Intervention Strategy for Bilateral Carotid Artery Stenosis

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Stroke is the main cause of long term disability, and significant carotid stenosis is one of the main causes of ischemic stroke. It has been estimated that carotid artery stenosis may be responsible for 10% of ischemic strokes.[1]

In asymptomatic patients with 70-99% carotid artery stenosis, the ipsilateral stroke rate at 5 years is 14.6%, compared to 0% in patients with 50-70% stenosis ($P < 0.0001$). For patients with 80-99% carotid artery stenosis, the ipsilateral stroke rate is 18.3%, compared to 1% for patients with 50-80% stenosis ($P < 0.0001$).[2] The results of the Asymptomatic Carotid Atherosclerosis study (ACAS) demonstrate aggregate risk reduction of 53% for carotid endarterectomy (CEA), compared to antiplatelet therapy alone in asymptomatic patients with > 60% carotid stenosis.[3]

In symptomatic patients with > 50% carotid stenosis, the stroke risk is 26% at 2 years. The North American Symptomatic Carotid Endarterectomy Trial (NASCET) and European Carotid Surgery Trial (ECST) demonstrate absolute risk reduction of 11.6-17% through CEA, compared to medical treatment in symptomatic patients.[4,5]

Management of carotid artery stenosis is an effective and safe strategy for ischemic stroke prevention. CEA with optimal medical therapy is the first-line treatment of choice for low surgical risk patients with carotid artery stenosis. Carotid artery stenting (CAS) is reserved as an alternative option for high surgical risk patients (Table 1).

Indications for CAS include stenosis ≥ 50% for symptomatic lesions and ≥ 70% for asymptomatic lesions, using the NASCET method.[6,7]

The frequency of severe bilateral carotid artery stenosis (BCS) varies among published studies from 3.2 to 39%.[6,9,10] Nevertheless, it carries a higher risk of stroke and complications

Table 1. Characteristics of high risk patients receiving CEA.[8]

Older than 75 years old
Bilateral carotid artery stenosis
Severe systemic co-morbidities
Contralateral laryngeal-nerve palsy
Previous radical/neck surgery or radiation therapy to the neck
Bad neurological condition (mRS ≥ 3)
Restenosis after CEA
High anatomic location of the carotid artery

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during an intervention procedure (e.g. periprocedural stroke, hemodynamic distress, and cerebral hyperperfusion syndrome). The optimal treatment strategy for BCS remains unclear.

Intervention options for bilateral carotid artery stenosis (BCS):

The intervention options for BCS include bilateral CEA, unilateral CEA with contralateral CAS and bilateral CAS.[9-16]

BCS is a risk factor for complications during CEA. Simultaneous bilateral CEA is rarely performed due to potentially severe injury to the phrenic pharyngeal nerve, vagus nerve, and stellate ganglion, and higher risk of serious neurologic complications during the intraoperative period.[16-18]

For BCS patients, a hybrid strategy involving initial CAS for the asymptomatic high grade carotid stenosis side, followed by subsequent CEA for the symptomatic side, can reduce the risk of this CEA. Although this strategy can avoid bilateral cranial nerve palsy and shorten the admission period over staged CEA, relatively high complication rates are still noted in the first CAS procedure (stroke, post-procedural persistent hypotension).[14]

Another hybrid procedure involving simultaneous CEA and CAS has been reported by Xu, et al.[19] They first treat the symptomatic or more severe side with CEA. However, if the blood flow of the anterior cerebral artery at the side scheduled for CEA comes from the contralateral side, they first treat the contralateral side by CAS. If the contralateral plaque is unstable (intra-plaque hemorrhage or ulceration) and/or the anatomic situation is suitable for intervention, they treat the contralateral lesion simultaneously.[19] With careful assessment and preparation in selected patients with BCS, simultaneous CEA and CAS may be considered as an alternative management strategy.

Nowadays, high-risk BCS patients are mostly treated with bilateral carotid artery stenting (BCAS). Staged BCAS is generally the preferred strategy over simultaneous BCAS due to concerns about cerebral hyperperfusion syndrome, and hemodynamic distress (hypotension and bradycardia)[10,20]

Staged bilateral carotid stenting (staged BCAS) for high-risk patients:

The BEACH registry prospectively compared outcomes of staged BCAS to those of unilateral CAS in patients at increased risk for CEA.[6] In the staged BCAS group, the most symptomatic stenosed artery was treated first, with the staged procedure scheduled for 30 days later. No statistically significant difference was noted regarding 30-day and 12-month clinical outcomes between staged BCAS and unilateral CAS. The 30-day incidences of all strokes were 4.5% in the unilateral- and 4.1% in the bilateral group, while the 30-day rates of ipsilateral stroke were 3.4% and 1.4%, respectively. The staged BCAS strategy is effective in BCS patients determined to be at high-risk for CEA.

Guidelines from the Society for Vascular Surgery recommend the optimal timing for primary carotid revascularization in recent stroke patients (modified Rankin scale score 0-2) with stenosis > 50% to be as soon as the patient reaches stable neurological status after 48 hours, but definitely within 14 days after symptom onset.[7] By contrast, the timing for staged intervention in BCS is controversial. The symptomatic side or more severely stenosed side should be treated first. The staged procedure is usually performed at least 30 days after primary CAS.[6,10] However, the reported time intervals between the primary and staged procedures have ranged from 24 hrs. to 2 months in previous studies.[8,20,21]

Compared to simultaneous BCAS, the staged procedures have some disadvantages, including delayed treatment of contralateral severe carotid stenosis, higher expenditure, inconvenience to patients, and delay of potentially lifesaving procedures (e.g. cardiac surgery).[9,20]

Simultaneous bilateral carotid stenting (simultaneous BCAS).

The first reported case of simultaneous BCAS was in 1997 by Mather et al.[22]

Subsequently, further studies were published supporting the safety and feasibility of simultaneous BCAS.[8,9,20,23-25] A representative case of simultaneous BCAS from Oshita et al. is shown in Figure 1.[25]

Studies comparing simultaneous BCAS with unilateral carotid artery stenting (UCAS) show no significant difference in safety and complication rates.

Dong et al. retrospectively compared the safety of simultaneous BCAS with unilateral carotid artery stenting (UCAS). Clinical outcomes including six-month and 30-day hemodynamic depression (HD), hyperperfusion syndrome (HPS), stroke, death, and myocardial infarction (MI) are assessed in this study. There is no statistically significant difference in the HD incidence (28.2% vs. 20.0%, P = 0.396), and HPS incidence (2.6% vs. 2.1%, P = 0.262) between the two groups at 30 days. There are also no differences in minor stroke, major stroke, MI, death and combinations thereof, between the two groups at 30 days and six-months after the procedure.[24]

Jiang et al. compared the composite risks of stroke, myocardial infarction, or death within 30 days or any ipsilateral stroke within 1 year between simultaneous BCAS and unilateral CAS. They show simultaneous BCAS produces no significant difference in adverse events, compared to unilateral CAS during the periprocedural period or within 1 year .[26]

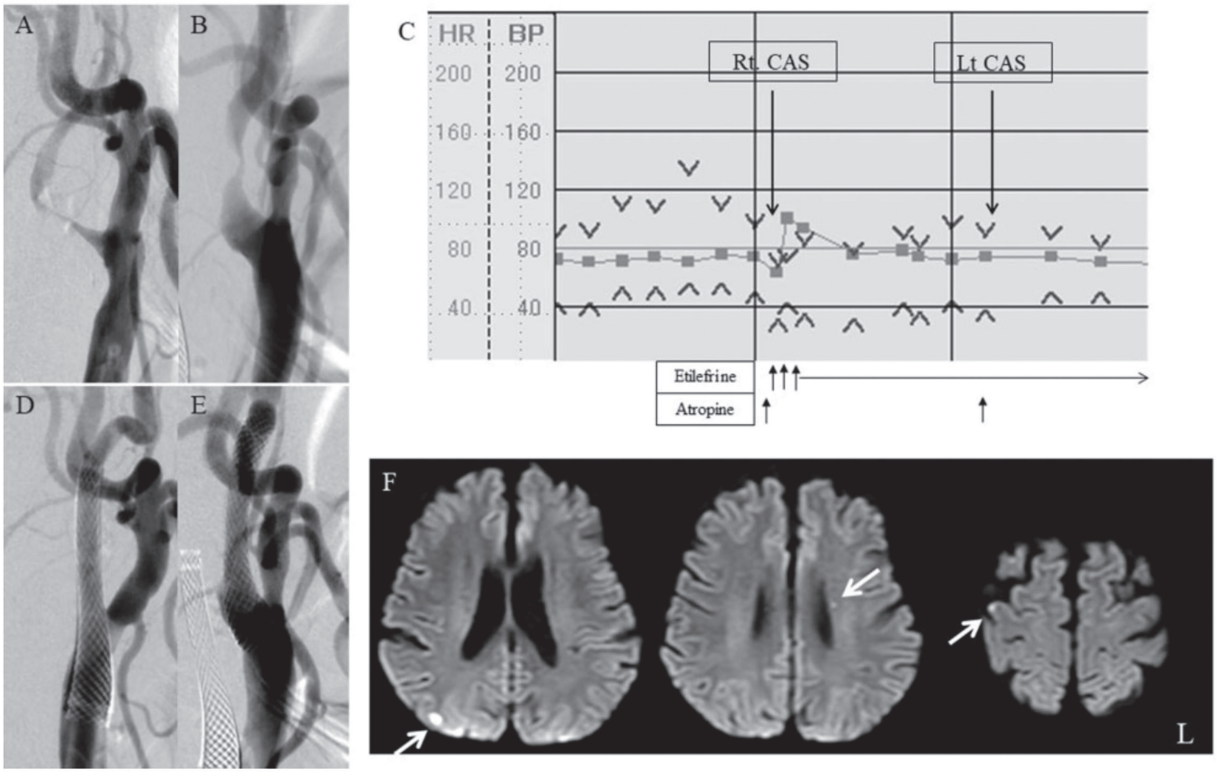

Figure 1. (A) and (B) show severe stenosis of the right ICA (A), and left ICA (B). (C) shows the intraoperative BP (□: systolic BP, V: diastolic BP) and HR (■). The BP decreased after right side stenting, and the left side stenting was done with administration of vasopressor. (D) and (E) show the postoperative images after BCAS. (F) shows high-intensity spots scattered in the bilateral cerebral hemispheres on diffusion-weighted imaging the day after simultaneous BCAS.

Systemic review and meta-analysis conducted by Lai et al. evaluated the safety and efficacy of simultaneous BCAS and unilateral CAS. They conclude that except for HPS, other complications including HD, stroke, and MI are comparable between the two groups. The technical success rate of simultaneous BCAS is 99.38%. The pooled incidences of complications are as follows: HD: 46.12%; HPS: 3.33%; stroke: 3.20%; myocardial infarction: 0.60%; and death: 1.20%. For the combination of any stroke, MI, and death it is 4.28%.[27]

Studies comparing simultaneous BCAS with staged BCAS also show no significant difference in safety and complications.

For example, Li et al. report that the hemodynamic depression rate is 57.4% in a simultaneous BCAS group, which is similar to patients receiving staged BCAS. In addition, the 30-day complication rates, including hyperperfusion syndrome and ischemic events are also similar for these groups (4.8 vs. 7.7 %, P = 0.633). They conclude that simultaneous BCAS may be feasible and safe for most patients with BCS.[9]

Henry et al. retrospectively evaluated the feasibility and safety of simultaneous BCAS with staged procedure. They note no difference in hemodynamic depression, transient ischemic attack, minor stroke, hyperperfusion syndrome, and myocardial infarction between simultaneous BCAS and staged BCAS.[20]

Oshita et al. retrospectively compared the perioperative and postoperative course of simultaneous BCAS to staged BCAS. The rates of intraoperative and postoperative hypotension and bradycardia are comparable between the simultaneous BCAS and staged BCAS groups. Although longer procedure time and higher frequency of high-intensity spots on postoperative diffusion-weighted imaging are noted in the simultaneous BCAS group, there is no increment in symptomatic ischemic complications and hospitalization duration, compared to the staged BCAS group. They suggest that the safety of simultaneous BCAS may not be inferior to staged BCAS.[25]

Medical management is also crucial in BCS patients. However, medical management alone is inferior to simultaneous BCAS. Ye et al. compared the effectiveness and safety of simultaneous BCAS with solely aggressive medical management (SAMM) in BCS patients. The cumulative probability of endpoint events including minor stroke, TIA, or death within 30-days, 6-months, and 1-year is significantly lower in the simultaneous BCAS group than in the SAMM group (5.71% and 38.89% respectively, $p<0.05$).[28]

Periprocedural considerations in simultaneous BCAS:

The techniques for simultaneous BCAS are similar. Most patients are under local anesthesia via femoral access. Commonly, the symptomatic side or more severely stenosed side is treated first.[10] However, it is also feasible to do CAS first on the side with less stenosis to lower the potential technical difficulty.[21,24]

During the procedure, heparin is given to achieve activated clotting time between 250 and 300 seconds, and embolic protection device is routinely used.

Atropine is always administered prophylactically before stenting to prevent bradycardia. To avoid hypotension during the procedure, normal saline hydration is the first line of treatment. If persistent hypotension develops, norepinephrine and/or dopamine can also be considered.[21,25] The optimal blood pressure (BP) control range during the procedure is systolic BP between 110 and 130 mm Hg.

After stent placement, post-dilation is performed if necessary. In order to minimize the baroreceptor response, post-dilation can be avoided after placement of the first stent.[29]

After the procedure, dual antiplatelet therapy with aspirin 100 mg and clopidogrel 75 mg once daily for a few months is prescribed. Aspirin is then continued indefinitely.

Patients who might NOT be suitable for simultaneous BCAS:

Although simultaneous BCAS is reported to be safe and feasible for selected patients, Wang et al. suggest that for patients whose perfusion computed tomography (CT) reveals poor cerebrovascular reserve capacity, staged BCAS should be considered instead of simultaneous BCAS.[21] Besides, for patients who develop hemodynamic instability, new neurological impairment, or restlessness after primary CAS, the second procedure should be postponed in a staged manner.[23]

Hyperperfusion syndrome (HPS)

HPS is of theoretical concern after simultaneous BCAS, because the increase in cerebral blood flow after simultaneous BCAS is greater than after unilateral CAS. HPS is defined as exhibiting symptoms such as an ipsilateral throbbing headache, seizure, or focal neurological symptoms without cerebral infarction. HPS occurs most frequently several hours after stenting. The neurologic deficits of HPS are mostly noted secondary to cerebral edema. However, more severe consequences may develop if intracerebral hemorrhage occurs.

Liu et al. reported that the risk of HPS in simultaneous BCAS and unilateral CAS were 16.8% and 2.9%, respectively (P = 0.014). However, no statistically significant difference was noted in stroke-, death-, or restenosis rates at 6 months. They suggest that careful monitoring and management of BP is required for at least 1 month after simultaneous BCAS to avoid HPS.[8]

However, Ye et al. report a lower HPS occurrence rate of 5.7% among their retrospective series 48hrs after simultaneous BCAS intervention. All HPS patients fully recovered without sequelae after meticulous BP control.[28]

The risk factors for HPS are listed in Table 2. The most important factor to prevent HPS is meticulous control of blood pressure. For patients receiving regular antihypertensive agents, the BP lowering therapy can be continued on the morning of intervention to prevent high blood pressure. However, the optimal choice of antihypertensive is controversial. Some studies suggest that blood pressure is preferably to be controlled using drugs such as labetolol and clonidine that do not increase cerebral blood flow, rather than angiotensin-converting-enzyme inhibitors, calcium-channel blockers, or vasodilators (e.g. nitroprusside and glycerol trinitrate).[30,31]

Table 2. The risk factors for hyperperfusion syndrome (HPS) [30-32].

Hypertension
High grade stenosis with poor collateral flow
Bilateral tight stenosis (one side >90 %, contralateral side >80 %)
Increased peak flow velocity
Decreased cerebrovascular reactivity
Recent contralateral CEA (<3 months)
Intraoperative distal carotid pressure of <40mmHg
Intraoperative ischemia

Conclusion

The optimal treatment for patients with BCS should be individualized. In selected patients, simultaneous BCAS is safe and feasible. Except for HPS, periprocedural outcomes of simultaneous BCAS are comparable with those of unilateral CAS. Although the HPS rate is higher with simultaneous BCAS than unilateral CAS, the absolute number of HPS is small. Under meticulous periprocedural preparation and blood pressure control, simultaneous BCAS can be used for BCS. Nonetheless, most studies of simultaneous BCAS are based on retrospective analyses. Therefore, further prospective and randomized, controlled studies are needed to confirm these results.

Keywords

bilateral carotid artery stenosis, carotid artery stenting

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