 3.800	44.341 ± 5.035	.455		44.01 ± 4.09	44.34 ± 5.24	.702	
Lymphocyte count	2.10 ± 0.67	1.95 ± 0.69	.134		1.98 ± 0.62	2.01 ± 0.74	.821	
Lymphocyte (%)	29.02 ± 9.101	26.958 ± 8.43	.116		28.27 ± 8.91	27.34 ± 8.57	.568	
Neutrophil count	4.53 ± 1.83	4.60 ± 1.57	.789		4.39 ± 1.70	4.60 ± 1.52	.488	
Neutrophil (%)	58.89 ± 10.000	61.25 ± 9.972	.111		59.35 ± 9.95	61.00 ± 10.02	.373	
Platelet count	230,355 ± 89.01	219,998 ± 65.61	.374		231,237.3 ± 92.68	218,457 ± 63.23	.383	
MPV (fL)	10.878 ± 9.23	11.034 ± 0.940	.265		10.87 ± 0.96	11.01 ± 1.01	.444	
PDW (fL)	13.0142 ± 2.202	13.498 ± 2.369	.185		13.06 ± 2.35	13.53 ± 2.67	.323	
Neutrophil/lymphocyte ratio	2.3806 ± 1.245	2.676 ± 1.505	.153		2.43 ± 1.20	2.63 ± 1.52	.452	
Platelet/lymphocyte ratio	125,366 ± 88226	124,388 ± 50,085	.927		132,972 ± 95,586	122,058 ± 51,779		
Hemoglobin/platelet ratio	0.0648 ± 0.024	0.065 ± 0.021	.907		0.0651 ± 0.02696	0.0657 ± 0.02123	.889	
PDW / platelet ratio (fL)	0.064 ± 0.027	0.0675 ± 0.025	.412		0.0652 ± 0.02950	0.0679 ± 0.02652	.599	
RDW-CV / platelet ratio (%)	0.0654 ± 0.024	0.0679 ± 0.022	.467		0.0660 ± 0.02627	0.0679 ± 0.02149	.670	

aOR CI 5–95, adjusted odds ratio confidence interval 5–95; *IND*, alterations on the neurologic examination during carotid clamping; *MCHC*, mean corpuscular hemoglobin concentration; *MPV*, mean platelet volume; *NC*, not confirmed on multivariable analysis; *PDW*, platelet distribution width; *RDW-CV*, red blood cell distribution width coefficient of variation; *RDW-SD*, red blood cell distribution width standard deviation.



	AUROC CI 5–95%	*P*
Clinical + RDW CV predictive model	0.716 (0.640–0.791)	**.000**
Clinical predictive model	0.686 (0.608–0.764)	**.000**

Clinical predictive model includes contralateral stenosis, ipsilateral stenosis, obesity, and age.
Clinical + RDW-CV predictive model includes clinical model plus RDW-CV.
AUROC, area under the receiving operating characteristic curve; *CI,* confidence interval; *RDW-CV,* red cell distribution width coefficient of variation

Fig 1. ROC curves of clinical and clinical plus hematological predictive models for symptomatic intraoperative cerebral hypoperfusion.

Table III
Thirty-d complications after carotid intervention

Variables at 30-d	Study population				After propensity matching			
	Control $n = 90$ (%)	IND $n = 90$ (%)	*P* value	Multivariate aOR CI 5–95	Control $n = 59$ (%)	IND $n = 59$ (%)	*P* value	Multivariate aOR CI 5–95
Stroke	3 (3.3)	13 (14.4)	.009	4.896 (1.345–17.827) (0.016)	2 (3.4)	9 (15.3)	.027	5.13 (1.058–24.87) (0.042)
PC	8 (8.9)	22 (24.4)	.005	3.316 (1.388–7.921) (0.007)	6 (10.2)	14 (23.7)	.05	2.748 (0.986–7.741) (0.051)
CNI	11 (12.2)	7 (7.8)	.320		7 (11.9)	4 (6.8)	.342	

aOR CI 5–95, adjusted odds ratio confidence interval 5–95; *CNI,* cranial nerve injury; *IND,* alterations on the neurologic examination during carotid clamping; *PC,* postoperative complications Clavien-Dindo ≥2; 30 days: stroke, surgical hematoma, and hyperperfusion syndrome.

thickness[28,29] and carotid plaque development and progression.[30] A population-based study with 26,879 patients with a mean follow-up of 15.2 years calculated the incidence of total stroke and its subtypes in relation to sex-specific quartiles of RDW.[29] It was found that increased values were linked to an increased incidence of stroke and cerebral infarction after adjustment for stroke risk factors and hematological parameters. In this study, neither intracerebral nor subarachnoid hemorrhage were associated with RDW. Bojakowski et al[31] concluded, in a retrospective study of 115 patients submitted to carotid thromboendarterectomy, that in patients with high risk for cerebrovascular events, RDW identifies those with an increasingly higher probability of vascular complications. In a prospective study, where 1,065 of 1,286 consecutive patients with asymptomatic CS were included, RDW was found to be significantly associated with all-cause mortality and with cardiovascular mortality.[32]

The underlying pathophysiology of RDW in atherosclerotic cardiovascular disease is not fully understood. Inflammation and oxidative stress, critical in atherosclerosis,[33] can have an inhibitory effect on erythropoiesis leading to an increase in RBC variation.[32] Additionally, oxidative stress augments vascular resistance by inducing adhesion between RBCs with endothelium and reduced RBC deformability, a possible explanation for worse outcomes in those with higher levels of RDW.[34] Moreover, the link of increased RDW with high oxidative stress and low levels of antioxidants has been associated with neuronal damage during cerebral ischemia and reperfusion, which could also influence functional outcome and mortality in this population.[35] Treatments for atherosclerosis targeting inflammatory pathways still have low-quality evidence, mainly based on either observational or small interventional studies.[36] Higher RDW-CV values are independently associated with inflammation, a critical factor in plaque progression, and vulnerability.[14] As such, some authors consider RDW a marker of inflammation.[37]

Furthermore, this study corroborates our previous findings that obesity, a lower degree of ipsilateral CS, and a higher degree of contralateral CS are clinical predictors of IND.[7] On the other hand, it is interesting to find that CS symptomatic status was not a significant predictor of IND, even though it is

unequivocally linked to a higher risk for 30-day stroke versus asymptomatic patients.[1]

Age presented a statistical significance for IND. It can be advanced that age-related mechanisms involving intracranial and cerebral atherosclerosis and arterial stiffness[38] ultimately alter cerebral blood perfusion.[39,40]

Multiple studies showed that female sex is associated with adverse outcomes after carotid artery interventions. The higher risk of perioperative stroke, combined with the lower natural history risk of stroke in CS, ultimately leads to a smaller stroke absolute risk reduction after CEA.[41] Hypotheses concerning sex-related different outcomes rely on smaller and less compliant arteries in women and plaque morphology (more stable plaques and smaller plaque area when compared with men). There are also different risk profiles as women undergoing vascular procedures are usually older, more often obese with hyperlipidemia or hypertension, and less likely to smoke, to have coronary disease or diabetes, and are more commonly without optimized medical therapy).[42–44] If these factors, alone or in interaction, can also increase the risk of IND is uncertain. However, female sex has been described as a risk factor for shunting owing to IND.[45]

Concerning obesity, the shorter neck length and adipose tissue hinder the surgical procedure, requiring more extensive dissection and consequently leading to longer operating times.[46] Consequently, obesity predisposes to IND by promoting higher cerebral hypoperfusion times and embolism, given the increased manipulation or the augmented carotid plaque instability associated with obesity.[47]

Cerebral perfusion is impaired in patients with CS. However, compensatory mechanisms are present, mainly through the contralateral carotid artery,[48] which probably explains the >70% degree contralateral stenosis as a predictor of IND. This result is corroborated by Kretz et al, who reported a higher probability of shunting owing to IND when the blood flow is low in the contralateral common carotid artery, while moderate flow is revealed to have a protective effect.[45] This study also detected a higher predisposition for IND in those with a smaller degree of ipsilateral CS, possibly reflecting a deficient activation of alternative blood flow pathways in response to ischemia, either from the vertebrobasilar system or an incomplete circle of Willis.[49,50] Tan et al monitoring cerebral perfusion through electroencephalogram for selective shunting achieved the same results, with moderate ipsilateral stenosis and severe contralateral stenosis associated with cerebral ischemia.[51] On the other hand, Pifarreti et al[52] identified hypertension and symptomatic CS as independent risk factors for CACC intolerance, a result not confirmed in the present study. The preoperative assessment of recruitable collaterals and maximal decrement in middle cerebral artery mean flow velocity after carotid compression could be useful predictors of carotid clamping intolerance.[53] The symptomatic status might represent a risk factor when associated with watershed stroke. The low-flow mechanism that causes the so-called border-zone, junctional, or watershed strokes could explain the symptomatic status as a risk factor.[54,55] Thus, in this series, the fine intraoperative blood pressure management with a permissive hypertension protocol could have diminished the role of this factor on the manifestations of cerebral hypoperfusion.

Additional findings are the worse 30-day outcomes in patients who presented IND, including stroke and postoperative complications Clavien-Dindo $\geq$2. Further analysis of the etiology of the neurological events unveiled that all 3 strokes reported in the control group were tissue strokes, which is consistent with an embolic event. Regarding the 13 events from the IND group, 7 were watershed events, while 6 were tissue strokes. Davies et al also reported similar results with IND patients having a 6-fold increase of postoperative stroke (6.6% compared with 1.1%; $P < .01$).[5] Furthermore, 22 patients in the IND group (24.4%) were selectively shunted, but no statistical difference concerning stroke was revealed.[26] These patients represent a high-risk class and probably would benefit from a tailored anesthetic and surgical approaches besides shunting, possibly with a more aggressive antithrombotic therapy or a possible preoperative selection to endovascular, with CAS, for patients in high risk of IND, by avoiding CACC.[56,57] This question can only be addressed on a prospective multicenter-study approach owing to the low incidence of IND.

This study supports a role for RDW-CV in the stratification of patients who have a higher risk, thus assisting in the decision-making process, identifying those who would probably benefit from closer monitoring and more aggressive adjuvant medical therapy. Moreover, a clinical plus hematological predictive model was validated, which further increases the predictive power for IND during CEA under RA.

Limitations

Limitations from this study arise from the long timeframe of recruitment owing to the low rate of patients with post-CACC neurologic deficit (8%), although a considerably large sample is presented alongside a control group. This cohort belongs to a large academic teaching institution performing a large proportion of CEA, which might condition validity to community hospitals with lower surgical volumes. The guideline and the center patient selection criteria for CEA did not change significantly during the study recruitment and follow-up, although some bias could not be excluded. The option to shunt after the diagnosis of clamping associated ND was left to the surgeon's discretion and experience and described elsewhere.[26] This option might interfere with the results, although the stroke rate was still raised compared with control patients (shunters versus control patients and nonshunters versus control patients).[26] The comorbidities were comparable among groups and suffered further adjustment when resorting to PSM. Furthermore, no evaluation of cerebral collateral pathways or blood flow measurements was obtained before the procedure, which could further enlighten the pathophysiological pathway for IND and postoperative stroke.

The criteria derived from this study need additional validation from other cohorts, with relevance to RDW-CV, because no previous data is found in the literature. Additional biomarkers are needed for further improvement of the model and the creation of an assertive preoperative score (area under the ROC >0.8) for patient stratification and/or selective shunt placement.

In conclusion, increased RDW-CV was found to have the ability to predict intraoperative neurologic deficits after CACC in CEA under RA. Additionally, age, obesity, a lower degree of ipsilateral CS, and a higher degree of contralateral CS revealed the same predictive value. Neurologic deficits associated with CACC were confirmed as a relevant risk factor for major adverse events, such as 30-day stroke and postoperative complications Clavien-Dindo $\geq$2, and so, given its wide availability and low-cost, RDW-CV could further assist in the stratification of higher-risk patients.

Further research on risk score selective prophylactic shunting or other strategies to prevent and reduce the development of IND is needed in order to improve perioperative outcomes.

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Conflict of interest/Disclosure

The authors have nothing to declare.

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Original communication

Efficacy of near-infrared spectroscopy cerebral oximetry on detection of critical cerebral perfusion during carotid endarterectomy under regional anesthesia

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Summary: *Background*: Patients undergoing carotid endarterectomy (CEA) may suffer from cerebral hypoperfusion during the carotid cross-clamping. Near-infrared spectroscopy cerebral oximetry (NIRS) is a non-invasive method of regional cerebral oxygen saturation measurement reflecting changes in cerebral blood flow during CEA. The main goal of the study was to evaluate the accuracy of the NIRS in detecting cerebral hypoperfusion during CEA under regional anesthesia (RA) and compare it with awake neurological testing. *Patients and methods*: A prospective observational study of 28 patients that underwent CEA in RA and manifested neurologic deficits, and 28 consecutive controls from a tertiary and referral center, was performed. All patients were monitored with NIRS cerebral oximetry and awake testing as the control technique. Subsequently, operating characteristic curve and Cohen's *kappa* coefficient were determined to evaluate the reliability of the monitoring test. *Results*: NIRS presented a sensitivity of 27.3% and a specificity of 89.3% in comparison to awake testing. Receiver operating characteristic (ROC) curve analysis demonstrated that a decrease of at least 20% in cerebral oxygen saturation is the best threshold to infer cerebral hypoperfusion. However, the respective area under the curve (AUROC) was 0.606 (95% CI: 0.456–0.756, $P = 0.178$) with a calculated Cohen's *kappa* of 0.179, $P = 0.093$. Regarding 30-days outcomes, only awake testing has shown significant associations with stroke and postoperative complications ($P = 0.043$ and $P = 0.05$), which were higher in patients with post-clamping neurologic deficits. *Conclusions*: NIRS demonstrated a reduced discriminative capacity for critical cerebral hypoperfusion, and does not seem to add substantial clinical benefits to the awake test.

Keywords: Carotid Stenosis, Carotid Endarterectomy, Cerebral Oximetry, Near-Infrared Spectroscopy, Neurologic Deficits

Introduction

Carotid endarterectomy (CEA) is the standard treatment for high grade asymptomatic carotid stenosis (CS) and > 50% symptomatic CS [1]. This procedure implies an intraoperative carotid cross-clamping (CACC) [2], carrying an increased risk of embolism and cerebral hypoperfusion, which may be particularly hazardous in cases of poorly developed collateral circulation, such as an incomplete circle of Willis [2, 3]. Carotid blood flow shunting adds

complexity to the operation and is associated with significant stroke risk, carotid artery dissection, shunt plaque embolization, and air embolism or shunt thrombosis [4, 5]. Therefore, some authors propose to use selective shunting based on reliable monitoring of cerebral perfusion [5].

CEA may be performed under regional (RA) or general anesthesia (GA), and no significant differences in the outcomes have been found [6]. Monitoring techniques include electroencephalography (EEG), and somatosensory evoked potentials, transcranial Doppler sonography (TCD), carotid artery stump pressure, or evaluation of the continuous cerebral oxygenation using noninvasive cerebral oximetry [3]. The monitoring of neurologic status in an awake patient is considered the accepted standard for the detection of cerebral ischemia during CEA with RA. Still, other noninvasive cerebral perfusion measurements should be taken into account since clinical neurological deterioration might go unnoticed after CACC due to missed diagnosis of minor deficits, particularly in the non-dominant hemisphere, and these measurements can be applied under GA when necessary [7]. In this regard, near-infrared spectroscopy cerebral oximetry (NIRS) is applicable in all patients and is a noninvasive and real-time method of regional cerebral oxygen saturation (rSO_2) measurement reflecting changes in cerebral blood flow during CEA [8]. Besides, NIRS is easy to use and to interpret by the anesthesiologist and surgeon [9].

The first aim of this study was to evaluate the diagnostic and discriminative value of the NIRS cerebral oximeter, a NIRS-based instrument, in detecting cerebral hypoperfusion during CEA under RA and, consequently, to decide the need for selective shunting. A secondary aim was to propose a cutoff value to determine high-risk neurologic deterioration when using NIRS.

Patients and methods

Study population

From January 2013 to January 2018, 28 consecutive patients from a tertiary and referral center, who underwent CEA with RA and manifested neurologic deficits after CACC persisting after hemodynamic adjustment, were selected. All patients were monitored with NIRS cerebral oximetry with awake. The following patient submitted to the same procedure who did not develop neurologic alterations after CACC was selected as a consecutive control. All patients were monitored with NIRS cerebral oximetry with awake testing as the control technique.

A vascular surgeon and an anesthesiologist evaluated the patients before the surgery. Patients were under high dose statin and single antiplatelet therapy for at least two days before surgery [10]. This center has an annual volume >100 CEA per year. RA is the standard anesthetic technique in this institution (>98%).

All patients were subjected to preoperative angiocomputer tomography (CTA) according to NASCET criteria [11] or Doppler ultrasound (US) to define severity according to velocimetric criteria (50–70%; 70–90%; 90–99%) and to evaluate the other vessels involved in cerebral vascularization [12]. These assessments provided a full study on the localization, specific topography, and the severity of stenosis using velocimetric criteria [12]. Posterior circulation disease was defined as the presence of vertebral artery stenosis with hemodynamic significance on ultrasound or superior to 50% in the CTA in either side of vertebrobasilar circulation [13].

Study design

This is a *post hoc* analysis of a prospective case-control study with a 1:1 allocation ratio of consecutive patients who presented alterations in the neurologic examination after internal carotid clamping during CEA and a consecutive control selection. Detailed information was gathered regarding demographics, comorbidities, indications for surgery, surgery details, and other adverse events.

As inclusion criteria, patients with diagnosed CS undergoing elective CEA with RA were eligible. Exclusion criteria included conversion to GA before CACC or concomitant cardiac surgery.

This study was reported according to the Strengthening the reporting of observational studies in epidemiologyreporting guidelines [14]. The database is available on a research registry, and the study protocol approved by the local Ethics Committee (Protocol 248-18) and respects the Declaration of Helsinki. Patient informed consent was not required.

Definitions

Symptomatic CS was defined according to reporting standard guidelines [1, 15].

Post-clamping neurological deficits (ND) were defined as any alteration in the neurologic examination during CACC (mostly dysphasia, contralateral hemiparesis, and change in cognitive/consciousness status) persistent after hemodynamic adjustment [16].

Postoperative complications are a composed outcome of the 30-day rate of stroke, cerebral hyperperfusion syndrome, and surgical hematoma. No 30-day mortality or myocardial infarction was recorded in this cohort. Therefore, standard major adverse events (stroke, myocardial infarction, and all-cause mortality) [1, 15] were not reported. All the postoperative neurologic events were confirmed and evaluated by a neurologist, and further reevaluation was performed in all patients between 30 days to two months after surgery.

Surgical technique

All patients were subjected to CEA under RA, and cerebral oximetry was continuously monitored through INVOS™ (Medtronic, Minneapolis, MN, USA) with a simultaneous initial neurologic examination followed by subsequent

evaluations at 5 minutes intervals (personal questions, facial mimics, limb mobilization) or direct feedback as demanded by the surgeon. The RA technique consisted of a deep and superficial cervical plexus block using 20 mL of ropivacaine 0.5% [17]. When necessary, additional local anesthesia (lidocaine 2%) was administered by the surgeon upon the request of the patient. Two oximeter electrodes were placed bilaterally, as high as possible, upon the forehead of the patients. The values of rSO_2 were continuously monitored and recorded at two perioperative moments: the beginning of the operation and the lowest measurement during CACC. Changes in rSO_2 were expressed as absolute and relative values. Shunt use (4 cases – 14.2%) was left to the surgeon discretion and was performed based mainly on neurological examination, with backing from rSO_2 values. In shunted-patients the measurement of rSO_2 obtained before shunt was used [18]. The Javid shunt was used in the period 2013–2015 [2] and changed to the Pruitt-Inahara® 2015–2018 [2] due to logistic options. All endarterectomies were performed or supervised by an experienced vascular surgeon.

The incidence of stroke, postoperative complications, and cranial nerve injury were recorded. In the following 30 days after the procedure, patients were reassessed through clinical examination and Doppler US.

Statistical analysis

The Kolmogorov-Smirnov test was used to check the normality of variable distributions. Continuous and categorical data were subject to univariate analysis through Student's *t*-test, chi-square, or Fisher's test, respectively. Mann-Whitney U test was used to assess ordinal skewed variables and presented as median and 5–95% confidence intervals (CI). Categorical variables are presented as percentages and continuous variables as mean ± standard deviation (SD). Assessment of cutoffs of NIRS rSO_2 and its accuracy compared to the cerebral monitoring tests were conducted by receiver operating characteristic (ROC) curve analysis and using the Youdens J statistic. Accordingly, the sensitivity and specificity of the test were also determined. The area under the ROC curve (AUROC) is defined with its value, 95% CI, and P-value. Cohen's *kappa* (κ) was additionally calculated to assess the agreement between the gold-standard test and NIRS cerebral oximeter.

Statistical analysis was performed with SPSS (IBM Corp., release 2017. IBM SPSS Statistics for Windows, version 25.0, Armonk, NY, USA). Statistical significance was defined at alpha below 0.05.

Results

Demographics and comorbidities

Fifty-six patients who underwent CEA with RA were enrolled, and the majority of the patients were male (82.1%). The mean age was 69.63 ± 9.5 years old. Twenty-eight patients presented neurologic deficits (ND group) during CACC: hemiplegia, 2 patients (7.1%); aphasia, 6 patients (21.4%); lower conscience status, 20 patients (71.4%), with significant overlap between symptoms), whereas 28 patients (Control group) did not show alterations in the neurologic examination. There were no statistical differences concerning age and gender between the groups ($P = 0.071$ and $P = 0.076$) (Table I).

Regarding symptomatic status (stroke or TIA), no significant differences were found in its distribution between the groups (56.3% vs. 43.8%, $P = 0.634$). Concerning the degree of the carotid stenosis, the average value of the ND group was 84.4 ± 10.1 (%), which was comparable to the stenosis found in patients of the control group (83.9 ± 10.3%, $P = 0.671$). No statistically significant differences were found regarding the degree of contralateral carotid stenosis ($P = 0.256$). Body mass index above 30 kg/m^2 was significantly associated to more frequent neurologic deficits (32.1%; $P = 0.005$). Other baseline patient characteristics, such as the presence of vertebrobasilar disease and cardiovascular risk factors, are found in Table I.

Cerebral oximeter and awake testing values

In accordance with the ROC curve analysis, the AUROC was 0.606 (95% CI 0.456–0.756, $P = 0.178$) with the maximum Youden Index for a decrease of $rSO_2 > 20\%$, revealing to be the optimal threshold considering all the other evaluated variables (Figure 1). The sensitivity and specificity were 27.3% and 90%, respectively (Table II). However, the accuracy of NIRS in detecting critical cerebral hypoperfusion was low, considering the prevalence of ND in our center is ≈ 8% [19], NIRS presents a positive predictive value of 18.1%.

A reduction of > 20% in rSO_2 detected by NIRS was measured in 19.6% (11 patients) of the sample. Nevertheless, of these patients, only 8 had neurologic alterations confirmed by neurological evaluation. More than two-thirds (71.4%) of cases were not detected by NIRS considering the above threshold. NIRS detected in 3 patients a reduction of rSO_2 of at least 20% that was not followed by any neurologic deterioration. A diagnostic Cohen's *kappa* value of 0.179 for the decrease of $rSO_2 > 20\%$ revealed a poor agreement between the two tests ($P = 0.093$). Considering a reduction of $rSO_2 > 15\%$, a κ of 0.143 ($P = 0.217$) was achieved, and the same conclusion was extrapolated (Table II).

Perioperative adverse outcomes

In this subpopulation of patients submitted to CEA, a total of 7 strokes were recorded at 30 days. Of these, only 2 patients had a registered decrease of at least 20% in rSO_2 (one intraoperative stroke vs three intraoperative strokes in the group without NIRS fall), although the awake test was effective in detecting most of the postoperative strokes (6 in 7 strokes – 85.7%). (Table III) On the other hand,

Table I. Demographics and comorbidities.

	Control n = 28 (%)	ND n = 28 (%)	*P*-value
Age (years)	67.32 ± 9.9	71.93 ± 8.7	0.071
Gender (male)	26 (92.9)	20 (71.4)	0.076
Hypertension	23 (82.1)	26 (92.9)	0.225
Smoking history	18 (64.3)	15 (53.6)	0.415
Diabetes	11 (39.3)	10 (35.7)	0.783
Dyslipidemia	23 (82.1)	25 (89.3)	0.445
CKD	2 (7.1)	2 (7.1)	1
BMI > 30 kg/m^2	1 (3.6)	9 (32.1)	0.005
PAD	8 (28.6)	8 (28.6)	1
CAD	5 (17.9)	10 (35.7)	0.131
COPD	7 (25)	4 (14.3)	0.313
CHF	5 (17.9)	3 (10.7)	0.445
Atrial fibrilation	1 (3.6)	1 (3.6)	1
ASA, median [CI 5–95%]	3 [2.65–3.06]	3 [2.72–3]	0.927
Asymptomatic	13 (46.4)	15 (53.6)	
Symptomatic	15 (53.6)	13 (46.4)	
TIA	2 (7.1)	3 (10.7)	0.693
Stroke	13 (46.4)	10 (35.7)	
Time to revascularization, median [CI 5–95%]	17 [13.50–40.60]	13.5 [3.7–49.20]	0.212
Preop Hb (g/L)	12.3 ± 3.0	12.7 ± 2.9	0.607
Side (left)	16 (57.1)	9 (16.1)	0.060
Ipsilateral stenosis (%)	85.0 ± 8.4	83.9 ± 10.3	0.671
Contralateral stenosis (%)	58.9 ± 12.0	61.4 ± 19.7	0.256
Vertebrobasilar disease	3 (11.1)	9 (25.0)	0.182

ACEI: Angiotensin-converting enzyme inhibitor; ASA: American Society of Anesthesiologist Physical Status Classification System; BMI: Body mass index; CAD: Coronary artery disease; CCB: Calcium channel blocker; CHF: Cardiac heart failure; CI: Confidence Interval; CKD: Chronic kidney disease (creatinine = 1.5 mg/dl); COPD: Chronic obstructive pulmonary disease; ND: Neurologic deficits; PAD: Peripheral artery disease; Preop Hb: preoperative haemoglobin.

despite the higher number of strokes in patients without a drop of rSO_2 > 20%, > 80% of patients with rSO_2 < 20% were 30-days stroke-free. However, the observed association was not statistically significant (P = 0.525). Similar results were found for rSO_2 > 15%, P = 0.816 (Table III). Postoperative complications were higher in the group presenting a decrease > 20% in rSO_2 (36.4% vs. 17.8%). An identical trend was observed in the rate of cranial nerve injury, 18.2% vs. 8.9%. Nevertheless, these associations were not significant, either for decreases > 20% or > 15% in rSO_2, (P = 0.178/P = 0.372 and P = 0.452/P = 0.61839, correspondingly).

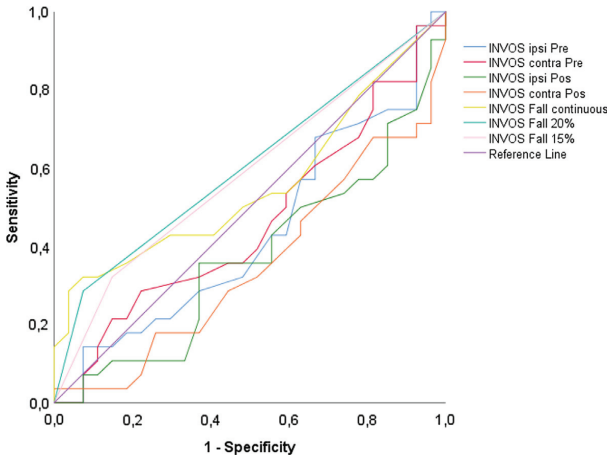
Regarding neurologic status assessment by neurologic examination, statistically significant associations were found when comparing 30-day stroke and postoperative complications (P = 0.043 and P = 0.05). Cranial nerve injury did not demonstrate significant association (P = 0.084) (Table III).

Discussion

Carotid cross-clamping during CEA predisposes to cerebral ischemic events [2]. Carotid shunting is the best method that might reduce the risk of perioperative stroke due to hypoperfusion. However, it is also associated with shunt related stroke [20]. In this study, the main findings were that monitoring the neurological status of the patients (mostly dysphasia or aphasia, contralateral hemiparesis and alteration in cognitive/conscience status) while performing the procedure under RA had shown a better capacity to predict critical cerebral hypoperfusion during CEA and post-operative adverse events than NIRS. These results are in agreement with other studies that found a very low positive predictive value in NIRS [21, 22].

Obese patients presented with a significantly higher risk of neurologic changes during the procedure. These patients can present higher intolerance to the surgery or higher level of dyspnoea associated with a shorter neck. Kardassis et al. found increased plaque area and thickness both in common carotid artery and bulb in obese patients, suggesting higher susceptibility to inflammatory stimuli and further hemodynamic stress [23].

The ROC curve demonstrated that a decrease of > 20% in rSO_2 is the optimal cutoff for hypoperfusion. This critical rSO_2 threshold is consistent with other studies [9, 21, 22, 24], although, in the literature, there is no consensus established [9, 25]. Kamenskaya et al. reported that a reduction at least 20% in rSO_2 on the ipsilateral side of the surgery is strongly associated with a 10-fold increased risk of stroke and an 8-fold amplified risk of cognitive disorders, which was not observed in this study [24].



	AUROC CI 5–95%	*P*=
Ipsilateral NIRS pre-clamp	0.434 [0.280–0.587]	0.400
Contralateral NIRS pre-clamp	0.461 [0.307–0.615]	0.619
Ipsilateral NIRS post-clamp	0.372 [0.224–0.520]	0.102
Contralateral NIRS post-clamp	0.353 [0.207–0.498]	0.060
NIRS fall (continuous)	0.558 [0.402–0.713]	0.464
NIRS fall >15%	0.587 (0.435–0.738)	0.270
NIRS fall >20%	0.606 (0.456–0.756)	0.178

INVOS Ipsi Pre: before ipsilateral carotid artery cross-clamping; INVOS Contra Pre before contralateral carotid artery cross-clamping; INVOS Ipsi Pos: lower value after ipsilateral carotid artery cross-clamping; INVOS Contra Pos lower value after contralateral carotid artery cross-clamping; INVOS Fall continuous: percentage of drop in rSO_2; INVOS Fall 20%: drop of at least 20% in rSO_2; INVOS Fall 15%: drop of at least 15% in rSO_2.

Figure 1. ROC curve of NIRS for symptomatic intraoperative cerebral hypoperfusion.

Table II. NIRS cerebral oximetry test evaluation.

	Control n = 28 N (%)	ND n = 28 N (%)	Sensitivity (%) CI [5–95%]	Specificity (%) CI [5–95%]	LR +	LR –	PPP (Prev 50%/8%) (%)	NPP (Prev 50% /8%) (%)	κ	*P* =
NIRS fall < 20% rSO_2	25 (44.6)	20 (35.7)	27.3 (13.3–45.5)	89.3 (71.8–97.7)	2.55	0.81	71.8 / 18.1	55.1 / 93.4	0.179	0.093
NIRS fall > 20% rSO_2	3 (10.7)	8 (28.6)								
NIRS fall < 15% rSO_2	23 (82.1)	19 (67.9)	32.1 (15.9–52.3)	82.1 (63.1–93.9)	1.80	0.83	64.3 / 13.5	54.7 / 93.3	0.143	0.217
NIRS fall > 15% rSO_2	5 (17.9)	9 (32.1)								

CI: confidence interval; κ: Cohens Kappa; LR: likelihood ratio; ND: Neurologic deficits; PPP: Positive post-test probability: Pre-test probability of 50% and 8%*; NPP: Negative post-test probability: Pre-test probability of 50% and 8%*; NIRS fall: percentual drop in forehead near-infrared spectroscopy cerebral oximetry oxygen saturation.
*Prevalence of neurologic deficits in the sample (50%) and total population (8%).

Table III. 30-Day adverse outcomes.

	No Stroke		30-day Stroke			No Postoperative complication		Postoperative complications			No cranial nerve Injury		Cranial nerve Injury		
	n = 49		n = 7			n = 44		n = 12			n = 50		n = 6		
	n	%	n	%	*P*-Value	n	%	n	%	*P*-Value	n	%	n	%	*P*-Value
NIRS fall > 20%	9	18.3	2	28.6	0.525	7	15.9	4	33.3	0.178	9	18	2	33.3	0.372
NIRS fall < 20%	40	81.6	5	71.4		37	84.1	8	66.7		41	82	4	66.7	
NIRS fall > 15%	12	24.4	2	28.5	0.816	10	22.7	4	33.3	0.452	12	24	2	33.3	0.618
NIRS fall < 15%	37	75.5	5	71.4		34	77.3	8	66.7		38	76	4	66.7	
ND (+)	22	44.9	6	85.7	0.043	19	20.4	9	75	0.05	23	46	5	83.3	0.084
ND (–)	27	55.1	1	14.2		25	56.8	3	25		27	54	1	16.6	

Postoperative complications (stroke, cerebral hyperperfusion syndrome; surgical cervical hematoma); ND: Neurologic deficit; NIRS fall: percentual drop in near-infrared spectroscopy cerebral oximetry forehead oxygen saturation.

The cutoff for rSO_2 might vary depending upon the type of equipment used [9, 26]. This is an important limitation as each device may require a previous calibration, and tested individually to establish the critical rSO_2 limits [9, 26]. As a consequence, alternative devices may show some variability in different optimal cutoff values [27]. The variation of rSO_2 value is also affected by the hematocrit, skin color, gender, and cerebral brain volume [28]. Nevertheless, as these factors are individually stable, the relative changes of rSO_2 can be used.

The calculated specificity of the test in this study was 90%, which is in accordance with some previous findings [29]. False-positive cases that were not confirmed by the neurologic examination could be due to the fact that subclinical cerebral ischemia could go unnoticed without subsequent clinical sequelae. Besides, many other factors may negatively affect cerebral oximetry, such as anatomical variations, hemodynamic instability, an incomplete circle of Willis, severe cerebrovascular disease, or alterations in hemoglobin parameters [30]. However, in this study, none of the latter two were statistically significant, as seen in Table I. A prospective study, including 185 patients from two vascular centers, found that NIRS using a foresight oximeter presented a sensitivity of 95% and 81% specificity to predict cerebral ischemia and the need for shunting. In the opinion of the authors, this would make NIRS an acceptable alternative to stump pressure for selective shunt use [27].

It is important to remember that cerebral autoregulation is preserved during RA surgery with a physiological rise in systemic blood pressure and cerebral oxygenation after the carotid clamping but lost in a proportion of patients during GA CEA [26]. The preservation of cerebral autoregulation may contribute to reducing ischemic episodes [31]. Cerebral blood flow (CBF) is more reduced than the cerebral metabolic rate of oxygen (CMRO) under GA, resulting in an increased ratio CMRO/CBF, increasing the sensitivity of INVOs under GA comparatively to RA since ischemic areas will further present a dissociation of this index [32]. Peripheral vasoconstriction might play a role in possible decreases in rSO_2 [22]. Short periods of CACC could also explain a reduction in rSO_2 > 20%, but this would not be sufficient to induce clinical manifestations. The low sensitivity of NIRS and consequently, the high rate of false negatives could be explained by the fact that the electrodes are placed in the forehead. Decrease in rSO_2 after CACC might not be detected through the oximeter because the frontal cortex is mainly supplied by the anterior cerebral artery. In contrast, the cerebral area more associated with symptomatic cerebral hypoperfusion, is supplied by the middle cerebral artery (MCA), which is in immediate contiguity with the internal carotid artery [21]. Furthermore, evidence supports that a reduced mean velocity of MCA during CACC is a predictor of early cognitive dysfunction [33]. Choi et al. demonstrated that when anterior circulation is patent, no significant decrease of rSO_2 is observed [34]. A lower threshold (decrease of at least 15% in rSO_2) was also evaluated in this study, and no clinically relevant findings were achieved with this cutoff.

The association between intraoperative ischemia and cerebral hyperperfusion following CEA has been shown previously [35]. Although, due to the design of this study for the detection of ND after CACC, it would be hard to find an association.

Limitations

Some limitations of this study should be acknowledged. The low rate of patients with post-CACC neurologic deficits (8%) made the prospective registry and case selection a difficult task. The study was restricted to a single tertiary referral center, with a specific population that could limit external validity. Furthermore, as previously mentioned, the device is limited to two monitors in the frontal region, leaving the middle cerebral artery territory unmonitored, and these cerebral areas are the most commonly affected region during CACC and by postoperative stroke. Also, the measurement of rSO_2 is only performed in the superficial brain cortex, and ischemia in deep brain structures may be missed [27]. The authors did not perform a comparative analysis of different NIRS monitoring techniques. It is likely

that any measure improving the reliability of NIRS technology may improve the accuracy of rSO_2 in the intraoperative evaluation.

Conclusions

If a monitoring device is validated successfully against the gold standard, it would seem reasonable that these findings could be performed to all patients during CEA under GA procedures. Unfortunately, the results of this study suggest that NIRS cerebral monitoring is not a reliable method to detect cerebral hypoperfusion in this type of surgery. The optimal cutoff that could potentiate the use of shunting would be an absolute decrease of at least 20% in rSO_2. The enhancement of this monitoring technique by developing oximeter sensors for the MCA territory is likely to overcome its limitation and improve the clinical utility. NIRS is not a consistent methodology that can predict 30-day stroke or postoperative complications in the postoperative period. As such, the NIRS does not seem to add substantial clinical benefits to the awake neurologic status evaluation during the surgery. A large randomized clinical trial is needed before the use of NIRS can be considered as a standard.

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Benefit of selective shunt use during carotid endarterectomy under regional anesthesia

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Abstract

Objectives: Carotid cross-clamping during endarterectomy exposes the patient to intraoperative neurological deficits due to embolism or cerebral hypoperfusion. To prevent further cerebrovascular incidents, resorting to shunt is frequently recommended. However, since this method is also considered a stroke risk factor, the use is still controversial. This study aims to shed some light on the best approach regarding the use of shunt in symptomatic cerebral malperfusion after carotid artery cross-clamping.

Methods: From January 2012 to January 2018, 79 patients from a tertiary referral hospital who underwent carotid endarterectomy with regional anesthesia for carotid artery stenosis and manifested post-clamping neurologic deficits were prospectively gathered. Shunt use was left to the decision of the surgeon and performed in 31.6% (25) of the patients. Demographics, comorbidities, imaging tests, and clinical/intraoperative features were evaluated. For data assessment, univariate analysis was performed.

Results: Regarding 30-day stroke, 30-day postoperative complications (stroke, surgical hematoma, hyperperfusion syndrome), and cranial nerve injury, no significant differences were found ($P = 0.301$, $P = 0.460$, and $P = 0.301$, respectively) between resource to shunt and non-shunt. Clamping and surgery times were significantly higher in the shunt group ($P < 0.001$ and $P = 0.0001$, respectively).

Conclusions: Selective-shunting did not demonstrate superiority for patients who developed focal deficits regarding stroke or other postoperative complications. However, due to the limitations of this study, the benefit of shunting cannot be excluded. Further randomized trials are recommended for precise results on this matter with current sparse clinical evidence.

Keywords

Carotid endarterectomy, carotid stenosis, regional anesthesia

Introduction

Carotid endarterectomy (CEA) itself entails the risk of transient intraoperative neurologic deficits (ND) caused by carotid cross-clamping (CACC), which exposes the patient to cerebral embolism or hypoperfusion.[1] Resorting to shunt after the occurrence of focal deficits during carotid clamping is widely advised as some intraoperative strokes are triggered by the temporary interruption of cerebral blood flow in patients who are not protected by adequate collateralization.[2] Therefore, carotid shunting has been described to reduce the risk of perioperative stroke due to hypoperfusion.[3,4] Paradoxically, it is also a stroke risk factor when associated with technical errors.[5–9] In a pragmatic surgical approach, shunt-related complications might cancel the benefits of selective shunting. The risks associated with shunting must be

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balanced against the benefit of shunting in light of the surgeon and the institution experience and preferences.[10] Opposingly, prolonged CACC time was demonstrated to amplify the risk of 30-day stroke and death, with an odds ratio of 1.1 for each 10-min increase in clamping time.[11] Alterations of the hemodynamic stability and both hypertension and hypotension were also reported supporting a faster intervention approach.[12]

Described factors predicting the need of shunt include female gender, age of 75 or older,[13] contralateral carotid occlusion,[13–15] moderate ipsilateral internal carotid artery (ICA) stenosis (50–69%),[14,15] symptomatic presentation,[14] arterial hypertension,[13] and shunting in the first CEA.[16] Despite these, the use of routine or selective shunt or no shunt is still controversial considering the current evidence.[2]

The reasoning for the present study is the assumption that patients developing ND during CACC have a higher risk of developing a perioperative stroke. Some ischemic lesions are associated with injury to the ischemic penumbra surrounding recent infarction, in addition to the traditional association between procedure-related embolization and intra- and postoperative stroke.[1] Before uninterrupted flow in the carotid shunt is guaranteed, the ipsilateral hemisphere is hypoperfused, thus compromising blood flow and potentially leading to local thrombosis and/or direct neuronal lesion.[17] The authors further propose that increased platelet activity could interact with cerebral hypoperfusion induced by CACC.

The aim of this study is to characterize and compare the approach (selective shunting or routine non-shunting) in regards of complication rates. Also, the authors would like to contribute to this critical subject presenting their experience in a group of patients submitted to regional anesthesia (RA) during the surgery.

Materials and methods

Study population

From January 2012 to January 2018, all patients from a tertiary referral hospital who required CEA for carotid artery stenosis (CS) were prospectively evaluated. The study consisted of a prospective analysis of the selected patients submitted to RA who presented alterations in a neurologic examination following ICA clamping and hemodynamic adjustment. Data were obtained from an ongoing prospective registry designed for this purpose.

Demographics and 30-day outcomes were recorded. Strengthening the Reporting of Observational Studies in Epidemiology statements was followed.[18] The study protocol was approved by the local Ethics Committee and respects the Declaration of Helsinki. Informed consent was deemed unnecessary.

Definitions

Symptomatic CS was defined as symptomatic if >50% and accompanied by ipsilateral ischemic stroke or transient ischemic attack (TIA) in the six months before intervention.[19] The index event was the first event stated as any ischemic neurologic event occurring in the six months before surgery.[20] Post-procedural stroke was defined as an episode of acute neurological dysfunction presumed to be caused by ischemia or hemorrhage, persisting at least 24 h or until death.[21] No patients were submitted to thrombolysis in this cohort due to the cervical incision. Mechanical thrombectomy was also not used since a big proportion of cohort precedes 2016, the year in which mechanical thrombectomy has started in this center. Surgical hematoma was defined as a significant cervical blood collection associated to respiratory airway compression and the need for surgical intervention. Postoperative complications are a composite outcome of the 30-day rate of stroke, hyperperfusion syndrome, and surgical hematoma. Cranial nerve injury and the other outcomes were defined according to the reporting standards for carotid interventions from the Society for Vascular Surgery.[22]

Clamping time was defined from CACC to clamp opening and surgery time from skin incision to skin suture. Cut-points of 30 and 50 min after clamping were established, based on previous reports, to measure the impact of CACC in subsequent complications.[11,23] The second peak of cerebral ischemia occurs 10 min after carotid clamping.[11] This late ischemia presumably is caused by relative hypotension, which reduces collateral blood flow through the contralateral carotid and vertebral arteries.

All patients were subjected to preoperative carotid ultrasound, and the severity of the stenosis was evaluated and reported according to velocimetric criteria.[24,25]

Posterior circulation disease was defined as the presence of vertebral artery stenosis with hemodynamic repercussion (Peak systolic velocity [PSV] > 90 cm/s) on ultrasound or superior to 50% in the computed tomography (CT)-angiography in any vertebral artery/basilar circulation.[26,27]

Surgical technique

Intraoperative monitoring was performed and consisted of consecutive brief awake neurological examinations and surveillance every 10 and 5 min during the operation and ICA clamping, respectively.[19]

Cerebral oximeter (INVOS^{TM}, Medtronic plc) was additionally placed after 2013 for complementary monitoring, even though the neurological examination prevailed in decision-making.[28] RA was performed resourcing to deep cervical block technique with supine position of the patient and the neck rotated opposingly to the side undergoing the surgery. Ultrasound guidance was used to place a 22 gauge insulated needle perpendicularly in the adequate location. Subsequently, 4–5 mL of ropivacaine 0.5% was administered in each spinal level (C2-C4) for deep blockade and/or 5 mL of ropivacaine 0.5% in the posterior border of the midportion of the sternocleidomastoid muscle was injected in regards of superficial blockade.[29,30]

Mean arterial pressure (MAP) was routinely measured using a 20-gauge catheter placed in the radial artery. Until the carotid artery was declamped, MAP was kept between baseline values to 20% above. If required, vasoactive medication was administered to increase MAP (ephedrine 5–10 mg bolus for hypotension and atropine 1 mg bolus for bradycardia). All the patients performed surgery with O_2 2 L/min nasal cannula, and a peripheral HbO_2 saturation of at least 95% was aimed. In patients who developed critical hypotension, unworkable agitation, or ND, conversion to general anesthesia (GA) with propofol was implemented.

Surgery consisted of CEA by eversion or followed by patch angioplasty based on the preference of the surgeon. Intraoperative anticoagulation protocol was initiated at least three minutes before CACC, and involved 100 U/kg of unfractionated heparin, with a minimum of 4000 U per patient. If any neurologic deficit was detected after CACC and persisted after blood pressure adjustment, the surgeon decided the use of shunt. Although the option to shunt was dependent on the decision of the surgeon, they consistently selected the same approach depending on the experience (selective shunters or routine non-shunters). Routine non-shunters who usually used eversion proceeded with the same technique. Routine non-shunters, who often used patch, frequently resorted to direct suture in favor of reducing clamping time. In selective shunters, patch angioplasty was the technique used in all the procedures (Figure 1). After the surgery, all the patients were sent to a post-anesthetic care unit with continuous clinical evaluation for 24 h. All the postoperative neurologic events were confirmed and evaluated by a neurologist. If any neurologic deficit/alteration was suspected, a brain CT was performed searching for ischemic lesions.

The Centro Hospitalar Universitário de São João, EPE Vascular surgery team, has a 30-day stroke rate after CEA of 2% and a stroke/death rate of 2%.[31] The result of the surgery was checked in the subsequent 90 days relying on clinical examination and Doppler ultrasound.

Statistical analysis

Statistics were performed with SPSS 25.0 (IBM Corp., released 2017. IBM SPSS Statistics for Windows, version 25.0, Armonk, NY, USA). Comparisons in univariate analysis were carried out using χ^2 or Fisher's tests for categoric variables, Student's t-test for continuous variables, and Mann–Whitney U test for ordinal skewed variables. The threshold for significance was set at 5% ($P < 0.05$).

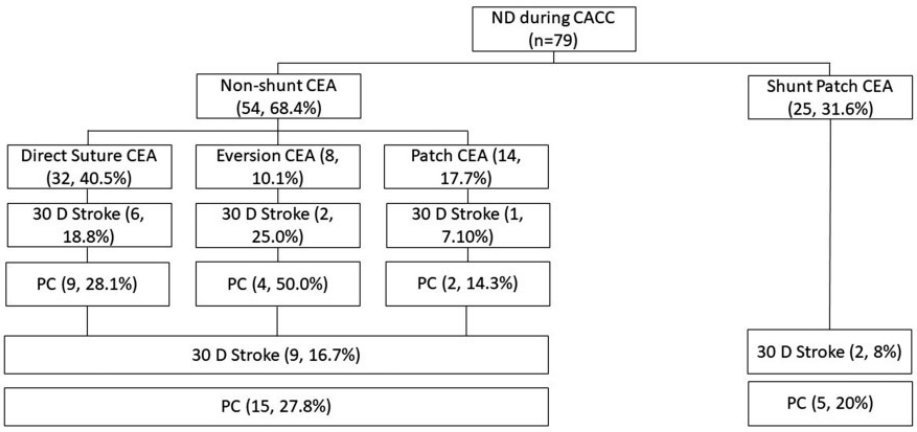

Figure 1. Postoperative complications by surgical technique.
CACC: carotid cross-clamping; CEA: carotid endarterectomy; ND: neurologic deficit; PC: postoperative complications.
Note: Postoperative complications: combination of stroke, surgical hematoma, and hyperperfusion syndrome at 30-days.

Results

Demographic data and comorbidities

The sample consisted of 79 consecutively selected patients who underwent CEA who presented neurological alterations (isolated aphasia 5 (6.3%), contralateral hemiparesis 2 (2.5), and alteration in cognitive/conscience status 72 (91%)) during CACC despite hemodynamic adjustments. Patients undergoing synchronous cardiac surgery were excluded ($n=6$). Although most of the patients presented alterations after the first three minutes of CACC, a small subset presented these neurological deficits at a later time. Patients who presented NDs were significantly more obese and with higher mean age and American Society of Anesthesiologists physical status score than patients who did not, as well as having a greater degree of contralateral stenosis with a lower degree of ipsilateral stenosis.[24] A total of 60 men (76.0%) and 19 women (24.0%) integrated the sample. Shunting was performed in 25 patients (31.6%) and both groups, shunt and non-shunt, were comparable regarding sex and age ($P=0.994$ and $P=0.678$, respectively) (Table 1). Although non-significant, patients submitted to shunt had an earlier onset of ND (<3 min after CACC) (non-shunt 45 (83.3%) vs. shunt 9 (16.7%), $P=0.301$).

Concerning cardiovascular risk factors, such as arterial hypertension, dyslipidemia, body mass index >30 kg/m^2, diabetes, or smoking, no significant differences were found between the shunt group and the non-shunt group. On the other side, chronic obstructive pulmonary disease was significantly higher in the non-shunt group (16.7% vs. 0%, $P=0.03$) (Table 1). All the patients were taking single antiplatelet (75 patients) or dual antiplatelet therapy (four patients).

Symptomatic presentation or the use/number of anti-hypertensives did not reach significant level as well as for other comorbidities regarding impairment of the posterior circulation ($P=0.518$) or degree of the contralateral carotid stenosis ($70\pm24.3\%$ vs. $68.5\pm22.4\%$, $P=0.787$). The degree of carotid stenosis undergoing surgery was also similar between the groups ($85\pm9.78\%$ vs. $81.3\pm11.10\%$, $P=0.167$).

Table 1. Demographics and characteristics of patients.

	Non-shunt $n=54$	Shunt $n=25$	*P*-value
Sex (male), *n* (%)	41 (75.9)	19 (76.0)	0.994
Age, mean ± SD	71.2 ± 9.4	70.80 ± 9.3	0.678
CV risk factors, *n* (%)			
Hypertension	51 (94.4)	22 (88.0)	0.315
Diabetes	25 (46.3)	12 (48.0)	0.888
Dyslipidemia	44 (83.0)	23 (92.0)	0.288
Smoking	30 (55.6)	14 (56.0)	0.970
BMI > 30 kg/m^2	13 (24.1)	6 (24.0)	0.994
CKD, *n* (%)	7 (13.0)	2 (8.0)	0.518
COPD, *n* (%)	9 (16.7)	0	0.030
Atherosclerosis, *n* (%)			
CAD	22 (40.7)	13 (52.0)	0.349
PAD	11 (20.4)	9 (36.0)	0.137
CAD or PAD	25 (46.3)	15 (60.0)	0.257
CHF, *n* (%)	7 (13.0)	7 (28.0)	0.104
Number of anti-hypertensive agents, mean ± SD	2.1 ± 1.1	2.2 ± 1.0	0.978
Anti-hypertensive agents, *n* (%)			
ACEI	40 (74.1)	21 (84.0)	0.328
Beta-blocker	17 (31.5)	9 (36.0)	0.691
CCB	27 (50.0)	11 (44.0)	0.620
Thiazide diuretic	19 (35.2)	12 (48.0)	0.278
Nitrate	6 (11.1)	3 (12.0)	0.908
CRP ($\times10^3$ mmol/L), mean ± SD	0.80 ± 1.28	1.83 ± 4.00	0.399
Hb (g/L), mean ± SD	13.2 ± 1.8	13.1 ± 1.8	0.878
ASA, median CI (5–95)%	3.0 ± (2.87–3.09)	3.0 ± (2.75–3.09)	0.534

ACEI: angiotensin-converting enzyme inhibitor; ASA: American Society of Anesthesiologists Physical Status Classification System; BMI: body mass index; CAD: coronary artery disease; CCB: calcium channel blocker; CHF: cardiac heart failure; CKD: chronic kidney disease (creatinine = 132.6 μmol/L/1.5 mg/dL); COPD: chronic obstructive pulmonary disease; CRP: C-reactive protein (no sensitive); CV: cardiovascular; Hb: hemoglobin; CI (5–95)%: confidence interval (5–95)%; PAD: peripheral artery disease; SD: standard deviation.

Regarding National Institute of Health Stroke Scale in symptomatic patients, no substantial differences were found (8.0 ± 4.8 vs. 6.9 ± 6.5, Mann–Whitney U test $P = 0.375$) (Table 2).

Surgical techniques and postoperative complications

For 31.6% (25) of the patients with post-clamping ND, patch endarterectomy with shunting was used. In the remaining 68.4% (54) patients, other approaches without shunt were used, including direct suture (59.2%), eversion (14.8%), and patch (26.0%). The surgical technique did not reach a significant level for stroke ($P = 0.439$), postoperative complications ($P = 0.263$), or cranial nerve injury ($P = 0.258$). Patch endarterectomy with shunt comparing with the combined non-shunt techniques did not demonstrate significant results regarding stroke rate (8.0% vs. 16.7%; $P = 0.301$), as well postoperative complications or cranial nerve injury (27.8% vs. 20%, $P = 0.460$ and 11.1% vs. 4.0%, $P = 0.301$, respectively) (Table 4). No 30-day deaths or myocardial infarction were reported. Therefore, the standard major adverse events composite outcome (stroke, myocardial infarction, and all-cause death) are not present in the results. A schematic representation of postoperative complications is shown in Figure 1.

Of the 54 non-shunt patients, 40 (72.7%) recovered immediately after carotid artery clamp release or after recovering from conversion to GA, 5 (9.3%). Of the nine strokes, six had ND persisting after discharge and needed further rehabilitation. Of the shunted patients, 16 (64%) recovered immediately after shunt placement, and 4 (16%) only after clamp release. The remaining three (12%) were converted to GA without any persisting deficits thereafter. The two identifiable strokes had persisting deficits after discharge. Cranial nerve injury was found to be lower in the group where patch techniques were undertaken in comparison with patchless methods (2.6% vs. 15.0%, $P = 0.052$). Regarding the stroke rate or combined postoperative complications, no significant results were obtained (7.7% vs. 20.0%, $P = 0.114$ and 17.9% vs. 32.50%, $P = 0.137$, respectively) (Table 4). Moreover, patchless techniques did not reach significance level concerning stroke, major complications, or cranial nerve injury compared to patch without shunt approach ($P = 0.267$; $P = 0.190$; $P = 0.493$).

In the shunt group, clamping and surgery times (56.9 ± 20.6 min and 132.9 ± 31.7 min, respectively) were significantly higher compared to the non-shunt group (30.44 ± 17.269 and 101.52 ± 36.851 min, $P = 0.0000$ and $P = 0.0001$, correspondingly) (Table 3).

Conversion from RA to GA due to patient neurological deficits or patient non-compliance was not

Table 2. Neurovascular symptoms.

	Non-shunt $n = 54$	Shunt $n = 25$	*P*-value
Symptomatic, *n* (%)	23 (42.6)	9 (36.0)	0.579
Time to revascularization (days), median CI (5–95)%	13.5 (12.5–50.5)	12.5 (3.6–76.7)	0.645
NIHSS, mean ± SD	6.9 ± 6.5	8.0 ± 4.8	0.704
Side (left), *n* (%)	32 (59.3)	17 (68.0)	0.457
Stenosis degree (%), mean ± SD	81.3 ± 11.1	85.0 ± 9.8	0.167
Contralateral stenosis (%), mean ± SD	68.5 ± 22.4	70.0 ± 24.3	0.787
Posterior circulation disease, *n* (%)	13 (24.1)	4 (17.4)	0.518

CI (5–95)%: confidence interval (5–95)%; NIHSS: National Institutes of Health Stroke Scale; SD: standard deviation.

Table 3. Shunt-related surgical techniques and outcomes.

	Non-shunt $n = 54$	Shunt $n = 25$	*P*-value
Intended surgical technique, *n* (%)			
Direct suture	32 (59.2)		
Eversion	8 (14.8)		
Patch	14 (26.0)	25 (100)	
Surgery time (min) (mean ± SD)	101.52 ± 36.851	132.90 ± 31.744	<0.001
Clamping time (min) (mean ± SD)	30.44 ± 17.269	56.94 ± 20.574	<0.001

PC: postoperative complications; SD: standard deviation.
Note: Postoperative complications: combination of stroke, surgical hematoma, and hyperperfusion syndrome at 30 days.

Table 4. All patients and subgroup analysis of perioperative complications.

Strategy followed	30 day-stroke $n=11$	*P*-value	30 day PC $n=20$	*P*-value	Cranial nerve injury $n=7$	*P*-value
Direct suture, *n* (%)	6 (18.8)	0.439	9 (28.1)	0.263	5 (15.6)	0.258
Eversion, *n* (%)	2 (25.0)		4 (50.0)		1 (12.5)	
Patch without shunt, *n* (%)	1 (7.10)		2 (14.3)		0	
Patch with shunt, *n* (%)	2 (8.0)		5 (20.0)		1 (14.3)	
Non-shunt, *n* (%)	9 (16.7)	0.301	15 (27.8)	0.460	6 (11.1)	0.301
Shunt, *n* (%)	2 (8.0)		5 (20)		1 (4)	
All patients, *n* (%)	11 (13.9)		20 (25.3)		7 (8.9)	

PC: postoperative complications; SD: standard deviation.
Note: Postoperative complications: combination of stroke, surgical hematoma, and hyperperfusion syndrome at 30 days.

Table 5. Other procedure techniques and perioperative adverse events.

	30 day-stroke $n=11$	*P*-value	30 day PC $n=20$	*P*-value	Cranial nerve injury $n=7$	*P*-value
Regional anesthesia (69), *n* (%)	10 (14.5)	0.701	18 (26.1)	0.679	7 (10.1)	0.291
Conversion to GA (10), *n* (%)	1 (10.0)		2 (20.0)		0	
Surgery time <110, *n* (%)	5 (16.1)	0.861	6 (19.4)	0.239	4 (12.9)	0.428
Surgery time >110, *n* (%)	6 (14.6)		13 (31.7)		3 (7.3)	
Clamping time <30, *n* (%)	5 (16.7)	0.771	8 (26.7)	0.642	3 (10.0)	0.711
Clamping time >50, *n* (%)	2 (13.3)		5 (33.3)		1 (6.7)	

PC: postoperative complications; GA: general anesthesia.
Note: Postoperative complications: combination of stroke, surgical hematoma, and hyperperfusion syndrome at 30 days.

associated with the occurrence of 30-day stroke (14.50% vs. 10.0%, $P=0.701$), 30-day postoperative complications (26.1% vs. 20%, 0.679), or cranial nerve injury (10.1% vs. 0%, $P=0.291$) (Table 5).

Discussion

In this series, the lower 30-day stroke rate in the shunt group compared to the non-shunt group did not reach statistical significance, failing to demonstrate additional benefit in this surgical approach for hard and soft outcomes. The reduced numbers of shunting brought by RA, 8% in this cohort vs. reported 43% in GA, also decreased shunt technical proficiency, which might lead to inferior results in this subpopulation.[3,32] Moreover, Chongruksut et al. did not find significant results in terms of 30-day stroke or death after CEA comparing shunting to non-shunting or selective shunting ($P=0.32$).[2] Recommendations do not advocate the use of routine shunting as evidence supports shunting only for severe persistent ischemia.[6,33] Literature reports conflicting results with evidence of beneficial,[15] detrimental,[8,11] or no effect[34,35] of selective shunting.

In patients with a higher risk of intraoperative cerebral hypoperfusion,[34,36] shunting did not display a clear benefit. Indeed, patients with severe stenosis or contralateral carotid occlusion reported a two-fold increase in postoperative stroke/TIA incidence under shunting placement.[34] In this study, no significant effect of selective shunting on the rate of stroke/TIA was observed, supporting the view that CACC-induced hypoperfusion is an uncommon cause of persistent neurologic alterations in CEA patients.[1,37]

The elevated stroke rates among groups could be explained by other described reasons, such as the concomitant use of antihypertensive drugs underlying baroreflex impairment after CEA.[12] Nonetheless, damaged and reduced collateral pathways, such as those provided by the vertebrobasilar circulation, may also play a role in stroke or TIA incidence.[38] Nonetheless, these patients presented neurologic deterioration during CACC, which denotes critical cerebral perfusion, resulting in an increased number of postoperative ischemic events in this subpopulation.

After the development of intraoperative focal deficits, the decision to speed-up the surgery can also be made, yet this option is only occasionally reported in the literature. This strategy might clarify the lower clamping times during patch without shunting procedures and the higher rates of the direct suture in the presented study group. Most of the NDs emerge at 3–10 min post-clamping, and after the longitudinal arteriotomy was made. At this moment, some surgeons favor the procedure celerity over the use of shunt or the

patch technique. On the other side, prolongation of CACC might be indicative of challenging vessel anatomy, surgical problems, leading to the shunt use. Therefore, these results might underlie unobserved confounders. Evidence on the effect of cross-clamp time on the clinical outcome is sparse in the literature.[11,39]

In the present study, patch angioplasty was compared with eversion and direct suture, without significant results. The rationale behind these comparisons is the theoretical quickness of patchless techniques. Shunt use in comparison with the latter two mentioned approaches was related to a decrease of cranial nerve injury events ($P = 0.052$). This finding should not be taken into consideration due to the short-term duration of cranial nerve injury and the fact that it could be easily unnoticed by patients or professionals in addition to the absence of a standardized method of evaluation, other than clinical evaluation.[40–42]

A limitation of this study is the lack of randomization, which might lead to selection bias, since it is possible that the most critically perfused patients could have been preferentially submitted to shunt over the patients with less marked ND. Additionally, patients with late-onset of symptoms could have been preferentially submitted to fast closure, since the difference in time to shunt (vs. fast closure) could be irrelevant. This cohort power to determine the differences in all post-operative complications is limited, and clinical benefit from shunting should not be excluded. On the other hand, extensive data of these patients were retrieved and might be applicable for future research.

Conclusion

In this study, results failed to demonstrate the superiority of selective-shunting for patients who developed focal deficits during CACC with RA. However, the possible benefits of shunting cannot be denied due to the sample size and design limitations of the study. Resorting to shunt appears to be an acceptable alternative in experienced hands when technical challenges emerge, although the decreasing experience with shunt in centers that routinely use RA might critically reduce the experience of surgeons. Reliability of shunting is still controversial in literature requiring further randomized controlled studies to clarify this issue.

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Onset of Neurological Deficit During Carotid Clamping With Carotid Endarterectomy Under Regional Anesthesia Is Not a Predictor of Carotid Restenosis

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Background: A number of awake patients undergoing carotid endarterectomy (CEA) present from test clamp neurological deficits (NDs) during the procedure. Current guidelines advocate tighter Doppler ultrasound (DUS) surveillance in these patients because of probable higher likelihood of hemodynamic stroke (class 1 grade C), although evidence is lacking regarding benefit. The aim for the study is the assumption that patients who present ND have a higher risk of developing a complete stroke if the ipsilateral carotid artery becomes occluded, and for this reason, surveillance over restenosis of endarterectomy in this group is justifiable; hence, the authors would like to contribute to this matter presenting their experience on restenosis in this specific group of patients.

Methods: Data were prospectively collected between 2009 and 2018 for patients of a university tertiary referral center who underwent CEA under regional anesthesia and developed alterations in the neurologic monitoring during internal carotid artery (ICA) test clamping. Control patients were consecutively selected as the next patient submitted to the same procedure but who did not develop neurologic alterations. Patients who did not present to the first postoperative evaluation were excluded (4–6 weeks). Primary outcome was any restenosis (>30%; >50%; >70%) detected by DUS evaluations between 16 and 30 months of follow-up. Clinical adverse events such as stroke, myocardial infarction, acute heart failure, and all-cause death were assessed 30 days after the procedure and in the subsequent long-term surveillance period. A multivariate analysis of factors with significant associations to restenosis identified in a univariate analysis was performed by binary logistic regression. Kaplan-Meier analysis and life tables were used to evaluate time-dependent variables.

Results: Ninety patients with ND and 94 controls were included. Those with ND had a higher prevalence of obesity, mean age, and scores of American Society of Anesthesiologist physical status, as well as a lower mean degree of ipsilateral stenosis (82.3% vs. 85.8%, $P = 0.032$) and a higher mean degree of contralateral stenosis (67.8% vs. 61.1%, $P = 0.030$). The incidence of restenosis after 2 years did not differ significantly between groups. The univariate analysis yielded two significant associations to restenosis >50%, which remained significant after

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adjustment: ipsilateral stenosis (1.927 + −0.656, $P = 0.02$) and peripheral arterial disease (3.006 + −1.101, $P = 0.048$). NDs were not found to be associated to restenosis ($P = 0.856$). After a median follow-up period of 52 months, patients with NDs did not have a higher incidence of stroke (90.6%, standard deviation [SD]: 3.5%; ND: 91.1%, SD: 3.6%, $P = 0.869$), major adverse cardiovascular events (ND: 69.2%, SD: 5.5%; control, 73.6%, SD: 5.2%, $P = 0.377$), or all-cause death (ND: 90.6%, SD: 3.5%; control: 91.1, SD: 3.6%, $P = 0.981$) than controls. The presence of any restenosis was not associated with later stroke rate (ND: 89.5%, SD: 3.2%; control: 100%, $P = 0.515$).

Conclusions: Cost-effective DUS surveillance after CEA requires the definition of evidence-based factors associated with restenosis and late stroke. The present study does not support the assumption that patients who presented NDs during the ICA test clamping present a higher risk of developing late stroke. This group of patients also did not present a higher incidence of restenosis. For these reasons, tighter DUS surveillance in this group seems not justifiable. Results from other groups are required to support this position.

INTRODUCTION

Carotid artery endarterectomy (CEA) is currently the gold standard for surgical treatment of symptomatic and asymptomatic carotid stenosis.[1–4] The procedure itself entails the risk of intraoperative and perioperative neurologic deficits (NDs) caused by carotid cross-clamping (CACC), due to embolic or hemodynamic ischemia,[5] with the former routinely managed by preoperative dual platelet antiaggregation. Notably, a number of patients present NDs during intraoperative internal carotid artery (ICA) test clamping. Factors independently associated with cross-clamping intolerance in literature are the presence of hemodynamic variations and control and severe renal failure, contralateral stenosis, and other anatomical factors related to the Circle of Willis.[6–8] Regional anesthesia (RA) allows monitoring of adequate cerebral perfusion after CACC by neurological examination and is currently considered the most efficient strategy for detection of critical hypoperfusion during CEA.[9–11] RA is as safe as general anesthesia while being associated with a decreased need to use shunts,[10,12] shorter operative times,[13] and lower risk of coronary events and mortality.[14]

One long-term complication that hinders the effectiveness of CEA is recurrence of carotid stenosis.[15] Carotid restenosis is defined as partial or total reocclusion of the ICA that may occur after surgical correction of original stenosis by either CEA or carotid artery stenting. It has typically been classified as early if developing up to 2 years after the procedure or late if detected after this period[16] and as mild (<30%), moderate (<50%), or severe (<70%) based on peak flow velocities detected via Doppler ultrasound (DUS) imaging.[1] When restenosis was detected on ultrasound, a computed tomographic angiography (CTA) was performed to confirm the results using the North American Symptomatic Carotid Endarterectomy Trial (NASCET) criteria.[2]

Several studies have attempted to ascertain whether restenosis is associated with an increased risk of ipsilateral stroke that might warrant routine DUS surveillance after the procedure.[17] However, restenosis rates, despite variable,[18,19] remain relatively low among studies, with a prevalence of 5.8% after a mean follow-up of 47 months having been described in a recent metanalysis.[18–20] Evidence is lacking regarding whether cerebral ischemic events detected during long-term follow-up are causally associated with arterial reocclusion or whether restenosis is benign in nature. In fact, a review of recent randomized clinical trials suggests that the proportion of strokes occurring after CEA attributable to restenosis is too low to justify the necessity and costs of routine surveillance, with most of the late strokes occurring in patients without restenosis.[20] Despite this, tighter DUS surveillance has been suggested in the European Society of Vascular Surgery guidelines for all patients who undergo a decrease in intraprocedural cerebral blood flow after ICA clamping.[21] After the development of intraoperative focal deficits, the decision to speed up the surgery can also be made despite it not being reported in literature and contribute to suboptimal results. The inexperienced use of shunt can also contribute to technical error and a higher restenosis rate.

The aim of this work was therefore to assess whether patients who demonstrate signs of insufficient cerebral perfusion by onset of NDs during CACC in CEA with RA are more prone to developing post-CEA restenosis (primary outcome). A secondary aim of this study was to address the occurrence of adverse cardiovascular events including stroke during postoperative and long-term follow-up and associated factors.

MATERIALS AND METHODS

Study Population

This is a prospective cohort study. From January 2009 to January 2018, data on patients of a university tertiary referral center (Centro Hospitalar Universitário de São João [CHUSJ], Porto) who underwent CEA and developed anomalies detected by neurologic examination during ICA clamping were prospectively collected. These patients constituted the study group. Postclamping NDs were defined as any alteration in the neurologic examination during CACC (mostly aphasia, contralateral hemiparesis, and alteration in the cognitive/conscience status). Control patients were consecutively selected as the next patient submitted to the procedure who did not develop neurologic alterations (unexposed group). Patients who did not present to the first postoperative evaluation (4–6 weeks) were excluded, as they were unable to provide their result on the primary outcome.

The study protocol was approved by the local ethics committee (protocol 248-18) and is in accordance with the Declaration of Helsinki.

Surgical Technique

All patients were subjected to CEA under RA with initial neurologic examination and further surveillance at 5-minute intervals as well as cerebral oximetry monitoring (INVOS™). Surgery consisted of CEA performed by standard open technique and closure with direct suture or patch or performed by the eversion technique. Shunt use was left at the surgeon's discretion. The CHUSJ Vascular Surgery team has a stroke rate in carotid endarterectomy of 1.10% and a death rate of 0.6% in symptomatic patients.[22] Postoperative surveillance by means of clinical examination and DUS in the subsequent 30–90 days was performed. The evaluation was repeated around 2 years after intervention (16–30 months).

Definition of Outcomes

Primary outcome. Restenosis was defined as, according to Aburahma et al.,[1] cutoff values of peak systolic velocity in the ICA distal to the CEA patch of 155 cm/s, 213 cm/s, and 274 cm/s corresponding to restenosis >30%, >50%, and >70%, respectively. All evaluations of restenosis were performed between 16 and 30 months of follow-up. The detection of restenosis by DUS was confirmed by CTA.

Secondary outcomes. Clinical adverse events such as stroke, myocardial infarction, acute heart failure, and all-cause death were assessed 30 days after the procedure and in the subsequent long-term surveillance period.

Major adverse cardiovascular event (MACE) was defined as a composite variable which included myocardial infarction, acute heart failure, stroke, and cardiovascular death. Myocardial infarction was defined according to the fourth universal definition.[23]

Other variables. Symptomatic carotid stenosis was defined according to the European Society of Vascular Surgery guidelines.[4] Therefore, the first event was the first stroke stated as the first ischemic neurologic event occurring in the 6 months before surgery.[24]

Statistical Analysis

The necessary sample size for a survival test was calculated resorting to WinPepi® V11.65, aiming for a statistical power (β) of 80% and an $\alpha < 0.05$. The sample was estimated (152) for an event rate difference of 20% between groups, although higher event rate differences have been described.[25,26]

Univariate analysis was assessed through χ^2 or Fisher's exact tests when concerning qualitative data and variance analysis for quantitative data. Baseline characteristics of patients with NDs were compared with those of patients without neurologic examination alterations. Multivariate analysis was performed resorting to binary logistic regression. SPSS 25.0 (IBM Corp., released 2017; IBM SPSS Statistics for Windows, version 25.0, Armonk, NY) was used.

Variables included in the multivariate analysis were those associated with the group with ND in univariate analysis and/or described in the literature as risk factors. The regressive final predictive model was created resorting to regression analysis and dimension reduction by the method of backward feature elimination. Kaplan-Meier analysis and life tables were used to evaluate patient restenosis, MACE, and survival.

RESULTS

Population Demographics and Comorbidities

Ninety-six patients were included in each group in the beginning of the study. After excluding patients who did not present to the first postoperative evaluation, 90 exposed patients and 94 nonexposed patients were included.

Among the 184 patients who underwent CEA, 149 (81%) were male, with a mean age of 70 ± 9 years (range of 46–87 years). Those with

Table I. Demographics and comorbidities among patients with intraoperative neurologic deficit and control patients

Variable	Controls ($n = 94$)	Postclamping deficits ($n = 90$)	P value
Sex (female), *n* (%)	14 (15.7)	21 (24.7)	0.140
Age (mean ± SD)	67 ± 9	71 ± 9	0.006
Cardiovascular risk factors			
Hypertension, *n* (%)	77 (86)	78 (91)	0.293
Diabetes, *n* (%)	33 (37)	39 (46)	0.216
Dyslipidemia, *n* (%)	76 (84)	74 (86)	0.765
Smoking, *n* (%)	45 (50)	46 (54)	0.643
BMI > 30, *n* (%)	5 (6)	19 (22)	0.001
CKD, *n* (%)	10 (11)	9 (11)	0.891
CAD, *n* (%)	31 (35)	36 (42)	0.339
PAD, *n* (%)	25 (28)	23 (27)	0.842
CHF, *n* (%)	19 (21)	16 (19)	0.650
C-reactive protein (mg/L, median ± IQR[a])	27 [12−87] (75)	33 [10−89] (78)	0.664
Hemoglobin (g/dL, mean ± SD)	12.8 ± 2.1	13.2 ± 1.7	0.252
ASA, *n* (%)			
II	22 (25)	9 (11)	0.044
III	62 (70)	71 (83)	
IV	5 (5)	5 (6)	

ASA, American Society of Anesthesiologist Physical Status Classification System; BMI, body mass index; CAD, coronary artery disease; CKD, chronic kidney disease (creatinine ≥1,5 mg/dL); IQR, interquartile range; Hb, hemoglobin; PAD, peripheral artery disease.
[a]Mann-Whitney-*U* test.

NDs significantly differed from control group patients in the higher prevalence of obesity (body mass index > 30 kg/m^2) (22% vs. 6%, $P = 0.001$), higher mean age (71 vs. 67 years, $P = 0.006$), and higher scores of American Society of Anesthesiologist Physical Status Classification System (ASA) physical status (11%, 83%, and 6% vs. 25%, 70%, and 5% of ASA II, III, and IV, respectively, $P = 0.044$). Although the prevalence of female sex in the group of patients with NDs was higher (25% vs. 16%), this difference did not reach statistical significance ($P = 0.14$). Aside from obesity, the two groups were homogenous regarding cardiovascular risk factors (arterial hypertension, dyslipidemia, smoking, and diabetes), comorbidities (chronic kidney failure, coronary artery disease, chronic heart failure [CHF], peripheral artery disease), and preoperative levels of C-reactive protein and hemoglobin (g/dL) (Table I).

Carotid Disease

Patients with NDs were found to have a significantly lower mean degree of ipsilateral stenosis (82.3% vs. 85.8%, $P = 0.032$) while having a significantly higher mean degree of contralateral stenosis (67.8% vs. 61.1%, $P = 0.030$). No significant difference was found between the two groups concerning the prevalence of symptomatic carotid disease before intervention (42% in the ND group versus 44% in the control group) (Table II).

Intraoperative Features

In patients with NDs, a patch was used less often (47% vs. 73%, $P < 0.001$) and resort to shunt was more frequent (31% vs. 8%, $P < 0.001$). All cases of conversion to general anesthesia occurred in the ND group (Table III).

Primary Outcome—Restenosis

In this cohort study, the incidence of restenosis after 2 years did not differ significantly between groups (Fig. 1). In the control group, restenosis of ≥70% occurred in 5% and a restenosis of 50−69% in 8% of patients, versus 6% and 7% of patients, respectively, in the ND group. The ND group had an additional incidence of 7% of restenosis 30−49%.

Univariate analysis of variables that might be associated to a restenosis of ≥50% yielded only three significant associations: ipsilateral stenosis ($P = 0.010$), contralateral stenosis ($P = 0.041$), and

Table II. Characteristics of carotid disease among patients with intraoperatory neurologic deficits and control patients

Variable	Control ($n = 94$)	Postclamping deficits ($n = 90$)	P value
Symptomatic, n (%)	39 (44)	36 (42)	0.845
TIA, n (%)	10 (11)	6 (7)	-
Stroke, n (%)	30 (34)	28 (33)	-
Stenosis degree (%, mean ± SD)	85.8 ± 9.56	82.3 ± 11.2	0.032
Contralateral stenosis (%, mean ± SD)	61.1 ± 16.8	67.8 ± 22.4	0.030

TIA, transient ischemic accident.

peripheral arterial disease ($P = 0.013$). When adjusted, the association remained significant for ipsilateral stenosis ($P = 0.020$) and peripheral arterial disease ($P = 0.048$), but not for contralateral disease ($P = 0.151$). Other demographic variables, comorbidities, and intraoperative features showed no significant association to >50% restenosis in univariate analysis, most notably the occurrence of ND ($P = 0.856$) (Table IV). The presence of restenosis was not associated with later stroke rate ($P = 0.130$) (Fig. 2).

Secondary Outcomes at 30 Days

NDs were not found to be associated with a higher incidence of stroke or any other complication in the 30 days after procedure (Table V). No 30-day deaths were reported.

Secondary Outcomes in Long-Term Follow-up

Median follow-up time was 52 months (95% confidence interval of 49−54). Patients with NDs did not have a significantly higher incidence of stroke (ND: 90.6%, survival estimate [SE]: 3.5%; control: 91.1%, standard deviation [SD]: 3.6%, $P = 0.869$), MACE (ND: 69.2%, SE: 5.5%; control: 73.6%, SD: 5.2%, $P = 0.377$), or all-cause death (ND: 90.6%, SE: 3.5%; control: 91.1, SD: 3.6%, $P = 0.981$) than patients in the control group (Figs. 3−5).

DISCUSSION

Patients who presented NDs were significantly more obese and with higher mean age and ASA physical status score than patients who did not, as well as having a greater degree of contralateral stenosis with a lower degree of ipsilateral stenosis. However, when followed up in the long term, the two groups did not differ significantly concerning the rates of restenosis and cardiovascular outcomes.

Factors Associated with NDs

Regarding the factors that were associated to patients with NDs, the lower degree of ipsilateral stenosis observed is likely a manifestation of a lower adaptability of the circulatory mechanisms to compensate for a sudden reduction in cerebral perfusion that results from CACC, which patients with higher degrees of ipsilateral stenosis might otherwise already have in place. In fact, severe ICA stenosis translates into a lower risk of transient ischemic accident and stroke owing to the presence of collateral pathways.[27] On the other side, the patency of the contralateral artery is of paramount importance to ensure sufficient cerebral perfusion in patients with unilateral stenosis. Increased surgical time and complications have previously been described in obese patients.[28,29] A lower tolerance to clamping and a tendency toward dyspnea could

Table III. Intraoperative features among patients with intraoperatory neurologic deficit and control patients

Variable	Control ($n = 94$)	Postclamping deficits ($n = 90$)	P Value
Patch, n (%)	65 (73)	40 (47)	<0.001
Shunt, n (%)	7 (8)	26 (31)	<0.001
Conversion of LA to GA	0	10 (12)	0.001

LA, local anesthesia; GA, general anesthesia.

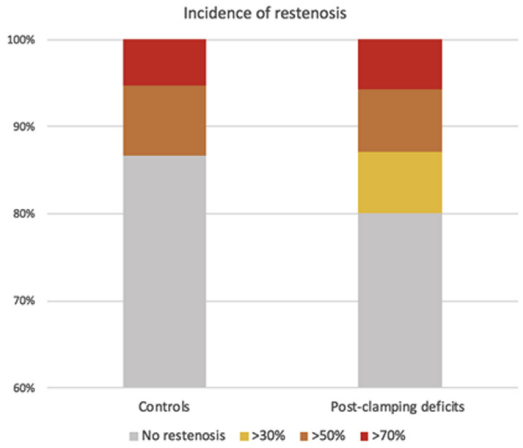

Fig. 1. Incidence of restenosis (homogeneity test, $P = 0.718$).

be ascribed to these patients because of their shorter neck length, while adipose tissue hampers surgical technique and leads to more extensive dissections or manipulations, predisposing to embolic accidents. CHF, smoking, diabetes, or arterial hypertension were not shown to be predictive factors for NDs. CHF is accompanied by a lower cerebral blood flow that might lead to intolerance to CACC.[30] However, the severity of CHF in our study sample might be mild and therefore not induce a significant degree of hypoperfusion. The significantly higher ASA scores in the ND group are backed by a report that highlights the role of more severe atherosclerosis in the genesis of greater plaque instability and therefore more frequent intraoperative NDs in these patients.[31]

Factors Associated with Restenosis

An effort has further been made in several observational studies to determine which factors might result in an increased risk for restenosis, the most commonly associated ones being female sex, dyslipidemia, smoking, hypertension, dialysis dependence, direct suture or eversion CEA, high-grade contralateral ICA stenosis, and high fasting glycemia in the context of metabolic syndrome or non–insulin-dependent diabetes mellitus, with the latter two most notably associated with severe (>70%) restenosis.[17,32,33] The effect of age on the risk of restenosis is conflicting between studies, with some reporting a higher incidence in patients with increasing age[32] and others in patients younger than 65 years[34] or 70 years. In spite of this, our study found two factors independently associated with relevant (>50%) restenosis: ipsilateral carotid disease and peripheral arterial disease, both maintaining significant associations after adjustment. These factors constitute manifestations of atherosclerotic

Table IV. Association between demographics, comorbidities, and intraoperative features including postclamping deficits and restenosis of >50% at 2 years in univariate analysis and in an adjusted analysis (multivariate binary logistic model including ipsilateral stenosis, contralateral stenosis, and PAD)

	Unadjusted			Adjusted		
Variable	ß (SE)	*P*	Exp (ß)	ß (SE)	*P*	Exp (ß)
Gender (male)	−0.431 (0.574)	0.453	-	-	-	-
Age	0.012 (0.027)	0.652	-	-	-	-
Hypertension	19.402 (11,147.525)	0.999	-	-	-	-
Diabetes	−0.101 (0.518)	0.845	-	-	-	-
Dyslipidemia	−0.325 (0.792)	0.681	-	-	-	-
Smoking	−0.92 (0.508)	0.857	-	-	-	-
Obesity	−0.470 (0.789)	0.551	-	-	-	-
CKD	0.903 (0.721)	0.211	-	-	-	-
CAD	0.157 (0.098)	0.754	-	-	-	-
PAD	1.296 (0.521)	0.013	3.654	1.101 (0.556)	0.048	3.006
CHF	−0.339 (0.668)	0.612	-			
Ipsilateral stenosis	0.731 (0.284)	0.010	2.077	0.656 (0.281)	0.020	1.927
Contralateral stenosis	0.230 (0.113)	0.041	1.259	0.180 (0.126)	0.151	-
Patch	−0.252 (0.519)	0.621	-	-	-	-
Shunt	−0.170 (0.0674)	0.801	-	-	-	-
PCD	−0.090 (0.493)	0.856	-	-	-	-

CAD, coronary artery disease; CKD, chronic kidney disease (creatinine ≥1,5 mg/dL); PAD, peripheral artery disease; PCD, postclamping deficit.

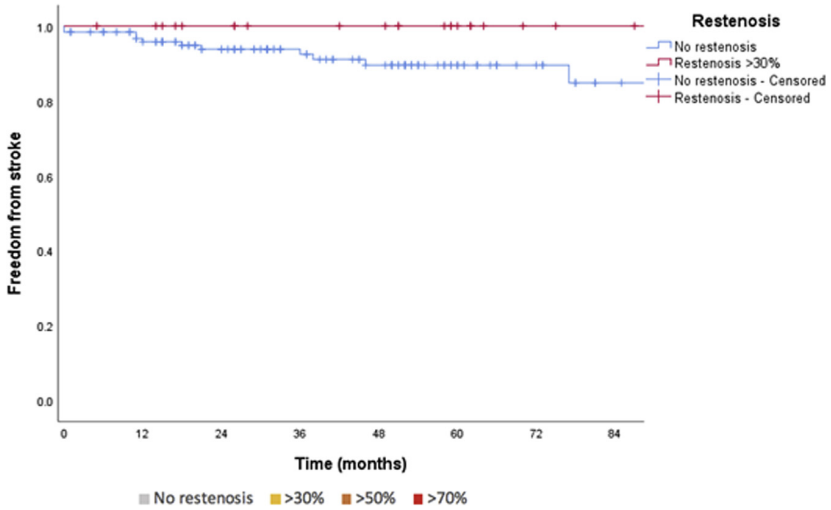

Fig. 2. Kaplan-Meier curves of freedom from stroke after CEA in patients with and without restenosis.

disease, suggesting a higher propensity for restenosis in patients with a higher burden of atherosclerosis. Interestingly, these findings challenge the theory that restenosis detected up to 2 years after intervention is due to benign physiological myointimal hyperplasia of the carotid wall, rather than evolution of vascular pathology.[16] It is unclear, however, if these factors are causes or markers of disease, but it might be interesting to study whether this subgroup of patients might benefit more from DUS surveillance.

Surveillance Recommendations

Owing to lacking consensus regarding routine post-CEA surveillance with DUS, the definition of eligibility criteria based on aforementioned evidence-backed factors associated with relevant restenosis could prove more cost-effective for the selection of patients for postprocedural surveillance.[35] The present study does not support the assumption that patients who presented NDs during ICA test clamping present a higher risk of developing late stroke. This group of patients also did not present a higher incidence of restenosis. For these reasons, tighter DUS surveillance in this group seems not justifiable. Results from other groups are required to support this position.

Nevertheless, the results of this study do not discourage post-CEA surveillance with DUS but rather support its limitation to a restricted cohort of patients. AbuRahma et al.[36] suggest the extreme of abandoning surveillance completely in the absence of contralateral stenosis. A less radical alternative, proposed by Kallmayer et al.,[37] would be to space surveillance at larger intervals, namely once every 12 months after the initial postoperative DUS. From our results, the recommendation that patients who present NDs after carotid clamping should not be considered for tighter surveillance than patients who do not thereby contradicts existing guidelines. Nonetheless, this study was dimensioned to detect differences upon rates of restenosis but not of stroke among restenosis groups, which is an even rarer event. For this reason, the authors cannot discard whether stroke related to restenosis in patients with NDs is more relevant, as the lack of cerebral vascular reserve

Table V. Secondary outcomes at 30 days

30-Day outcomes	Control ($n = 94$)	Cases ($n = 90$)	*P* value
Stroke, *n* (%)	0	3 (3.3)	0.117
AMI, *n* (%)	0	1 (1.1)	0.495
AHF, *n* (%)	1 (1.1)	0	0.508
MACE, *n* (%)	1 (1.1)	1 (1.1)	0.743
Neuropraxia, *n* (%)	4 (4.3)	7 (7.8)	0.244
Hematoma, *n* (%)	4 (4.3)	7 (7.8)	0.244

AMI, acute myocardial infarction; AHF, acute heart faillure.

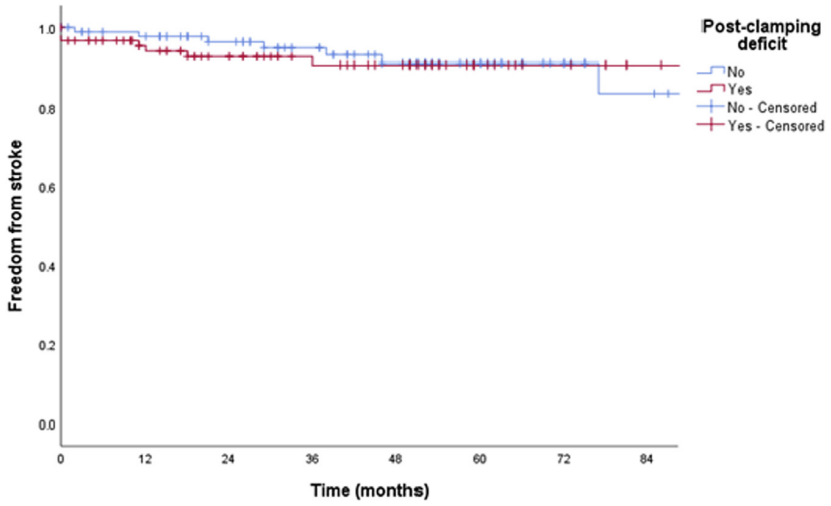

Fig. 3. Kaplan-Meier curves of freedom from stroke after CEA in patients with postclamping deficit and controls.

that leads to deficits during clamping might also lead to less tolerance to progression of restenosis. Post-CEA surveillance with DUS might, therefore, be beneficial not because restenosis is more frequent in this group but because of the increased incidence of restenosis-related stroke, something the authors could not assess.

Limitations

There are several limitations to this cohort study. Although patients were selected based only on their response to clamping, the two groups differ in other variables that might lead to selection bias. However, comorbidities were comparable among groups, partly lowering the risk of confounding.

Because they missed the postoperative appointment, 2 controls and 6 cases had to be excluded from the analysis. A sensitivity analysis of demographic variables, comorbidities, and carotid lesions did not show differences between excluded patients and the remaining cohort. Owing to the small number of stroke events and the lack of events in any restenosis group, an increased sample size would have been required to detect differences in stroke rates that could add to a more global understanding

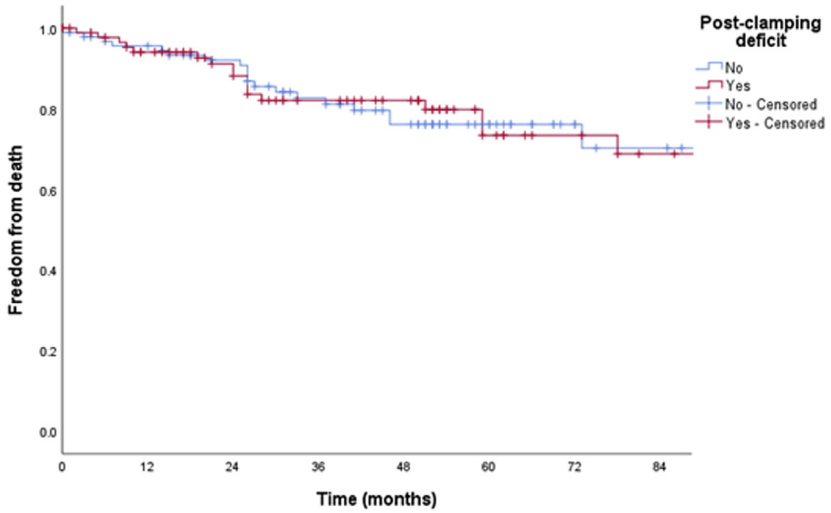

Fig. 4. Kaplan-Meier curves of survival after CEA in patients with postclamping deficit and controls.

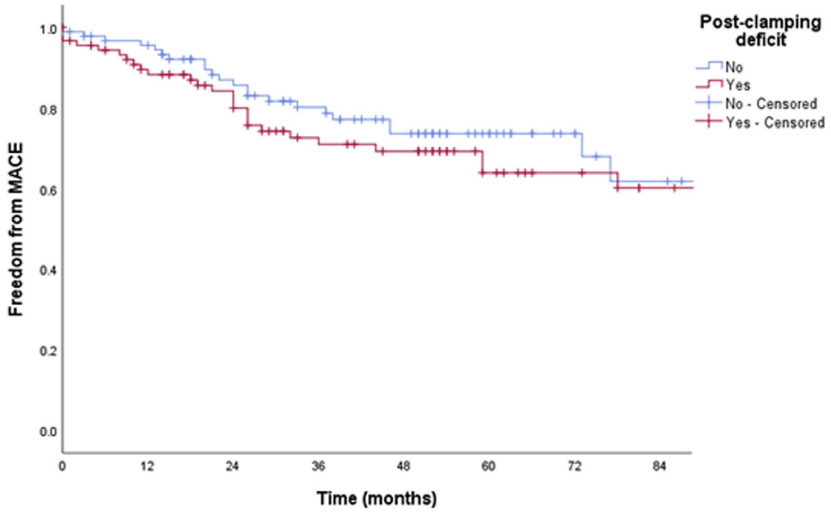

Fig. 5. Kaplan-Meier curves of freedom from MACE after CEA in patients with postclamping deficit and controls.

of the real clinical relevance of restenosis after CEA. Finally, the occurrence of restenosis was assessed only between 16 and 30 months of follow-up, leading to an absence of data on restenosis occurring after that period.

CONCLUSION

Despite this study's shortcomings, this was the first of its kind to prospectively collect data referring specifically to patients who suffer from NDs during CEA in a large study population. We believe the insights offered by this study might further our understanding of what factors influence the recurrence of stenosis after intervention and promote further studies on this topic. Patients who suffer from NDs while awake during CEA do not have a higher incidence of restenosis and long-term stroke than those who do not. Instead, the grade of ipsilateral carotid stenosis and peripheral artery disease were found to be associated with relevant restenosis. Therefore, we cannot recommend tighter surveillance in patients with NDs but urge that further studies be made, in larger study populations, to corroborate these findings.

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DISCUSSION

Study cohort

The patients submitted to CEA under RA and presenting with IND after CACC during CEA were consecutively included, in the period between January 2012 to January 2020, in the Serviço de Angiologia e Cirurgia Vascular of the Centro Hospitalar Universitário de São João, EPE (CHUSJ), a tertiary referral center. The control group was the immediately consecutive patient submitted to CEA under RA without the development of neurologic deficits during CACC with a 1:1 ratio.
Patients were evaluated before surgery by a vascular surgeon and an anesthesiologist. When previously symptomatic, patients were also assessed by a neurologist. Carotid stenosis was detected and quantified by a duplex ultrasound exam or a computed tomography angiogram (NASCET) or an additional duplex ultrasound exam performed by a different independent operator. Participants were evaluated postoperatively with clinical examination and Doppler ultrasound at 30 to 90 days after discharge and at 12 and 24 months of follow-up. The extraction of data was done minimizing the rate of missing data in the main demographic and outcome variables. The variables examined reported 0 - 1% missing data. RDW-CV had a 3% missing rate.
These studies were reported according to STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) and Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis (TRIPOD) guidelines (135, 136).
The study protocol (number 248-18) was approved by the Ethics Committee of the Faculdade de Medicina da Universidade do Porto/Centro Hospitalar Universitário São João, EPE and respected the Declaration of Helsinki. This trial is registered in the ClinicalTrials.gov public website with the identifier NCT04347785.

Clinical relevance of Intraoperative Neurologic Deficits

Neurologic clinical monitoring is only possible when the patient is awake, as in a RA setting or conscious sedation (137). Nonetheless, most of the available evidence concerning cerebral ischemia during CEA was obtained in patients under GA. The prevalence of IND in patients undergoing CEA with RA ranges between 2.4-11% in literature (98, 138-141), and the results obtained within this cohort of patients might offer a glimpse into the mechanism of perioperative stroke.
The main hypothesis of this thesis is the assumption that patients developing IND during CACC manifested some degree of cerebral ischemia. Therefore, these patients may entail a higher risk of developing a perioperative stroke. Results demonstrated that, in the present cohort, IND has a high predictive value for 30-day stroke (aOR>4; absolute risk 3.3% vs. 14.4%; after PSM 3.4 vs. 15.3%). Other postoperative adverse events with Clavien Dindo classification ≥2 (142) also shown a high predictive value, as a combined outcome (aOR>2.5 absolute risk 8.9 vs. 24.4%)) composed of surgical hematoma, hyperperfusion syndrome, hypotension with the need for aminergic support and surgical infection (143-145). The same results were obtained by Piffaretti et al., in a study with 385 patients, found a strong significant association between IND and subsequent postoperative ischemic events, presenting an aOR of 6.60 (CI: 1.65–26.36, P = 0.008), (146).
Patients with compromised cerebral perfusion have a significantly higher risk of ischemic stroke occurrence during CEA and that prolonged CACC time may enhance the ischemic damage in border-zone territories (147, 148). Jean-Baptiste et al. reported similar results during CEA when the blood flow is low in the contralateral common carotid artery (148). Some ischemic lesions are associated with injury to the ischemic penumbra surrounding recent infarction (149, 150), in addition to the traditional association between procedure-related embolization and intra- and postoperative stroke (88).

Preoperative predictors

Preoperative predictors of IND are crucial as hemodynamic stroke during CACC can be pottencially averted

(92, 151). The main clinical characteristics that increased the risk for IND were advancing age and obesity (body mass index (BMI) ≥30). Radiological findings such as higher degrees of contralateral CS and lower degrees of ipsilateral CS were also associated with IND. Finally, the hematologic marker RDW-CV greater than 14% was independently related with the outcome.

Age-related mechanisms involving intracranial and cerebral atherosclerosis and arterial stiffness (152) ultimately affect cerebral blood perfusion (153, 154). Nonetheless, stroke and mortality rates among octogenarians remain acceptable, and guidelines still classify this population as eligible for surgery according to the actual evidence (155). Obesity is known to lead to increased surgical time and complications (156, 157). Due to the quantity of adipose tissue present in these patients, the surgical technique might display more difficulties leading to higher extensive dissection or additional manipulation predispositing to embolic incidents. A short neck length may reduce the tolerance to clamping and a tendency towards dyspnea (143). Other factors such as an increased plaque area and intima-media thickness in the common carotid and bulb of obese patients were described, suggesting increased hemodynamic stress and higher susceptibility to inflammatory stimuli (158). The visceral adipose tissue secretes cytokines and chemokines attracting macrophages that contribute to a systemic proinflammatory and proatherosclerotic state associated with worse outcomes (157, 159).

The evaluation of the degrees of strenosis of both carotids using imaging techniques is important as it is related to the impairment of cerebral perfusion and compensatory mechanisms (160, 161). These compensatory mechanisms are present, mainly through the contralateral ICA (162), which can explain the greater than 70% degree contralateral stenosis as a predictor of IND (93, 96), given the advanced state of vascular disease. This finding is supported by Kretz et al., who observed a higher probability of shunting due to IND when the blood flow is low in the contralateral common carotid artery (93). It is not surprising, therefore, that the contralateral CS is an exclusion criteria in clinical trials, due to the increased perioperative stroke risk (163, 164).

The lower degree of ipsilateral stenosis as a predictive factor is likely a manifestation of the reduced adaptability of the circulatory mechanisms to compensate for a sudden reduction in cerebral perfusion that results from CACC, which patients with higher degrees of ipsilateral stenosis might otherwise already have in place. Stenosis greater than 90% allows for a minimal continuous brain blood flow and, consequently, decreases the susceptibility to low flow-periods, reflecting a smaller relative loss of ipsilateral flow resulting from clamp placement (95, 165), allowing better CACC tolerance. A higher predisposition for IND in patients with a decreased degree of ipsilateral CS could reflect a deficient activation of alternative blood flow pathways in response to ischemia, either from the vertebrobasilar system, leptomeningeal vessels, or an incomplete circle of Willis (160, 161, 166).

Concerning RDW-CV, present results have further demonstrated that it is associated with long-term adverse outcomes after CEA, specifically AMI and all-cause mortality (167). Bojakowski et al. also suggest that increased baseline RDW-CV was significantly associated with a combined outcome of CV death, restenosis, transient ischemic attack, or any other carotid reintervention (168). Previously, several studies focused on the association between RDW-CV and carotid atherosclerosis. In fact, RDW-CV was associated with long-term stroke (169). The RDW increase was also associated with carotid intima-media thickness and carotid plaque development and plaque progression (167).

The underlying pathophysiology of RDW in CV diseases is not fully understood. Inflammation and oxidative stress, critical in atherosclerosis (44), can have an inhibitory effect on erythropoiesis leading to an increase in RBC volumetric variation (45). The release of inflamamatory cytokines such as tumor necrosis factor-α or interleukin-6 decreases the half-life of RBCs that may induce accelerated erythrocyte production (170, 171). Additionally, oxidative stress enhances the vascular resistance by inducing adhesion between RBCs with the endothelium and decreasing RBC deformability that can explain the worse outcomes in patients with higher levels of RDW (172). The increased RDW with oxidative stress and low levels of antioxidants may be associated with the poor clinical outcomes and mortality during acute cerebral infarction and reperfusion, inducing poor clinical outcomes and mortality(173).

Some ischemic lesions are associated with injury to the ischemic penumbra surrounding recent infarction, in addition to the traditional association between procedure-related embolization and intra- and postoperative stroke (88, 144). The symptomatic status might also represent a risk factor, specially when associated with

watershed stroke. The low-flow mechanism that causes the border-zone, junctional, or watershed strokes could explain the symptomatic status as a risk factor (144, 147, 174). Thus, the fine intraoperative blood pressure management with a permissive hypertension protocol might reduce the role of this factor on the manifestations and consequences of cerebral hypoperfusion (175). Prolonged CACC time augments 30-day stroke and death risks, increasing each 10-minutes (91).
Arterial hypertension was some years ago reported as an independent risk factor for clamping intolerance (95, 145, 176). The present data confirms that blood pressure in steady high-normal values has been crucial to preventing symptomatic cerebral ischemia during CEA, which is highly related to hypotension after clamping (175, 177). It is important to note that intraoperative arterial pressure control has assumed a relevant role and could have diminished the effect of hypertension as a risk factor (146, 175, 178).

Intraoperative predictors – Near-infrared spectroscopy

The use of parallel neuromonitoring tools in CEA under RA is inconsistent across the literature, denoting the need for a standardized, validated neuromonitoring protocol. The hypoxic threshold based on cerebral NIRS monitoring for intervention is currently defined as a relative decrease of 15 to 20% (79, 81, 99, 179-184).
The ROC curve obtained in this study also demonstrated that a decrease of greater than 20% in rSO2 is the optimal cutoff for hypoperfusion. Nevertheless, NIRS was unable to relate to hard or soft postoperative outcomes. Postoperative complications were higher in the group presenting a decrease greater than 20% in rSO2 (36.4% vs. 17.8%), and a similar trend was observed in the rate of cranial nerve injury (18.2% vs. 8.9%) (180). These associations were not significant as observed in the literature (99).
A diagnostic test accuracy meta-analysis by Duarte-Gamas et al. assessed the accuracy of NIRS in comparison to the awake test (99). The partial AUC-ROC was of 0.646, with a summary sensitivity of 72.0% (CI: 58.1-82.7%) and a summary specificity of 84.1% (CI: 78.5-88.4%) (99). The point estimate of the sensitivity of intraoperative NIRS for predicting postoperative stroke was low with a broad confidence interval, mirroring the low frequency of stroke events.
False-positive cases, i.e., NIRS positive without objective changes in the neurologic examination, could be attributed to the subclinical cerebral ischemia that might pass unnoticed without subsequent clinical sequelae (99). Additionally, many other factors may negatively affect cerebral oximetry, such as anatomical variations, hemodynamic instability, an incomplete circle of Willis, severe cerebrovascular disease, or alterations in hemoglobin parameters (144, 185, 186). This cerebral autoregulation is maintanined during RA surgery (76). As a result, the preservation of cerebral autoregulation may contribute to the reduction of ischemic episodes. The physiological rise in systemic blood pressure and brain oxygenation after the carotid clamping is lost in a percentage of patients under GA (75, 187), while peripheral vasoconstriction might play a role in possible decreases in rSO2 (188, 189). Short periods of CACC could also explain a reduction in rSO2 greater than 20% but not enough to induce clinical manifestations. Furthermore, a precise decrease in rSO2 after CACC might not be detected through the oximeter that evaluates the anterior cerebral artery that mainly irrigates the frontal cortex. The MCA, not evaluated by NIRS, supplies the cerebral regions originating the signs of cerebral hypoperfusion (190-192). Accordingly, evidence supports that a reduced mean velocity in the MCA during CACC is a predictor of early cognitive dysfunction (193), and when the anterior circulation is patent, significant decreases of rSO2 are not observed (194). Finally, these reductions might go undetected, as oxygen metabolism of extracranial origin can influence oxygen monitoring.

Shunters vs. non-Shunters

In these studies, the lower 30-day stroke rate in the shunt group compared to the non-shunt group did not reach statistical significance, failing to demonstrate an additional benefit for hard and soft outcomes. The reduced

numbers of shunting brought by RA, 8% in this cohort vs. the reported 40% in GA, also decreased shunt technical proficiency, which might lead to inferior results in the patients manifesting IND (144, 186).
After the development of IND, the decision to speed up the surgery can also be made. Yet, this option is only occasionally reported in the literature (92). This strategy might clarify the lower clamping times during patch without shunting procedures and the higher rates of the direct suture. Most of the INDs emerge at 3 to 10 minutes post-clamping and after the longitudinal arteriotomy is made (105). At this moment, some surgeons favor the procedure celerity over the use of shunt or the patch technique. In contrast, prolongation of CACC might indicate challenging vessel anatomy and surgical problems, leading to shunt use. Other authors argue that the shunt use is unnecessary because cerebral hypoperfusion is a relatively uncommon cause of perioperative stroke in patients who undergo CEA and because the actual placement of a shunt can precipitate carotid arterial injury or the generation of distal emboli (195-197). However, when followed-up in the long-term, the two groups did not differ significantly concerning the rates of restenosis and other CV outcomes (198).
The option to shunt after diagnosing clamping-associated IND was left to the discretion and experience of the surgeon (199). Presently, no method of routine or selective shunting has been linked to the production of better outcomes, although the stroke rate was still rised compared to the patients with IND who did not undergo carotid shunting (shunters vs. non-shunters) (199). The data gathered in this dissertation supports that current evidence is too limited to either support or contest the use of routine or selective shunting in CEA (92).

Restenosis

The incidence of restenosis within 12-month period following the surgical procedure varies between 6% and 37% (200). The type of arterial closure following CEA has been associated with the rate of restenosis, with routine patching providing significant reductions in restenosis when compared to primary closure (4.3% vs. 13.8%, respectively) (69, 134, 201). As a matter of fact, when a patient develops IND, the option to speed the surgery by direct closure or the lack of experience in applying carotid shunts, may contribute to a higher restenosis rate. (195-197). The present results also exposed two factors independently associated with relevant (greater than 50%) restenosis: ipsilateral carotid disease and PAD. These associations suggest a higher propensity for restenosis in patients with a higher burden of atherosclerosis.
The reason behind the restenosis risk, lies in the endothelial damage triggering the neointimal hyperplasia during therapeutic surgical or endovascular procedures by inducing a cascade of inflammatory mediators, including free oxygen radicals, mitogenic and chemotactic factors. Intimal proliferation, even if an endothelial response to manipulation mainly causes it, may be accelerated by external factors (e.g., DM) and inflammatory mediators such as C-reactive protein, platelet-derived growth factor, and other agents (202, 203). Inflammation also plays a role in early carotid restenosis after CEA, which is as well associated with advanced atherosclerotic disease(202, 204). Interestingly, these findings could challenge the theory that restenosis detected up to 2 years after the intervention is due to benign physiological myointimal hyperplasia of the carotid wall rather than the evolution of vascular pathology (121).
Due to lacking consensus regarding routine post-CEA surveillance with DUS, the definition of eligibility criteria based on the aforementioned evidence-backed factors associated with relevant restenosis could prove more cost-effective for selecting patients for post-procedural surveillance (205). It has been advanced that patients developing neurological symptoms with carotid clamping during CEA under RA could have an increased susceptibility to carotid restenosis consequences, requiring closer surveillance during follow-up, although this enhances a gap in evidence (198, 206). One suggestion by Aburahma et al. goes so far as to advise forgoing surveillance entirely in the absence of contralateral stenosis (207). A less radical alternative, proposed by Kallmayer et al., would be to space surveillance at larger intervals, namely once every 12 months after the initial postoperative DUS (208).
The results of this thesis do not discourage post-CEA long term surveillance with DUS but rather support its restriction to a specific cohort of patients. The number of patients with 50% or more restenoses was greater than patients with 70% or more restenosis. More importantly, the small number of strokes ipsilateral to a 70–99%

restenosis in the International Carotid Stenting Study precluded meaningful statistical analyses being undertaken (129). However, in the actual routine, a surgeon rarely considers redoing carotid endarterectomy or carotid stenting in patients developing an asymptomatic 50–70% restenosis. In Fokkema's et al. meta-analysis an absolute stroke risk of 5% is present if a restenosis >70% (126). The benefit of long-term routine DUS surveillance after CEA is doutbtfull, considering that the perioperative risks of redo-CEA or carotid stenting are estimated in 3%, falling little behind the regular evolution of the disease (209).
The available evidence suggests that there is little benefit in entering CEA patients into routine long-term surveillance, since reintervention would add minimal benefit (198). The population of the cohort was dimensioned to detect differences upon restenosis rates, but it is undersized for stroke among restenosis groups, an even rarer event (198). For this reason, it cannot be discarded whether stroke related to restenosis in patients with IND is more relevant, as the lack of cerebral vascular reserve that leads to deficits during clamping might also induce less tolerance to the progression of restenosis. Therefore, post-CEA long-term surveillance with DUS might be beneficial, not because restenosis is more frequent in this group of patients, but due to the increased incidence of restenosis-related stroke, an extent that the authors could not assess.

Limitations

Several limitations are inherent to the papers that are the basis of the present dissertation. The low incidence rate of positive awake tests makes the conception of a RCT to englighten some unsolved matters hard to implement. The lack of randomization option might have interfered with the results, although the stroke rate was still rised compared to the patients with IND who did not undergo carotid shunting (shunters vs. non-shunters) (199). Patients were selected based only on their response to clamping, so the two groups might differ in other variables leading to selection bias. However, comorbidities were comparable among groups, and when further resorting to propensity score matching and multivariable regression models, the risk of confounding was partly reduced.
The possibility of selection bias is also present in the subset of patients who presented IND and analyzed regarding the use of shunt (105). It is possible that the most critically perfused patients could have been preferentially submitted to shunt over the patients with less marked neurologic deficits (105). Additionally, patients with late-onset symptoms could have been preferentially submitted to fast closure since the difference in time to shunt (vs. fast closure) could be irrelevant. The cohort's power to determine the differences in all postoperative complications is limited. On the other hand, extensive data of these patients were retrieved and might be applicable for future research.
Due to the small number of strokes and the lack of events in any patient of the restenosis group, an increased sample size would have been required to detect differences in stroke rates that could add to a more global understanding of the actual clinical relevance of restenosis after CEA (198). The occurrence of restenosis was assessed only between 16 and 30 months of follow-up, leading to an absence of data on restenosis occurring after that period.
Finally, limitations also arise from the long recruitment time frame due to the low rate of patients with post-CACC neurologic deficit (8%), although a considerably large sample is presented alongside a control group. The guideline and the center patient selection criteria for CEA did not change significantly during the study recruitment and so as the follow-up, although bias could not be excluded. The cohort also belongs to a large academic teaching institution (CHUSJ), which might condition the external validity to community hospitals that perform a large proportion of CEA.
The criteria derived from this dissertation need further validation in independent cohorts for direct clinical application. Additional serologic or clinical imaging markers are needed for further improvement of the model and the creation of an assertive preoperative score for patient stratification and/or selective shunt placement (144).
The characteristics and mechanism of each reported postoperative stroke would benefit from additional detailed analysis, based on the predefined variables captured and possible additional biomarkers. However, due to the low absolute number (23 events), this evaluation was not possible.

Future Perspectives

The most common cause of postoperative stroke is thrombosis or embolism from the endarterectomy zone. Platelets play a central role in intravascular thromboembolism, with several studies reporting variability in platelet deposition within the endarterectomy zone (210). Moreover, there is a recognized uncertainty in assessing and quantifying the efficacy of antiplatelet drugs (211). A subset of patients with genetic polymorphisms might resist antiplatelet therapy (212). Identifying patients with insufficient response to antiplatelet drugs is paramount to adjust perioperative antiplatelet medication (213). To accomplish this, some recent reports have examined platelet aggregability as a valuable metric for evaluating antiplatelet drug efficacy (214).

Increased platelet activity can potentiate cerebral ischemia induced by CACC, particularly in patients developing symptomatic neurologic ischemia after circulation shutdown. Exploring potential differences in platelet deposition in patients submitted to CEA to clarify the pathophysiology of postoperative stroke and potentially tailor antiplatelet drug therapy depending on the predisposition to platelet deposition within the endarterectomy zone might improve surgical outcomes (210). Platelets from patients who develop postoperative stroke might be more responsive to stimulation by physiologic agonists than those from patients with low embolic potential. Identifying the specific platelet stimulatory pathway with the strongest association with postintervention thromboembolic events may allow targeted antiplatelet therapy, enabling a better balance between hemostasis and thrombotic risk.

To date, few relevant biomarkers for patient selection have been introduced in clinical practice concerning carotid artery disease. The 2017 European Society of Vascular Surgery Guidelines expose this gap in the knowledge demanding further investigation for additional plasma biomarkers to evaluate if excessive endothelial activation has any potential for guiding risk stratification in patients with asymptomatic carotid disease (11). It is crucial to find practical but straightforward prognostic markers to better identify patients at a high risk of adverse events and guide clinical decision-making.

Main findings:

- Neurologic deficits during carotid clamping are a major predictor of perioperative stroke.
- Age, BMI≥ 30Kg/m2, a lower degree of ipsilateral stenosis, and a higher degree of contralateral stenosis are independent predictors of neurologic deficits and, therefore, might play a role in the prevention of procedure-related stroke. Increased RDW-CV may also predict IND.
- Selective shunting did not demonstrate superiority for patients who developed focal deficits regarding stroke or other postoperative complications.
- NIRS demonstrated a reduced discriminative capacity for critical cerebral hypoperfusion comparing to the awake test.
- NIRS seems not to add substantial clinical benefits to the awake test due to its low association to postoperative outcomes.
- Patients who presented neurological deficits during ICA test clamping do not present a higher risk of developing stroke on the long-term follow-up.
- This group of patients did not incur in a higher incidence of restenosis. For this reason, tighter DUS surveillance in this group is not advisable.

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