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The Effect of Contralateral Carotid Occlusion in Patients Undergoing Carotid Artery Endarterectomy

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ABSTRACT

INTRODUCTION: Contralateral carotid occlusion (CCO) is considered a high-risk condition for patients undergoing carotid artery endarterectomy (CEA). Patients with a CCO may be intolerant to carotid cross-clamping during CEA, thus prone to postoperative adverse neurological outcomes. Patients with CCO may also have a higher burden of atherosclerotic disease, leading to a higher rate of cardiovascular events.

METHODS: A Medline search was performed in order to identify publications focused on the impact of CCO on outcomes after CEA.

RESULTS: Patients with CCO present a higher incidence of intolerance to carotid cross-clamping. The rates of shunt use are higher in patients with CCO. In the postoperative period, patients with CCO show a higher rate of stroke. Evidence regarding the effect of CCO on long-term outcomes remains controversial, with most studies reporting a lack of association between CCO and adverse long-term outcomes after CEA.

CONCLUSION: Patients with CCO have an increased risk of postoperative adverse outcomes. The best strategy for this group of patients should be based on a case-by-case approach.

Keywords: Carotid arterial disease; Carotid endarterectomy.

INTRODUCTION

Carotid artery endarterectomy (CEA) is the first line treatment for symptomatic carotid artery stenosis >50% and selected patients with an asymptomatic stenosis >60% with acceptable perioperative risk and a 5-year life expectancy.[1] The benefit of CEA in preventing stroke is mostly counterbalanced by the high-risk baseline cardiovascular profile the typical patient presents, with an increased mortality in the long-term. The 2-year MACE rates after CEA have been described as 6–9%,[2,3] with an average cardiac-related mortality of 2.9% per year after CEA.[4] Therefore, identification of patient-related risk factors for adverse outcomes following CEA is paramount.

Atherosclerosis is often a systemic disease, involving multiple vascular beds, such as the coronary arteries, arteries of the lower extremities and carotid arteries.[5] Bilateral carotid occlusive disease is estimated to occur in less than 10% of patients with carotid artery disease[6,7] and is considered a high-risk condition for CEA.[8] Patients with bilateral carotid disease may have a more severe burden of systemic atherosclerosis, which result in worse outcomes following CEA. Contralateral carotid disease may also pose a technical issue, as these patients may not tolerate carotid cross-clamping and may be prone to suffer intraoperative hemodynamic strokes.

The aim of this review is to provide an overview of the literature regarding the relevance of contralateral carotid occlusive disease in patients submitted to CEA, in terms of short and long-term outcomes.

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METHODS

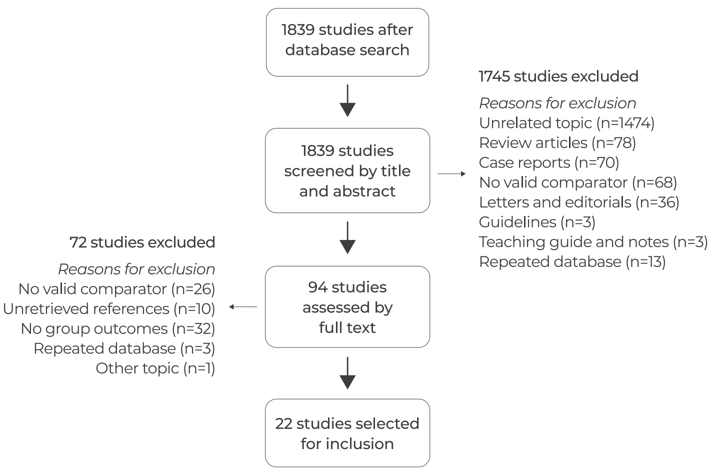
A MEDLINE search was performed in order to identify articles focused on contralateral carotid occlusive disease in patients submitted to CEA. The following query was used in order to obtain the references: ("Endarterectomy"[MeSH Terms] OR "Endarterectomy, Carotid"[MeSH Terms] OR "carotid endarterectomy" [All Fields] OR "Carotid Endarterectomy" [MeSH Terms]) AND ("bilateral" [All Fields] OR "contralateral" [All Fields]). Additional articles of scientific interest for the purpose of this non-systematic review were included by cross-referencing. Obtained records were screed by two independent authors, blinded to each other, with any discordances being resolved by a third author.

Eligible studies were required to include patients submitted to carotid endarterectomy and with a documented contralateral internal carotid occlusion (CCO), as well as patients without CCO. Data of interest included the preferred anaesthesia type and the protocol regarding shunt use. Main outcomes of interest included intraoperative changes in neurological function or monitoring tests during carotid cross-clamping, adverse neurological events and mortality in the 30 days period and in the long-term. Both prospective and retrospective studies were included.

SEARCH RESULTS

The search yielded 1839 records, with 94 being considered for inclusion after title and abstract screening. Twenty-two references were selected for inclusion after full text appraisal the former. The selection flowchart is displayed in Figure 1.

Figure 1. Reference selection flowchart



SYNTHESIS OF EVIDENCE

Intra-operative outcomes

In eight studies, most patients were intervened on under general anesthesia[9-16], while 4 studies reported the use of general anesthesia in all patients.[17-20] Regional anesthesia was used in the majority of patients in 4 studies[21-24] and used in all patients in 2 studies.[25,26] Four authors did not report the type of anesthesia used (Table 1).

Table 1. Type of anesthesia and shunting protocol used by study.

Author, year	N	Anesthesia type	Shunt protocol
Baker et al, 2000 (ACAS)	1662	NR	NR
Karmeli et al, 2001	94	Mostly regional	selective
Grego et al, 2005	1381	All general	routine
Ferguson et al, 1999 (NASCET)	1415	Mostly general	selective
Ballota et al, 2002	336	All general	selective
Rockman et al, 2002	2420	Mostly general	selective
Domenig et al, 2003	1950	Mostly general	routine
Cinar et al, 2004	429	All general	routine
Fitzpatrick et al, 2005	221	Mostly general	selective
Dalainas et al, 2007	3332	Mostly general	selective
Maatz et al, 2008	1960	NR	routine
Bagaev et al, 2010	335	Mostly general	routine
Goodney et al, 2012	5632	Mostly general	Both routine and selective
Kretz et al, 2012	1212	All general	selective
Faggioli et al, 2013	1218	NR	Routine
Capoccia et al, 2014	1639	Mostly general	selective
Ricotta et al, 2014	11614	Mostly general	selective
Taboada et al, 2016	434	All general	selective
Kong et al, 2017	301	All general	routine
Pothof et al, 2017	15487	Mostly general	selective
Turley et al, 2019	11948	NR	NR
Clouse et al, 2019	80230	Mostly general	selective

NR: not reported

Compared with non-CCO patients, patients with CCO were more likely to be intervened on under general anesthesia in 4 studies[11,13,15,22], regional anesthesia one study[24], while 3 studies reported no difference in the anesthesiologic strategy between the two groups.

The majority of studies where selective shunting was utilized reported higher rates of shunt insertion in patients with CCO (Table 2).

Table 2. Intraoperative outcomes in patients with CCO

Author, year	N	Outcomes in patients with CCO
		Intraoperative outcomes
Karmeli et al, 2001	94	Higher rates of shunt insertion, based on post-clamping neurological symptoms. No difference in anesthesia type.
Grego et al, 2005	1445	Higher rates of post-clamping EEG changes
Capoccia et al, 2015	1639	Higher rates of shunt use, based on EEG or TCD changes. More likely to be operated on under regional anesthesia
Ballota et al, 2002	336	Higher rates of post-clamping EEG changes and shunt use
Rockman et al, 2002	2420	Higher rate of shunt use. More likely to be operated on under general anesthesia
Cinar et al, 2004	429	No difference in rates of shunt use
Fitzpatrick et al, 2005	221	No difference in rates of shunt use; More likely to be operated on under general anesthesia
Dalainas et al, 2007	3332	Higher rate of shunt use, based on EEG changes. No difference in anesthesia type
Bagaev et al, 2010	335	No difference in anesthesia type
Goodney et al, 2012	5632	Higher rate of shunt use. More likely to be operated on under general anesthesia
Kretz et al, 2012	1212	Higher rates of shunt use, based on post-clamping neurological symptoms
Ricotta et al, 2014	11614	Higher rates of shunt use
Taboada et al, 2016	434	Higher rate of shunt use, based on EEG changes
Pothof et al, 2017	15487	Higher rates of shunt use. More likely to be operated on under general anesthesia

EEG: electroencephalogram; **TCD:** transcranial doppler; **CCO:** contralateral carotid occlusion

Gregoetal.foundinaretrospectivestudyof1445CEAcasesthat patients with CCO had more often electroencephalographic (EEG) changes during carotid cross-clamping compared to patients with a patent contralateral ICA, even though there were no significant differences in terms of post-operative neurological events.[17] In a study comprising 3332 CEA patients, Ballota et al. denoted an increased rate of shunt insertion, based on post-clamping EEG changes.[18] Three other studies where EEG was used as a neuromonitoring tool reported similar findings.[19,23,24] These findings suggest a disruption of the Willis polygon compensation mechanism during carotid cross-clamping.

Short-term outcomes

Most of the literature focuses on the impact that CCO has on the postoperative (first 30 days) outcomes. Nineteen studies compared postoperative outcomes in patients with a CCO with patients with a patent contralateral internal carotid artery. Among these, 11 studies reported an increased incidence of postoperative neurological events in the presence of a CCO[9,12-16,18,24,27-29], while 8 studies reported no differences[10,11,19,20,22,23,25,26] (Table 3).

Table 3. Short and Long-term outcomes in patients with CCO

Author, year	N	Outcomes in patients with CCO
		Short-term (30-days) outcomes
Ferguson et al, 1999 (NASCET)	1415	Higher incidence of stroke/death (aRR 2.2 95%CI: 1.1-4.5)
Ballota et al, 2002	336	Higher incidence of contralateral TIA (12% vs 1%, p<0.0001) but not stroke nor mortality
Rockman et al, 2002	2420	No difference in rates of neurologic events (3.0% vs 2.1%, p=0.34) nor mortality
Domenig et al, 2003	1950	No difference in stroke rates (3.6% vs 1.8%, p=NS) nor mortality
Cinar et al, 2004	429	Trend towards higher incidence of stroke (3.6%vs 0.5%, p=0.059) nor mortality
Fitzpatrick et al, 2005	221	No difference in stroke rates (6.3% vs 2.6%, p=0.39) nor mortality
Dalainas et al, 2007	3332	No difference in stroke rates (2% vs 1.8%, p=0.6) nor mortality
Maatz et al, 2008	1960	Higher incidence of stroke (5.6% vs 2.1%, p=0.012). Mortality not analyzed
Bagaev et al, 2010	335	Higher incidence of stroke in the first 24h (11% vs 3%, p=0.006) but not mortality
Goodney et al, 2012	5632	Higher incidence of stroke (4% vs 1.8%, p=0.002) but not mortality
Kretz et al, 2012	1212	No difference in neurological event rates (1.2% vs 1.5%; p=NS) nor mortality
Faggioli et al, 2013	1218	Higher incidence of neurological events/ death (13.5% vs 3%, p=0.001) but not mortality
Capoccia et al, 2014	1639	Higher incidence of stroke (4.4% vs 1.2%, p=0.009) but not mortality
Ricotta et al, 2014	11614	Higher incidence of stroke (3.1% vs 1.1%, p<0.001) but not mortality
Taboada et al, 2016	434	No postoperative strokes in patients with CCO
Kong et al, 2017	301	No difference in stroke rates (2.3% vs 2%, p=0.824) nor mortality
Pothof et al, 2017	15487	Higher incidence of stroke/death (OR 2.2, 95% CI:1.4–3.6, P = .001), any in-hospital stroke (OR 2.9, 95% CI: 1.7–4.9, p<0.001), in-hospital ipsilateral stroke (OR 2.1, 95% CI: 1.1–4.0, p=0.02), in-hospital contralateral stroke (OR 7.1, 95% CI: 2.8–17.9, p<0.001).
Turley et al, 2019	11948	Higher incidence of stroke/death (aOR 1.73 95%CI: 1.08-2.76).
Clouse et al, 2019	80230	Higher incidence of non-ipsilateral stroke (aOR 1.9 95%CI: 1.3-2.8). Mortality not analyzed
		Long-term outcomes
Gasecki et al, 1999 (NASCET)	1415	Higher rates of ipsilateral stroke (HR 2.18, 95% CI: 1.15-4.11), any stroke (HR 1.89, 95% CI: 1.01-3.53) and stroke/death (HR 1.89, 95% CI: 1.06-3.38)
Ballota et al, 2002	336	No difference in stroke-free survival rates
Grego et al, 2005	1381	No differences in disabling or fatal stroke or mortality

Table 3. Short and Long-term outcomes in patients with CCO (continuation)

Author, year	N	Outcomes in patients with CCO
		Long-term outcomes
Baker et al, 2000 (ACAS trial)	1662	No difference in ipsilateral stroke
Fitzpatrick et al, 2005	221	No difference in stroke-free survival
Taboada et al, 2016	434	No difference in mortality
Kong et al, 2017	301	No difference in stroke, myocardial infarction or mortality

TIA: transient ischemic attack; **CCO:** contralateral carotid occlusion.

Considering the largest studies, Pothof et al. studied the influence of contralateral carotid stenosis or occlusion on perioperative outcomes in a cohort study of 15487 patients from the Vascular Study Group of New England (VSGNE) registry (USA). Multivariable regression analysis demonstrated an independent association between CCO and 30-day stroke/death (OR 2.2, 95% CI:1.4–3.6, P = .001), any in-hospital stroke (OR 2.9, 95% CI: 1.7–4.9, p<0.001), in-hospital ipsilateral stroke (OR 2.1, 95% CI: 1.1–4.0, p=0.02), in-hospital contralateral stroke (OR 7.1, 95% CI: 2.8–17.9, p<0.001), and prolonged length of stay (OR 1.7, 95% CI: 1.4–2.0, p<0.001), but not 30-day mortality (OR 1.1, 95% CI: 0.5–2.8, p=0.8). Interestingly, neither moderate (50-79%) nor severe (80-99%) contralateral carotid stenosis were associated with 30-day stroke/death or in-hospital stroke.[15] These findings were corroborated by another large cohort study of patients from the Society for Vascular Surgery Vascular Registry. In this study, Ricotta et al. demonstrated that patients with CCO submitted to CEA have higher rates of perioperative major adverse cardiovascular events (4.2% vs 1.8%, p<0.001) and stroke (3.1% vs 1.1%, p<0.001).[14] Turley et al., have also found in a study of 11948 CEA patients from the American College of Surgeons National Surgical Quality Initiative Project (ACS NSQIP) that CCO was associated with higher rates of postoperative stroke.[29] The largest study yet is drawn from the Vascular Quality Initiative (VQI, USA), encompassing 80230 patients, where Clouse et al. found an independent association between CCO and postoperative non-ipsilateral stroke (aOR 1.9 95%CI: 1.3-2.8).[16]

Interestingly, no study found an association between CCO and increased post-operative mortality, which suggests that increased incidence of postoperative events is mainly due to non-fatal stroke.

Among 11 studies where selective shunting was used 6 studies reported higher rates of postoperative neurological events in patients with CCO[9,14-16,18,24], while among 7 studies where routine shunting was the standard practice, 3 studies reported a higher incidence of postoperative neurological events.[12,27,28]

General anesthesia was utilized in 11 studies, 7 of which reported increased rates of perioperative neurological events in patients with CCO.[9,12-16,18] Five studies reported using mainly regional anesthesia, with only one study reporting a higher incidence of perioperative neurological events in patients with CCO.[24]

Meanwhile, other studies have not confirmed the association between CCO and adverse outcomes. Rockman et al. reviewed a prospective database of 2420 CEA patients. There was no significant differences in terms of perioperative neurological events between patients with and without CCO (3.0% vs 2.1%, p=0.34).[22] Similarly, in a study involving 3332 patients, Dalainas et al, found no significant differences in terms of postoperative stroke rates.[23] In a smaller study by Taboada et al., 434 patients were submitted to CEA, among which 40 had CCO, none of whom suffered any perioperative stroke.[19]

Long-term outcomes

While most studies have focused on perioperative outcomes, a few studies have presented long-term outcomes in patients with CCO (Table 3). In the study by Grego et al., at 6 years, there were no significant differences between patients with and without CCO in terms of disabling or fatal stroke or mortality. However, CCO conferred an increased risk of neurological events in the hemisphere ipsilateral to the occluded carotid artery.[17] In a post-hoc analysis of the ACAS trial, patients with and without CCO had similar rates of ipsilateral stroke at 5 years after CEA (5.5% vs 5.0%, p=0.86).[30] Taboada et al. did not find any significant differences in mortality between groups, with an average follow-up of 75.5 months.[19] Two other studies did not find a difference between patients with a patent contralateral carotid artery or CCO in stroke-free survival.[11,18]

By contrast, in a post-hoc analysis of the NASCET trial, at 2 years of follow-up patients with CCO had higher rates of ipsilateral stroke (HR 2.18, 95% CI: 1.15-4.11), any stroke (HR 1.89, 95% CI: 1.01-3.53) and stroke/death (HR 1.89, 95% CI: 1.06-3.38).[31]

DISCUSSION

Contralateral carotid occlusion has long been considered a risk factor for adverse outcomes following CEA. Overall, the existing evidence in the literature points to a higher incidence of brain hypoperfusion during carotid cross-clamping in this subgroup of patients. In a study by Montisci et al., 71 patients who underwent CEA were evaluated preoperatively with magnetic resonance angiography of the circle of Willis (CoW). The presence of two or more agenesiae in the CoW was significantly associated with carotid cross-clamping intolerance.[32] Another study by Banga et al found an increased incidence of immediate neurological events after CEA in patients with an isolated middle cerebral artery (incomplete anterior and posterior semicircle).[33] Contralateral carotid occlusion could compromise the compensatory mechanism of CoW, analogous to agenesiae of communicating arteries. This is further suggested in a study by Pennekamp et al., where CCO was independently associated with selective shunt use, even after accounting for the morphology of the CoW.[34] It is possible that preoperative CoW imaging and routine shunt use in patients with unfavorable CoW anatomies could lower the incidence of perioperative neurological events.

Although there are some conflicting results in the literature, the evidence provided by the largest studies, many of them from national registries (VSGNE, VQI, ACS NSQIP), points to a higher incidence of postoperative stroke in patients with CCO.[14-16,29] One pitfall is the lack of etiological description of these postoperative strokes. Hemodynamic strokes account for only 10% of all postoperative strokes after CEA.[35] It is unknown if these are more prevalent in the presence of CCO. The use of shunts could theoretically avoid cerebral hypoperfusion in this group of patients. Although a Cochrane meta-analysis found no differences in terms of stroke between no shunting, routine shunting and selective shunting[36], Goodney et al. reported in a cohort study of patients with CCO that the incidence of postoperative stroke was lower when surgeons used routine shunting, compared to selective shunters.[13] The potential benefit of shunting based on clinical signs of post-clamping brain ischemia in patients under regional anesthesia was studied in the General Anesthesia versus Local Anesthesia for Carotid Surgery (GALA) trial. However, there was no difference in the primary endpoint, consisting of stroke, death or myocardial infarction between randomization and day 30 after CEA, between general and regional anesthesia.[37]

The Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy (SAPPHIRE) trial compared CEA with carotid artery stenting (CAS) in patients with both symptomatic and asymptomatic carotid stenosis and with at least one condition considered to be high risk for surgery, including CCO. In the postoperative period there was no difference in terms of stroke/death between groups, although the authors provided no subgroup analysis for patients with CCO.[38] Others authors have reported a low incidence of in-hospital neurological events after CAS in patients with CCO.[39] However, this may not apply to centers with low volume of CAS cases. To date there are no randomized controlled trials comparing medical vs interventional treatment in patients with CCO. Therefore, particularly for patients with CCO, indication for carotid revascularization should be based on a case-by-case analysis.

Controversy remains regarding CCO as a long-term predictor of adverse outcomes. The NASCET trial found an association between CCO and long-term stroke and death (31) while another study found an association between CCO and later stroke in the hemisphere ipsilateral to the occlusion (17). Long-term cardiovascular mortality in patients with carotid artery disease is high, as shown in the ACAS trial, where 50% of deaths during follow-up were due to cardiac causes.[40] Therefore, while outcomes in the postoperative period seem to be higher in patients with CCO, there may be a catch-up phenomenon in the long-term in patients with a patent contralateral carotid artery.

This review provides an up-to-date insight to the clinical relevance of CCO in patients submitted to CEA. It gathers a large number of studies, some of them from large databases, with an adequate level of evidence. It is nonetheless a narrative review, providing the evidence in individual studies, without a pooled estimate.

The optimal management of patients with CCO should be tailored to the individual risk of stroke on medical therapy, symptomatic status of the patient, comorbidities and life expectancy and surgeon experience, until further randomized controlled studies for this specific population.

CONCLUSION

Patients with CCO have a higher incidence of intolerance to carotid cross-clamping and higher rates of adverse postoperative outcomes. An individual based approach should be adopted for this group of patients.

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