

All Asymptomatic Patients with Carotid Stenosis of 70-80% Should Undergo Surgery or Stenting Before Myocardial Revascularization Surgery

Agonist

L. Mariano Ferreira¹

Managing patients scheduled for cardiac surgery with significant carotid artery disease is a controversial issue that usually produces very polarized opinions, even in the literature. Discussion focuses on determining if carotid disease, concomitant with the need for coronary artery bypass, is an important etiologic factor for post-surgical stroke, or simply a marker of increased risk of vascular disease.

There are different clinical situations and therapeutic alternatives for patients with carotid-coronary artery disease. Carotid artery stenosis can be symptomatic or asymptomatic, unilateral or bilateral, stenotic or occlusive. Furthermore, the treatment can be both conservative and endovascular or open, sequential or simultaneous, and the order can also be changed. In some cases, the evidence is fully established, but unfortunately, in other cases it has to be drawn up according to the patient and the experience of the treating group.

Whether or not a consequence of carotid atherosclerosis, coronary artery bypass surgery in the presence of carotid artery disease faces a greater risk of stroke, even when most of the cerebrovascular events are not mechanically associated with carotid artery stenosis. The published reports indicate that cardiac surgery without carotid artery bypass surgery in patients with symptomatic carotid artery stenosis is associated with high rate of stroke (OR 3.6), and even higher if stenosis is > 50% (OR 4.3, CI 95%, 3.2-5.7). Internationally, morbidity and mortality of combined surgery is close to 10%. By contrast, separately, cardiac surgery in the presence of severe symptomatic carotid disease shows a 2-22% rate of stroke, while carotid surgery in the presence of severe or unstable coronary artery disease has a rate of acute myocardial infarction (AMI) that may reach 40%. For that reason, the AHA/ASA consensus recommends (Class IIa recommendation) carotid artery bypass (carotid endarterectomy [CE] or carotid angioplasty and stenting [CAS] and brain protection system) for those patients with stenosis > 80%, provided they

have had hemispheric or ocular symptoms over the past six months (Level of Evidence C).¹

Our patient, however, is a candidate for coronary surgery, and he is accidentally or deliberately diagnosed with severe carotid stenosis. If stenosis was severe, bilateral or contralateral occlusive, the reply would be easy, yet poorly supported by the evidence. In these patients, my reply would probably be to protect the patient from a perioperative stroke with a combined carotid-coronary artery surgery. However, the evidence is even less conclusive for the patient under discussion. The rate of stroke in coronary surgery without carotid artery disease is < 2%, but with unilateral asymptomatic stenosis, it is > 50%, scale from 3% to 5%, bilateral 5% to 7%, and with occlusive disease, from 7% to 11%.

Different societies have expressed their opinions about this group of patients. Consistent with the two important randomized studies on asymptomatic patients, which require a rate of stroke < 3%, the 2004 Class IIa recommendation from the American College of Cardiology/American Heart Association² was to perform a routine preoperative Doppler echocardiography in patients candidates for myocardial revascularization surgery (MRS), and in cases of stenosis > 80%, to perform a carotid endarterectomy (CE). But, on the contrary, both the AHA/ASA and the European Society for Vascular Surgery, in their consensus published at the beginning of this year, 1,3 have determined that, in patients candidates for cardiac surgery with asymptomatic unilateral carotid stenosis, whether it is severe or not, in the absence of evidence that proves its safety and efficacy, the best approach is the individualization of each patient (IIb recommendation; Level of Evidence C). Therefore, in the absence of studies that support one or another approach, it would be acceptable to try and find the patients who really benefit from a combined or sequential approach, if it indeed exists.

The SAPPHERE study determined that carotid angioplasty with stenting (CAS) is the best alternative

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for patients at high cardiac risk.⁴ However, with an almost prohibitive rate of stroke close to 6% in patients with “asymptomatic disease”, they far outweigh the level of risk accepted by the ACAS trial. Moreover, in this case, coronary artery disease would be a contraindication in itself for carotid treatment. Some authors have described the chances of performing two procedures at least 48 hours apart, whose published evidence does not seem to be different from the combined and simultaneous procedure. In a recent meta-analysis published in the *EJVES*, the combination of carotid angioplasty and MRS had a mortality rate of 5.5%, an ipsilateral stroke of 3.3%, and an AMI of 1.8%.⁵

In a published registry of 27,084 patients who underwent simultaneous surgeries (CE/CAS + MRS) in the United States from 2000 to 2004, the rate of stroke and stroke/mortality associated with CAS (3.3% of the total of patients) was 2.4 and 6.9% respectively, as opposed to 3.9% and 8.6% for CE combined with MRS (96.7%) ($p=0.1$). However, in-hospital mortality rates were similar in both approaches (5.2% versus 5.4%). Although carotid stenting and angioplasty may be a reasonable alternative to CE in this situation, endoluminal carotid interventions require the perioperative use of potent platelet inhibitors like clopidogrel, which considerably increases the risk of major bleeding associated with coronary artery bypass surgery.⁷ In addition, antiplatelet delay increases the risk of stent thrombosis and stroke. Another strategy is to perform carotid intervention immediately before coronary surgery, and to administer intravenous heparin between these procedures, but this approach and the optimal bypass strategy have not been properly evaluated. In the ACC/AHA 2004 Guidelines, the recommendation was to discontinue the utilization of clopidogrel within five days before coronary artery bypass surgery.² According to the different international registries and studies, carotid stenting has a higher rate of stroke and associated mortality than surgery.^{8,9} Potential complications including hypotension and persistent bradycardia, hyperperfusion syndrome, problems at the femoral access site, or contrast nephropathy have also been reported.

Off-pump coronary surgery can also reduce the rate of perioperative stroke. In a review published in 2009, twelve studies were identified, including data of 324 simultaneous surgeries CE + OFF-PUMP MRS. Operative mortality was 1.5%, the combined risk of death or ipsilateral stroke was 1.6%, the risk of death or any stroke was 2.2% (CI 95%: 0.7 to 3.7), and the risk of death, myocardial infarction or stroke was 3.6% (CI 95%: 1.6 to 5.5).¹⁰ While outcomes are better than those published for on-pump surgery, only a few patients were referred, which may be a bias of the lack of publication about patients with unfavorable outcomes, or the pre-selection of cases. These findings are encouraging and may actually show a side benefit

to less manipulation of the aorta.

A total of 132 patients were evaluated in a recent retrospective study about combined surgery presented by the Leicester's team, carried out between 1995 and 2009.¹¹ Perioperative mortality rate was 5.3%, ipsilateral stroke was 1.5% (2 patients, one with bilateral stenosis and the other with contralateral occlusion), and any stroke rate was 3.0%. There were no significant differences when stratified by sex, age, presence of neurological symptoms, and severity or bilaterality of carotid disease, or the fact that whether the cardiac procedure implied a primary coronary artery bypass or a more complex surgery. The rate of stroke for symptomatic patients was 2.5%, and for asymptomatic patients, 1.2%. But the interesting thing is that 57% of the patients had contralateral lesions. Of these, 32 had stenosis between 70% and 99%. The only case of contralateral stroke was reported in that group (1/32, 3.1%), which exceeded the rate of stroke for carotid surgery in asymptomatic patients. This is even more supported by the approach of selecting patients with severe asymptomatic carotid artery stenosis for combined surgery.

The policy of our team for this select group of patients with severe symptomatic coronary artery disease and severe asymptomatic carotid artery stenosis has always been to combine both surgical procedures –CE and MRS– in only one, and under the effect of heparin and aspirin. Technically, endarterectomy is performed at the same time as sternotomy and internal mammary artery dissection. All the procedures are performed with shunt, under intraoperative transcranial Doppler monitoring, and performing patch-graft arterioplasty. The wound is virtually blocked during coronary surgery, and finally closed after hemostasis is controlled at the end of MRS. Our current approach is the result of combining a careful pre-screening of patients in the context of a refined surgical technique. Our surgical outcomes in carotid artery surgery, 0.5% for stroke in asymptomatic patients,¹² are significantly lower than the incidence of stroke in MRS with associated carotid artery stenosis. With an international recommendation of strict screening of patients, and based on our own experience in combined carotid surgery, our position is to perform these simultaneous procedures in patients with asymptomatic carotid artery stenosis greater than 80%.

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The author declares no conflict of interest.

Antagonist

Conrado J. Estol¹

“Theories can be changed any time, results cannot.”

FRED SANGER

From the revascularization viewpoint and from the clinical and medical aspect, there are several reasons by which an asymptomatic carotid patient should not be operated, and even less before a cardiac surgery. Prior to listing those reasons, it is worth analyzing the title of this controversy in detail. First of all, the meaning of ‘asymptomatic’ has to be clearly defined, since many doctors consider that individuals who have had loss of consciousness, cognitive disturbances, isolated sensory symptoms, and vertigo or dizziness are carriers of symptomatic carotid artery, coexisting with carotid artery stenosis. The explanation is relevant because these features –commonly found in daily medical practice– are not manifestations of carotid artery disease, and therefore stenosis is asymptomatic in this group of patients. When being attributed symptoms that are not caused by carotid artery disease, patients are exposed to the unnecessary risk of bypass surgery, when the etiology of their problem is different (arrhythmia, autonomic dysfunction, degenerative cognitive decline, vestibular disease). The papers published in 1970s and 1980s by Miller-Fisher, Pessin and Caplan thoroughly describe the mechanisms and symptoms of carotid artery disease, a topic beyond the focus of this discussion. In this analysis, the arbitrarily called “stenosis of 70%-80%” does not justify bypass surgery (I will provide my reasons below). In any case, it would be more appropriate to speak about a stenosis “greater than 80%”, and explain that it should be determined

by catheter angiography because of the errors (false positives and negatives) that are inevitable when using Doppler, even in the most experienced hands.¹ Further analyzing the title, the alternative between “surgery or stenting” should not be such, since several studies published during 2010, and a meta-analysis, revealed further complications with the endovascular method compared with conventional surgery.^{2,3} With the exception of specific patients or situations, these recent publications point out that endarterectomy is the procedure of choice for carotid artery bypass surgery. Due to an increased incidence of myocardial infarction in patients treated with endarterectomy, when bypass surgery is performed in young patients with significant coronary artery disease, and carotid plaque is not irregular, endovascular treatment with stent would be highly recommendable. These data show that there is no equipoise to allow for the alternative between surgery ‘or’ stenting –depending on the choice of the treating physician–, and that a strict screening of potential candidates for stenting should be performed. Only the term ‘before’ is included after the treatment options, while in practice, a large proportion of patients undergo carotid artery surgery together with coronary artery disease (simultaneously or sequentially). Therefore, it would be more accurate to add ‘before or during...’. I have purposely left the first word of the title for the end: “All...”. When life expectancy is longer than one decade, carotid artery stenosis is > 80% and coronary status allows for elective coronary artery bypass surgery, a patient may be candidate to first undergo carotid surgery, and a few weeks later, coronary artery bypass surgery. If this

were the focus of interest in the debate, then the title should start as follows: "Exceptionally, a patient...", since cases like the one described are very uncommon.

If we carry out this analysis from the point of view of bypass surgery, it should first be defined what the risk of asymptomatic carotid artery stenosis is in patients without coexisting cardiac lesions. In 1995, the ACAS trial reported surgical benefit for patients with asymptomatic stenosis > 60%, but absolute risk reduction of stroke was very low (from 2% to 1% per year).⁴ The surgical benefit is questionable because of the 2% annual risk of stroke in patients with untreated asymptomatic stenosis (it is worth remembering that this risk is lower than the risk a symptomatic patient undergoing a successful endarterectomy will have after surgery), even with low surgical morbidity and mortality rate. A meta-analysis of prospective randomized trials confirmed the low absolute risk of stroke in asymptomatic patients.⁵ Another study, with a median follow-up of ten years in asymptomatic patients, showed that the risk of stroke remains low during long-term follow-up.⁶ The population-based Oxford Vascular Study, found that the risk of ischemic ipsilateral stroke was 0.34% (CI 95%, 0.01-1.87) in 101 patients with a mean age of 75 years and with > 50% stenosis.⁷ In short, the natural history of asymptomatic carotid artery occlusive disease is benign, with a low incidence of stroke. Another way of mapping the natural history of the disease is reflected in the number of patients to be treated for stroke prevention at one year. It is necessary to operate 8 patients with symptomatic carotid artery stenosis > 70%, and 83 patients with asymptomatic stenosis > 60% (an order of magnitude difference) to obtain the same benefit. Being simple, it is clear that if we walked along the street wearing a helmet, the consequences of a pot falling over our heads would be minor. But the question is: How significant is the likelihood of pots falling as to justify wearing helmets in the street?

In the second place, it should be noted that there is no evidence suggesting that stenosis in an asymptomatic carotid artery is predictive of a higher rate of complications in the context of myocardial revascularization surgery. This is also independent of the percentage of arterial occlusion, and this is typical, because the ACAS trial did not show a greater benefit for surgery regarding increasing degrees of stenosis (whereas in the NASCET study on symptomatic carotid artery disease, surgical benefit increased considerably with the increased deciles in the stenosis degree). In other words, there is no evidence that a patient with asymptomatic stenosis of 60%, 70%, 80% or 90% has an increased risk of stroke during a coronary artery bypass surgery (even though the physician subjectively gets 'impressed', and biases when a patient has stenosis of "80% or 90%"), as well as paradoxically, and as opposed to the NASCET study, the ACAS did not show greater benefit when patients

with stenosis of 80%, for example, underwent surgery, compared with those who had 60%.

When it is performed as previous surgery, carotid artery bypass surgery on a patient with indication for coronary surgery is associated with increased risk of myocardial infarction. Hertzner et al reported that at Cleveland Clinic perioperative morbidity and mortality was three times higher when carotid and coronary artery bypass surgeries were performed simultaneously. Considering the experience and the context of work of this group, it is reasonable to assume that this risk is even higher with surgical teams with lower volume of patients. This information leads us to pose the need for reliable data on morbidity and mortality rates from each surgical and endovascular treatment group. These data are rarely available, and their validity depends on what medical specialist is in charge of the audit (which should be independent of the facility where the procedures are carried out). In a study of 16,000 endarterectomies, general perioperative risk of death and stroke was 5.6%. However, the risk ranged from 7.7% –when calculated by neurologists– to 2.3% –when reported by surgeons.⁸ Most physicians who indicate an invasive procedure do not have reliable data about the risk of such procedure. In a US national survey, fewer than 20% of physicians reported knowing the surgical morbidity and mortality rates at their hospitals.⁹ This is crucial, since a 2% increase on the accepted 3% morbidity and mortality rate for asymptomatic carotid artery results in a 30% reduction of the expected benefit.¹⁰ Surprisingly, surgeons who participated in trials on carotid surgery obtained a lower morbidity and mortality rate when operating patients included in the trial –in the same operating room, at the same hospital, and with the same surgical team.¹¹

Also, there are no data to justify surgery on patients with bilateral stenosis or contralateral occlusion, two scenarios that often trigger asymptomatic carotid surgery, particularly in patients undergoing coronary surgery. By contrast, a reassessment of the ACAS trial revealed a worse surgical prognosis when patients with contralateral occlusion were performed surgery.¹² Age, aortic calcification, peripheral vascular disease, and pump-time are the independent predictive factors of perioperative stroke in coronary surgery.¹³

Since studies on carotid surgery were published in the 1990s, morbidity and mortality rates associated with these procedures have not changed significantly. However, medical treatment did improve to the point of achieving a 70% reduction of vascular events in the population at risk.¹⁴ Recent studies have shown that medical treatment significantly reduces the risk of stroke, without the potential complications of revascularization.^{15,16} For example, between 1993 and 1996, only 17% of the randomized patients in studies on carotid surgery were administered statins, compared with a 90% of patients included in vascular

studies since 2004. A proper medical treatment implies the use of antiplatelet drugs, maximum doses of statins regardless of LDL, ezetimibe addition, niacin and fibrates as needed, the indication of ACE inhibitors, ARBs and diuretics among other antihypertensive drugs, and the addition of metformin or pioglitazone in insulin resistant patients. A progressive regression of the atheroma plaque area in the carotid artery was targeted in patients treated according to the algorithm described, and this phenomenon was associated with lower incidence of vascular events.¹⁷ Unfortunately, most vascular patients do not receive proper treatment, and this is particularly evident in hypertension.¹⁸ It is prudent to speculate that if the main studies on carotid surgery completed at the beginning of (1991 NASCET) and in mid (1995 ACAS) 1990s were repeated today with the same scientific design, the outcomes would probably be different due to the increased use of medication to treat vascular risk factors.

In the last 25 years I have devoted primarily to the treatment of cerebrovascular disease in several institutions of the United States and Argentina, following the principles of scientific evidence available, I do not recall any case –among the dozens of patients evaluated and followed up– with asymptomatic carotid artery stenosis of up to 90% whom we have performed coronary surgery only and who has suffered a perioperative stroke. In the patients reported in literature, stroke is usually located in the hemisphere opposite the stenosis, which suggests that the operating mechanisms are different from the one associated with the stenosed carotid artery and, most probably, with a cardio-aortic embolism associated with the cardiac surgery.

The term “antagonist”, used to identify my presentation in this debate, implies the existence of two valid, opposing positions. This does not seem to be the case in this analysis, because the indication for carotid artery bypass surgery in asymptomatic patients, prior to or simultaneously with a coronary surgery, is a practice with no scientific evidence that justifies it, and with increased surgical risk for the patient. It is said that a procedure is safe when the risk of not using it is greater than the risk of using it. In asymptomatic patients, medical treatment should be given priority, with emphasis on the control of vascular risk factors. The only valid indication for carotid and cardiac surgeries –simultaneous or in tandem– is for the unusual cases of symptomatic carotid artery disease in patients undergoing cardiac surgery. The most suitable title for this text could be “All asymptomatic patient with carotid stenosis greater than 60% should be medically treated before and after a myocardial revascularization surgery”.

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The author declares no conflict of interest.

AGONIST'S REPLY

Let's go from the 'intuitively reasonable' concept to the evidence. Why do I say this? Because, undoubtedly, medical treatment improves day by day, and plaque remodelling, incidence of events, and adherence to treatments have been changing over the years. But carotid endarterectomy (CE) "has not"; CE remains a very safe procedure to prevent stroke in patients at high risk for it. For this reason, the AHA/ASA (2011) Practical Guidelines have determined the following: 1. In asymptomatic patients with carotid artery stenosis > 70%, performing CE is reasonable if the perioperative risk of stroke, AMI, and death is low (NR IIa).

That is why the ACC/AHA (2004) determined (NR IIa) that:

1. The CE is recommended before or simultaneously with MRS in patients with symptomatic or asymptomatic, unilateral or bilateral stenosis greater than 80%.

For that reason, the Guidelines of the European Society of Vascular Surgery (2009) recommend:

2. Simultaneous management of carotid and coronary artery diseases should be individualized specifically depending on each patient's risk.

But there is a well-specified constraint in these lines, which is the need for a morbidity and mortality rate lower than 3% in the surgical team.

Finally, an extensive meta-analysis published in May 2011 reports the events in neurologically asymptomatic patients with 50-99% stenosis who 'suffered' a MRS. Mortality rate was 4.8%, 2% (95% CI: 1%-3.8%) of ipsilateral stroke, and a combined rate of death and stroke of 5.7% (2%-13%). However, when stenosis was bilateral, combined rate climbed to 9.1%. In patients with bilateral carotid artery stenosis undergoing simultaneous surgery, the rate of stroke in the hemisphere corresponding to 80-99% non-operated, contralateral stenosis was 5.7% (CI 2.9%-11.5%). Therefore, it seems reasonable to offer these patients a procedure with a MM < 2%. Indication for simultaneous surgery is precise (ACC/AHA 2011). I reiterate, "in selective patients candidates for coronary surgery with severe asymptomatic unilateral carotid artery stenosis, the best approach is to individualize each patient, each procedure, and each surgical team". This controversy may serve to encourage the development of a national study that provided an evidence with greater statistical weight.

L. Mariano Ferreira

ANTAGONIST'S REPLY

"It is easier to disintegrate an atom than a prejudice."

ALBERT EINSTEIN

Dr. Mariano Ferreira based the arguments of his debate on an increased risk of stroke in patients with asymptomatic carotid and cardiac surgery (MRS). He concludes by describing "... an accurate screening...", which is inconsistent with his proposal to operate all the patients with severe stenosis requiring MRS. However, the key question is whether stroke has a causal relation with carotid artery in these patients. Clearly, the answer is "no", and I will summarize the reasons below: 1) the incidence of carotid artery stenosis in patients with stroke in MRS is low, so most of these episodes have another origin; 2) in MRS, stroke ipsilateral to carotid stenosis is rare; 3) in some series, stroke is more common in patients without stenosis; 4) when stroke is ipsilateral to carotid artery, the artery is generally occluded, which precludes any treatment; 5) most post-MRS strokes are secondary to aortic complications (atheromas quadruple the risk) and cardiac complications—debris, AF (30% post-MRS), ventricular dysfunction—; 6) different series have shown that lacunar infarctions and intracranial stenosis are a common cause of perioperative stroke in MRS; 7) studies on autopsies and images reported that carotid stenosis was not responsible for stroke; 8) less than 3% of bilateral strokes have bilateral carotid stenosis; 9) there is no evidence of increased carotid stenosis embolism during MRS; 10) studies on the cerebral blood flow have shown: a) normal or increased flow ipsilateral to stenosis during MRS, b) only a 10% increase in post-MRS cerebral blood flow; 11) in 4 studies on MRS including 258 patients with carotid artery stenosis of 70-99%, no perioperative stroke was reported.

Carotid stenosis is simply one more marker of atherosclerotic disease. It is not possible to demonstrate the causal relation between carotid artery stenosis and perioperative stroke in MRS. Carotid artery bypass surgery in asymptomatic patients with indication for MRS exposes the patient to an unreasonable risk of morbidity and mortality.

Conrado J. Estol