Carotid Artery Stenting prior to Cardiac Surgery

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Carotid Artery Stenting prior to Cardiac Surgery

Stentplaatsing in de halsslagader voorafgaand aan hartchirurgie

(met een samenvatting in het Nederlands)

Proefschrift

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Table of contents

Part IV: Cerebral perfusion

Part V: Embolic protection devices and antiplatelet therapy

Part VI: General discussion

PART I

General Introduction

Chapter 1

General introduction, aims and outline of the thesis

(Published in part)

Will Carotid Angioplasty Become the Preferred Alternative to Staged Or Synchronous Carotid Endarterectomy in Patients Undergoing Cardiac Surgery?

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Revascularisation strategy in patients with severe concurrent severe carotid and coronary artery disease: "Failure to move forward is reason to regress."

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Guidelines

The management of concurrent severe carotid and coronary artery disease is controversial. The heterogeneity of this subset of patients is key to understanding this controversy. The fact that atherosclerosis does not affect selective vascular territories is not surprising because it is a generalized degenerative process. The important practical question arises as to what effect the presence of severe atherosclerosis in one part of the circulation has on the risk of revascularization directed to another territory. The potential for stroke following cardiac surgery (CABG) has led many to advocate combined or staged prophylactic carotid endarterectomy (CEA)-CABG in all patients with significant carotid stenosis, whether symptomatic or not. Current ECS guidelines on the diagnosis and treatment of peripheral artery diseases state that carotid revascularization in symptomatic patients and corresponding carotid artery disease undergoing CABG is recommended in 70–99% carotid stenosis (Class I; Level of Evidence C), may be considered in 50–69% carotid stenosis, depending on patient-specific factors and clinical presentation (Class IIb; Level of Evidence C) or is not recommended if the carotid stenosis is <50% (Class III; Level of Evidence C). For asymptomatic patients undergoing CABG carotid revascularization may be considered in patients with bilateral 70–99% carotid stenosis or 70–99% carotid stenosis and a contralateral occlusion (Class IIb; Level of Evidence C).[1] However guidelines from different working groups are not always concordant. The American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the American Stroke Association state that carotid revascularization by CEA or CAS with embolic protection before or concurrent with myocardial revascularization surgery is reasonable in patients with greater than 80% carotid stenosis who have experienced ipsilateral retinal or hemispheric cerebral ischemic symptoms within 6 months (Class IIa; Level of Evidence C). In patients with asymptomatic carotid stenosis, even if severe, the safety and efficacy of carotid revascularization before or concurrent with myocardial revascularization are not well established (Class IIb; Level of Evidence C).[1]

Incidence

The incidence of perioperative stroke during cardiac surgery is 2%, however in the presence of severe carotid disease a fourfold increased risk has been described.[2,3] This risk rises to 5% in those with bilateral carotid stenosis and to 11% in patients with carotid occlusion. Symptomatic patients are associated with an 8.2% incidence of stroke.[2] The incidence is significantly higher in prospective as opposed to retrospective studies. There is no evidence that the risk of stroke has changed the last three decades.[3] Stroke risk increases with age. For those aged between 70 and 80 years of age the stroke rate is between 4 to 7% and for the octogenarians the stroke rate is between 8 to 9%.[3] This association with age is important as the proportion of patients undergoing cardiac surgery has significantly increased over the last decade.[2,4] Therefore, stroke remains the major noncardiac complication after CABG.

The reported frequency of carotid stenosis in patients scheduled for CABG depends on the screening methods used and on the definition of "severe" carotid stenosis. Relying on duplex ultrasonography, the figure varies between 8.5 to 18 %, attributed to the older age of patients undergoing CABG.[5,6] Based on angiographic findings, it was found that the frequency of carotid artery disease (diameter stenosis ≥ 50%) increased from 5% in patients with 1-vessel coronary artery disease to 25% in 3-vessel disease and reached 40% in patients with left main stenosis.[7]

Mechanism of stroke and hemodynamic response during cardiopulmonary bypass

Multifactorial mechanism

The mechanisms of perioperative neurological events during cardiac surgery are multifactorial. Although carotid artery disease is an important etiological factor in post-CABG stroke, it is probably only responsible for about 50% of post-CABG strokes.[8] Atherosclerosis of the ascending aorta may lead to stroke via macro-embolisation to the cerebral vessels. The crucial role of ascending aorta atherosclerosis still needs to be elucidated, nevertheless it might be seriously underestimated. Despite the fact that heightened stroke risk during CABG has been related to the degree of carotid stenosis, it has been demonstrated that more than half of all territorial infarctions on computed tomography (CT) or autopsy are not related to carotid disease alone.[3] Therefore, preoperative assessment of the aortic arch disease could also be considered.

Major evidence suggests that in many patients, hypoperfusion due to a severely stenotic carotid artery or micro-embolisation from an ulcerative plaque are the predominant mechanisms.[9,10] Hypotension induced ischaemic neurological injury during cardiopulmonary bypass is hard to avoid in patients with severe carotid stenosis. During cardiopulmonary bypass cerebral autoregulation is severely impaired, making cerebral blood flow directly proportional to cerebral perfusion pressure.[6]

Cerebral perfusion

In one of the few randomized trials, Gold et al. assigned 124 patients to a low mean arterial pressure group (50 to 60 mm Hg) and 124 patients to a high mean arterial pressure group (80 to 100 mm Hg) during cardiopulmonary bypass. Those in the high pressure group had fewer combined cardiac and neurological complications (4.8% versus 13%) and fewer strokes (2.4% versus 7.2%).[12] Caplan and Hennerici have suggested that decreased flow may result in reduced washout of microembolic materials from the brain, and that the watershed areas are particularly susceptible to this combination.[13] This latter hypothesis thus brings together two of the putative underlying mechanisms for vascular damage during CABG, suggesting that microembolism in the context of hypoperfusion may be associated with greater risk of ischemic injury.

Using single photon emission computed tomography (SPECT) with acetazolamide to predict the risk of hemodynamic stroke in patients with extracranial artery disease, Kuroda et al. demonstrated that cerebral blood flow alters readily in response to changes in blood pressure.[14] Consequently, asymptomatic patients with reduced cerebral perfusion pressure and impaired reactivity to acetazolamide have been shown to have higher risk for ipsilateral ischemic stroke. Such patients, even when asymptomatic, may tolerate perioperative reductions in cardiac output or blood pressure poorly, with increased risk of cerebral infarction.

Nakamura et al. described reduced cerebral perfusion reserve in 11 of 40 patients with significant carotid disease, of whom 7 underwent prophylactic cerebrovascular interventions (in the remaining 4 patients prophylactic intervention was technically impossible).[15] Follow-up SPECT studies confirmed improvement of cerebral perfusion reserve in all 7 patients, none of whom sustained a perioperative stroke. In 29 of these 40 patients normal cerebral perfusion on SPECT was visualized and no ipsilateral periprocedural stroke was reported.

Carotid artery stenting: technique and procedure

Carotid stenting procedure

Most procedures are performed via femoral access. An 8 French short femoral introducer sheath is inserted and heparin is administered intravenously to maintain the activated clotting time (ACT) between 250-300 seconds. The common carotid artery is selectively engaged with a diagnostic catheter (Sidewinder II, 5 Fr, Cordis J&J) and exchanged for a long 0.018 inch stiff wire (SV-5, 300cm, Cordis J&J) positioned proximal to the target lesion. Following this a 8 French percutaneous coronary angioplasty guiding catheter is placed in position (MP A1, 8 French Cordis J&J), if required supported by a telescopic diagnostic catheter (MP A1 5 French, 125cm, Cordis J&J). After the lesion is crossed with the premounted filter system and deployment in the minimum landing zone is performed, a low-profile undersized angioplasty balloon (3.0-3.5x20 mm) is used to predilate the lesion, followed by the placement of an appropriately sized self-expandable stent. In order to maximize stent deployment and vessel scaffolding, post-dilatation is performed with an appriopriately sized balloon (varying from 5.0 to7.0x20 mm, dependent on the reference diameter) after administering intravenous Atropine (0.5 mg). Finally, the filter is retrieved using a dedicated sheath.

TCD Monitoring

The TCD monitoring of the ipsilateral middle cerebral artery (MCA) is usually performed during the CAS, using a 2 MHz pulsed Doppler transducer (Pioneer TC4040, EME, Madison, WI), gated at a focal depth of 45 to 60 mm. The transducer is placed over the temporal bone to insontate the main stem of the ipsilateral MCA and is fixed with a head strap. The number of isolated microembolic signals (MES) in the MCA is registered according to the criteria described by the consensus committee.[10h] If the number of MES is too high to be counted separately, heartbeats with microemboli are counted as microembolic showers. During the procedure the MES and the showers are counted and presented as totals or as numbers during the different phases of the procedure: spontaneous, wire manipulation, deployment of the protection filter, predilation, stentdeployment, stent post-dilation and retrievement of the filter.

To Incise or Stent?

Albeit limited evidence regarding the benefit of carotid revascularisation prior to or together with cardiac surgery, patients with advanced carotid and coronary disease are frequently treated with a staged or synchronous carotid/coronary surgical revascularization. The initial studies of such surgical procedures in these patients were conceived in an attempt to reduce perioperative mortality and neurological morbidity.[17] To be beneficial in reducing stroke rates, carotid revascularization and CABG need to be performed with low cardiac and neurological morbidity.

In a systematic review, Naylor et al. reported a 10-12% risk of death, stroke or myocardial infarction (MI) for staged or synchronous operations and concluded that staged or synchronous operations might be able to reduce death or stroke rate when compared to isolated coronary artery bypass grafting (CABG).[3] Notwithstanding these encouraging results of combined CEA and CABG, these surgical procedures require long operative times with an increased risk for infection, prolonged ventilation and renal failure.[18] An alternative approach would be carotid angioplasty and stenting (CAS) prior to cardiac surgery. CAS has shown to be a feasible and effective minimal invasive technique not requiring an incision in the neck, leading to less cranial nerve injury, reducing psychological trauma and leading to a shorter hospital stay.[19-25] CAS with cerebral embolic protection is currently reserved primarily for high-risk patients with severe carotid stenosis, including those with severe coronary artery disease.[26,27] In favour of the latter, Ziada et al. firstly reported significant fewer adverse events in patients who underwent CAS prior to cardiac surgery, despite a higher baseline risk profile as compared to those undergoing combined CEA and CABG.[28] The CAS-CABG strategy was associated with a lower incidence of stroke (2% vs. 9%) and MI (3% vs. 13%). Considered separately, these associations did not reach statistical significance. However, using the composite end point of stroke or MI, a statistically significant difference was found in favour of CAS-CABG (5% vs. 19%, p= 0.02). No difference occurred in mortality or in the combination of stroke and death between the two treatment strategies, but a trend was noted toward a reduced composite end point of death, stroke or MI in favour of CAS-CABG. In line with these encouraging studies, Kovacic et al. reported a death, stroke, or MI rate of 10% and a death, persistent stroke or MI rate of 5% among 20 patients undergoing staged CAS-CABG.[29] McKhann et al. reported that double procedures (CABG/valve or aortic surgery) can increase the perioperative stroke rate to 7.9% and up to 8.7% for aortic repair.[30] This finding

advocates a progressive preoperative risk stratification and a dedicated management by selecting the optimal treatment to pursue the lowest complication rate. In contrast to the above mentioned studies, unfavourable results were reported by Randall et al. in a much smaller prospective study in 52 patients undergoing CAS followed by cardiac surgery. Despite the lack of periprocedural neurological events after CAS, a total death or stroke rate at 30 days after CABG of 19.2% was registered in consequence of high cardiac mortality rate. This was attributed to a prolonged delay to performing CABG.[31]

The reported data by Babatasi et al.(n=12, death or any stroke rate 8.3%), Gross et al.(n= 85, death or any stroke rate 11.7%) and Lopes et al.(n=49, death or any stroke rate 16.3%) should be interpreted differently, taking into account the fact that standard CAS procedure was not yet applied.[32-34] Consequently, as distinct from the recent systematic review by Guzman et al.,[35] it is our contention that the outcome of these 3 studies is not representative for nowadays clinical practise.

Reduction of Myocardial infarction

The frequent concurrence of severe multivessel coronary disease and left main disease in CEA patients and the increased perioperative risk of death or MI has been previously established.[36-39] Ziada et al. demonstrated a low MI rate following CAS-CABG.[28] The reported total periprocedural MI rate of 3.6% is in contrast with observational studies of CEA and CABG, which vary from 3.6% (synchronous) to 6.5% (staged).[3] The exact mechanism by which CAS is associated with a lower risk of perioperative MI remains unclear.

The incidence of MI can not easily be compared due to variability in the definition of MI. In most studies no systematic perioperative collection of serum enzymes is done in asymptomatic patients. The SAPPHIRE trial was an exception.[40,41] MI was defined as a more than twofold increase in total creatine kinase with a positive MB fraction, and the study demonstrated a significantly higher incidence of MI with CEA than with CAS. However, SAPPHIRE did not address the question of perioperative MI in the setting of cardiac surgery. Ziada et al. adopted a definition based on the peak creatine kinase-MB serum level with a cut-off (≥ 10 times normal) similar to, or even higher than, that shown by others to influence survival adversely after coronary surgery.[28,42-44]

A uniform definition of MI facilitating comparison in future studies is recommended.

Distal protection devices

Whereas the CAS versus CEA debate is ongoing, the need to fine-tune technique in the former is evident. Taking this into account, the role of the embolic protection device (EPD) has been evaluated many times, though only twice by means of a prospective, randomized controlled study.[45-48] This probably evolves from the common sense view that a filter, per definition, captures debris and therefore protects brain. Barbato et al. (n=35; ±15% asympt; ±60% coronary disease) reported that the use of filters during CAS provided no demonstrable reduction of microemboli.[47] The expected reduction with the use of EPD of new ischemic lesions as detected by DW MRI did not materialize. McDonald et al. (n=30, 100% symptomatic; 0% coronary disease) found similar results.[48] The clinical significance of these findings requires further study.

Selective preoperative screening

Guidelines

Although auscultation of the neck is easy and inexpensive, it lacks specificity. Nevertheless, the presence of a cervical bruit is often associated with the presence of a carotid stenosis, and it has been demonstrated that the risk of stroke after CABG is 3.9-fold higher when a cervical bruit is present.[49,50] Auscultation of a cervical bruit should therefore be followed by duplex ultrasonography. The American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the American Stroke Association state that carotid duplex ultrasound screening is reasonable before elective CABG surgery in patients older than 65 years of age and in those with left main coronary stenosis, peripheral artery disease, a history of cigarette smoking, a history of stroke or TIA, or carotid bruit (Class IIa;Level of Evidence C).[2]

Duplex ultrasonography and diagnostic cervical-cerebral angiography

On the duplex ultrasonography a carotid artery stenosis is considered “significant” when a diameter reduction of at least 70% is measured in symptomatic patients or more than 90% in asymptomatic patients.[51] The severity of stenosis defined according to angiographic criteria by the method used in NASCET corresponds to assessment by sonography, CTA, and MRA, although some methods may overestimate stenosis severity. Catheter-based angiography may be necessary to resolve discordance between noninvasive imaging findings. When significant on duplex, a cervical-

cerebral angiography can be performed according to standard technique with intracranial views determining the patency and the completeness of the circle of Willis. A “three-dimensional computed rotational” angiography is performed in order to obtain detailed information of the target stenosis.[52] Three-dimensional images can provide absolute artery diameters besides high-quality 3D images of the contrasted vasculature and juxtaluminal calcification. When an artery becomes nearly occluded, the reduced pressure and flow will eventually reduce the distal-ICA diameter. As the distal-ICA becomes narrower, a NASCET ratio will increasingly underestimate the stenosis grade. Significant carotid artery disease is defined as a target lesion in the common carotid artery, internal carotid artery, or at the bifurcation with a angiographic stenosis severity of more than 50% of the luminal diameter in symptomatic patients or a stenosis of more than 80% in those without symptoms according to NASCET criteria.[51,53]

Patients should be accepted for the percutaneous approach by a consensus decision involving the neurologist, the cardiovascular surgeon and the interventional cardiologist.

Timing and medical management

Timing for cardiac surgery after CAS is an important feature, affected adversely by a long waiting period. In case of reoccurrence of coronary events after CAS, accelerated cardiac surgery should be considered. Consequently the relevance of the antiplatelet therapy is emphasized. The ideal strategy for the discontinuation of antiplatelet agents, would have to take into account both adequate timing for complete carotid stent endothelialization with decreased platelet activation and a brief waiting time for cardiac surgery in order to reduce cardiac events.[54-56] The balance between bleeding during CABG and thrombotic event after CAS is difficult to determine and to date there is no clear consensus on the optimal antiplatelet regimen.

In general, to avoid an increase in bleeding complications associated with dual antiplatelet treatment during CABG, and the thrombotic complications after CAS if dual antiplatelet treatment is prematurely discontinued, patients need to wait approximately 30 days between interventions.[57] The clopidogrel is then stopped 5 to 7 days before cardiac surgery. In contrast to the natural history of patients who undergo major surgery with suspension of antiplatelet therapy within 6 weeks

of coronary stenting, carotid stent thrombosis does not occur frequently. It is possible that the wider diameter of a carotid stent abrogates the incidence of stent thrombosis.[58,59]

Ziada's patients received oral aspirin and clopidogrel before CAS and in 50 patients adjunctive glycoprotein IIb/IIIa platelet inhibition was used. After discharge from CAS they were treated for 2 to 4 weeks with aspirin and clopidogrel. The latter was stopped 1 week before surgery which was performed after a median time of 40 days.[28] In Kovacic's population aspirin and clopidogrel were commenced prior to cardiac surgery. If possible, CABG was not scheduled within 4 weeks of carotid stenting. The mean interval between carotid stenting to CABG was 69.6 ± 39.6 days. Antiplatelet therapy was ceased > 3 days prior to cardiac surgery in 10/20 patients and continued up to and including the day before surgery in the remainder.[29] In Randall's study the routine use of dual antiplatelet therapy before stent insertion was introduced during the study period, with 82.7% of patients pretreated with combined aspirin and clopidogrel. The timing of cardiac surgery after stenting was at the discretion of the cardiac surgeon with no further detail mentioned. After the introduction of routine use of clopidogrel in carotid stenting, it was recommended that this was continued for ≥14 days.[31]

Under clinical circumstances demanding urgent cardiac surgery after CAS immediate transfer to the operating room administrating aspirin or unfractionated heparin, even in combination with glycoprotein IIb/IIIa receptor antagonist has been described without increased periprocedural complication rates.[60] Mendiz et al. reported in thirty patients no strokes or neurological deaths, immediately transferring patients from the catheterization laboratories to the operating room. Aspirin and unfractionated heparin were administrated during CAS and clopidogrel after CABG.[61] Kramer et al. reported no deaths or neurological events among 37 patients treated with CAS who underwent CABG within 48 hours.[62] The antithrombotic therapy during and after CAS consisted of unfractionated heparin and the glycoprotein IIb/IIIa receptor antagonist eptifibatide (continued ≤ 6hours before CABG). Other options are performing CAS under dual antiplatelet therapy which is then not stopped prior to performing an urgent CABG or to consider combined CEA and CABG.

New antithrombotic therapy might involve second generation thienopyridines, such as prasugrel and cangrelor, which have a faster onset of action, as well as more potent, and less variable, inhibition of platelet function ex vivo.[63]

Aims and outline of the thesis

This thesis concerns the management and treatment of patients with concomitant significant carotid and coronary artery disease. In chapter 2 the controversion on this subject is discussed and a clarification of the evidence is given from both 'believers and non-believers' to justify their claims. In Chapters 3 and 4 a single centre experience in both asymptomatic and symptomatic patients with carotid artery disease undergoing cardiac surgery is described, accompanied by an editorial comment on the approach in both patient groups. In chapters 5 and 6 the effect of stenting on cerebral perfusion in symptomatic and asymptomatic patients with carotid artery stenosis by using CT perfusion analysis is examined. In chapter 7 the role of embolic protection devices during carotid stenting prior to cardiac surgery in asymptomatic patients is questioned. In chapter 8 high versus standard clopidogrel loading in patients undergoing the staged treatment is studied. Finally, in chapter 9 a case of acute fracture of a carotid stent during post dilation is described.

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PART II

Is carotid artery disease responsible for perioperative strokes after coronary artery bypass surgery?

Chapter 2

Is carotid artery disease responsible for perioperative strokes after coronary bypass surgery?

Part one: Carotid disease is rarely responsible for stroke after coronary bypass surgery

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Part two: Carotid disease is responsible for the increased risk of stroke after coronary bypass surgery

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The coronary and extracranial carotid vascular beds are often simultaneously affected by significant atherosclerotic disease, and stroke is one of the potential major complications of coronary artery surgery. As a result, there is no shortage of reports in the vascular surgery literature describing simultaneous coronary and carotid artery revascularizations. Generally, these reports have found this combination of operations safe, but have stopped short of proving that it is necessary. Intuitively, simultaneous carotid endarterectomy and coronary artery bypass surgery could be justified if most perioperative strokes were the result of a significant carotid stenosis, either directly or indirectly. At first glance this appears to be a fairly straightforward issue; however, much of the evidence on both sides of the argument is circumstantial. One significant problem in analyzing outcome by choice of treatment in patients presenting with both coronary and carotid disease is the multiple potential causes of stroke in coronary bypass patients, which include hemorrhage and atheroemboli from aortic atheromas during clamping. But this controversial subject is now open to discussion, and our debaters have been given the challenge to clarify the evidence to justify their claims.

Part 1: Carotid disease is rarely responsible for stroke after coronary bypass surgery

Significant carotid stenoses (SCS), defined as 50% stenosis in diameter, are associated with an increased risk of postoperative stroke after coronary artery bypass grafting (CABG) surgery.[1-3] Evidence in support of this statement is robust and compelling. The data implicating SCS as the primary cause of the increased stroke risk are neither, even though there seems to be a trend of higher incidence of stroke with more severe carotid stenosis.[1,3-5] In our opinion, the impression of a causal relationship between stroke risk and asymptomatic SCS in cardiac surgery has been largely based on a few false assumptions. To bring these to light, we frame our discussion around these areas to test their validity.

Assumption 1

The incidence of SCS is high, and most perioperative stroke during CABG occurs in the subgroup of patients with SCS. Data gleaned from preoperative carotid ultrasound imaging would suggest the contrary. The incidence of SCS is fairly low, ranging from 2% to 22%, with an average of 8% to 9% in patients undergoing CABG.[3,6] Therefore, SCS is not implicated in the mechanism of perioperative stroke in the overwhelming majority of operative patients. Analysis of the status of the carotid arteries in patients with perioperative stroke also bears this out. For example, Wijdicks et al[7] reported that among the 13 patients with postoperative stroke who also had carotid evaluation, only 1 patient had an ipsilateral SCS. In one prospective study, 34 of the 38 perioperative strokes (89%) occurred in patients with 80% carotid stenosis.[8] Our recent retrospective analysis indicated that 58 of the 76 perioperative strokes (76%) occurred in patients without SCS.[9] The low incidence of SCS in patients undergoing CABG suggests it is unlikely to be a major contributor to the perioperative stroke risk.

Assumption 2

The perioperative stroke in patients undergoing CABG occurs primarily in the territory of carotid artery. To the contrary, analysis of the laterality and regional distribution of perioperative strokes on brain imaging indicates that most of these strokes occur in the territory of multiple vessels, the hemisphere contralateral to existing carotid stenosis, or in the distribution of vertebrobasilar arteries. For example, Hise et al[10] reported that 8 of 15 patients (53%) with evidence of acute infarction on computed

tomography scan demonstrated a stroke in the posterior cerebral artery distribution or the cerebellum. Barbut et al[11] examined 19 patients with infarction on computed tomography scan and found 15 patients (79%) and 14 patients (74%) had stroke in the cerebellum and posterior cerebral artery territories, respectively. Wityk et al12 used magnetic resonance imaging (MRI) to examine 14 patients, and 9 of 10 patients (90%) with acute lesions on diffusion weighted imaging (DWI) showed multiple strokes in bilateral hemispheres. In one of the most comprehensive reviews to date, Naylor et al[3] concluded that primary carotid thromboembolic disease alone is not responsible for up to nearly 60% of strokes based on computed tomography scan or autopsy studies.[3] Such a distribution pattern of perioperative stroke also holds true for patients with SCS.[9,13,14] Therefore, most perioperative strokes occur outside of a single carotid territory. Because 3% of patients undergoing CABG have bilateral SCS,[3] neither unilateral nor bilateral carotid stenosis is likely responsible for most of the perioperative strokes based on the infarction territory.

Assumption 3

Although SCS could be a small contributor to perioperative stroke risk, preoperative carotid revascularization would eliminate stroke in some of these patients and hence should be offered. Data from the North American Symptomatic Carotid Endarterectomy Trial suggested that in patients with SCS, stroke could still be due to small vessel lacunae, thrombotic infarction due to intracranial diseases, or even cardioembolic infarction, but carotid endarterectomy should not help to prevent such strokes.[15] The incidence of lacunar infarction and intracranial atherosclerosis may not be trivial in patients undergoing cardiac surgery. For example, Libman et al[16] reported that 16% of the postoperative strokes after cardiac surgery can be lacunar syndromes secondary to small vessel disease. Yoon et al[17] reported that 30% of patients undergoing CABG had stenosis in the intracranial arteries. In multivariate analysis, the presence of intracranial disease was also found to have an independent association with the development of perioperative strokes. Furthermore, existing data strongly suggest that most perioperative strokes are cardioembolic, mainly due to the presence of aortic atherosclerosis or atrial fibrillation, or both. Using intraoperative echocardiography, Katz et al[18] identified protruding atheroma in the aortic arch in 23 of 130 patients undergoing cardiac surgery, and perioperative stroke developed in 5 (22%), whereas the stroke risk was only 2% in patients without such atheroma. Gardner et al[19] reported that the perioperative stroke risk jumped

approximately fourfold higher to 14% in patients with intraoperative evidence of severe aortic atherosclerosis. A multivariable logistic regression analysis of a multicenter database of [19], 224 CABG patients suggested that calcified aorta was the single most significant variable associated with perioperative stroke, with an odds ratio of 3.01, whereas the presence of carotid disease was also associated with an odds ratio of 1.59.[20] In another multivariate analysis, calcified aorta was an independent predictor of perioperative stroke, but SCS was not.[8] Microembolism from the aorta or heart to the brain has been well documented by multiple studies using transcranial Doppler, correlating with the onset and releasing of aorta clamping.[21-23] Furthermore, D'Agostino et al[13] reported that atrial fibrillation occurred in approximately 30% of postoperative patients, and perioperative stroke occurred in 4.6% of patients with atrial fibrillation compared with 1.5% patients without. Lahtinen et al[24] discussed that recurrent atrial fibrillation preceded symptoms of cerebral ischemia in 36.5% of patients with perioperative stroke by a mean of 21.3 hours. In the subgroup of high-risk patients with new postoperative DWI lesions, 75% also had postoperative atrial fibrillation.[25] Therefore, in patients undergoing CABG, cardioembolism and probably intracranial arterial stenosis or small vessel disease are the primary mechanisms of stroke. Preoperative cervical carotid revascularization would not prevent these events.

Assumption 4

SCS reduces distal internal carotid blood flow and hence puts the ipsilateral cerebral hemisphere at risk for ischemia during cardiopulmonary bypass. The carotid plaque at the bifurcation may cause regional hypoperfusion or act as an embolic source in causing a stroke. So far, there are no data to suggest that carotid plaque becomes a more active source of embolism during CABG. Although often asserted as facts, there is very little evidence to suggest that unilateral asymptomatic SCS reduces ipsilateral hemisphere blood flow significantly. Perioperative strokes include both border zone (watershed) and territorial infarctions on brain imaging. Watershed infarctions are now more readily identified on MRI studies.[26,27] Although the development of a watershed infarction is frequently attributed to low cerebral flow, this has been challenged repeatedly by autopsy studies. Watershed infarction may occur without SCS or documented intraoperative hypotension.[28] Embolic calcified material or cholesterol crystals were detected in vessels adjacent to the watershed infarction in patients after cardiac surgery.[29,30] Watershed infarctions can be caused by microemboli

consisting of atheromatous material or tumor masses lodged preferentially in the brain border zone.[31] Angiography in three patients with watershed infarction did not show SCS in two patients and revealed an embolic occlusion of the arterial branch corresponding to the site of the infarct in another patient.[28] These brain border zones appear to be favored destinations for microemboli. On the other hand, there is no compelling evidence that cerebral blood flow is significantly reduced distal to SCS in association with cardiopulmonary bypass. Lundar et al[32,33] described that blood flow in the middle cerebral and internal carotid arteries actually increased rather than decreased during cardiopulmonary bypass as a result of hemodilution. A study that used positron-emission tomography in patients with asymptomatic unilateral SCS found most patients had normal cerebral flow.[34] Hupperts et al[35] reported 10 of 37 patients with perioperative strokes had infarction in the vascular border zones. Registered periods of hypotension, lowest mean arterial pressure, and lowest hematocrit were similar among the subgroups of patients with border zone, territorial infarction, or no infarction. Therefore, in patients with unilateral asymptomatic SCS undergoing CABG, the ipsilateral hemispheric blood flow is unlikely to be significantly altered in most patients if significant and prolonged hypotension can be avoided perioperatively. Furthermore, it is arguable whether carotid revascularization would significantly improve cerebral blood flow. Waaijer et al[36] studied cerebral perfusion in 36 patients with SCS and a mean degree of stenosis of 86%. On average, there was merely a 10% increase in cerebral blood flow after carotid stenting or endarterectomy.

Assumption 5

Preoperative carotid endarterectomy is necessary to avoid carotid territory stroke in patients undergoing CABG. To the contrary, studies suggest that conservative management of SCS can be safe for patients undergoing cardiac surgery. Gerraty et al[37] reported 53 patients with SCS or occlusion (28 patients with 80% stenosis or occlusion) underwent vascular or cardiac operations. No ipsilateral perioperative strokes were reported, despite 22 patients experiencing a period of hypotension.[37] Safa et al[38] reported that in 94 patients with SCS undergoing cardiac surgery, 71 had unilateral (80%-99%), 17 had bilateral (80%-99%), and 6 patients had unilateral SCS together with a contralateral carotid occlusion. Only one patient developed a perioperative stroke in the hemisphere contralateral to the carotid stenosis. Ghosh et al[39] reported 50 patients with asymptomatic SCS (20 with bilateral 80%-99% disease, and 5 with unilateral occlusion and 70%-79% contralateral stenosis) underwent CABG

with optimal medical prevention. No strokes occurred 30 days of surgery. Baiou et al[40] reported 61 cardiac procedures in patients with unilateral asymptomatic 70% to 99% stenosis (56% of patients also had a contralateral 50%-69% stenosis). No strokes occurred in the 30-day postoperative period. Although larger confirmation studies are still needed, it appears safe and effective in most cases to conservatively manage CABG patients with SCS without the need for preoperative corrective carotid revascularization.

Conclusions

There is compelling evidence to conclude that SCS is not the primary cause of most strokes after CABG surgery. This is consistent with the analysis by Stamou et al,[41] who reported that only 6% of the perioperative 333 strokes were secondary to carotid disease, and was borne out in our own single-center retrospective analysis of 4335 patients undergoing cardiac operations. Of the 76 patients with perioperative strokes, 72 (95%) were not related to SCS at the bifurcation.[9] Does SCS play a significant role in causing stroke after CABG under any circumstance? Exceptions might exist in patients with symptomatic SCS, patients with bilateral critically severe carotid disease (80% diameter reduction), and patients with recent carotid occlusion. Overall, 95% of the carotid stenosis in patients undergoing CABG is asymptomatic and 1.5% patients have such bilateral critically severe carotid disease.[3] Only a small fraction of patients would fit in this category. How then is the observed increased risk of postoperative stroke in patients with SCS explained? One likely explanation is that carotid stenosis is an epiphenomena serving as a marker of severe underlying systemic atherosclerotic disease. Patients with concomitant cerebrovascular and coronary artery disease represent a subset of patients with advanced arteriosclerosis, not only in the coronary and cerebrovascular vessels but also other areas of arterial system.

In patients with SCS, the incidence of other vascular complications such as coronary ischemic events is much higher than the stroke risk.[42] Similar to SCS, there appears to be a positive correlation between the incidence of perioperative stroke and the severity of aortic atherosclerosis.[43] During the last 20 years, many prospective randomized trials were undertaken in carefully selected patients with symptomatic and asymptomatic SCS.[44-48] All trials showed clear benefits of carotid revascularization

in reducing subsequent stroke risk in patients with SCS, but most excluded patients with symptomatic and severe coronary artery diseases. The results of these trials have undoubtedly had a major influence on medical decision making, but caution should be taken in extending these results to patients with concomitant carotid and coronary artery diseases. More recently published data suggested that under intense medical therapy, the stroke risk for asymptomatic stenosis is exceeding low, as low as 0.5% annually.[49,50] In the population of patients undergoing CABG, more effort should be geared toward reducing the overall risk of vascular complications with intense medical therapy and preventing cardioembolism, which remains to be the major source of stroke after cardiac surgery.

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Part 2: Carotid disease is responsible for the increased risk of stroke after coronary bypass surgery

Stroke remains the major noncardiac complication of coronary artery bypass grafting (CABG), with an absolute incidence of 2%. Severe carotid artery disease has been associated with a fourfold increased risk of perioperative stroke after CABG.[1-4] It is well recognized that there are a number of potential etiologies for perioperative stroke in the cardiac surgical patient, including embolization of atherosclerotic debris or thrombus from the aortic cannulation site, air embolus, dislodgement of a left ventricular thrombus, aortic dissection, low cardiac output, and intracerebral disease, in addition to significant extracranial carotid artery disease.[5-7] Although clinically significant carotid disease may be responsible for only a part of the perioperative strokes in this patient population, it remains the one etiology that can be identified preoperatively and noninvasively and can be prevented by timely intervention.[8] A recently published systematic review by Naylor et al[9] described favorable clinical outcome without any stroke in patients with carotid and coronary artery disease undergoing isolated CABG.[9-12] However, these data represent a fraction of data compared with the vast amount of previous information demonstrating a high stroke incidence of 9.2% to 11.5% in isolated CABG and also describe different patient populations (off-pump and on-pump bypass surgery).[9-14]

Nevertheless, this information provides indirect proof and does not clarify the true etiology of stroke caused by significant carotid stenosis during cardiac surgery.

Cerebral hemodynamics and measurements

Normally, vasodilation of cerebral arteries allows the brain to tolerate a mild to moderate reduction of cerebral perfusion pressure. In patients with significant cerebrovascular disease, maximal autoregulatory vasodilation is already compensating for chronic circulatory insufficiency. In addition, "poor" cerebral collateral flow, defined by an impaired circle of Willis (visualized through absent crossfilling on selective carotid angiogram or dampened, low-velocity middle cerebral artery velocity spectra on transcranial Doppler) contributes to the reduced hemodynamic response during cardiopulmonary bypass, causing cerebral hypoperfusion. Atheroembolization does play a role in the origin of perioperative stroke in patients undergoing cardiac surgery. However, it seems likely that the effects of atheroembolic particles are influenced by the presence of perfusion deficits.[15] These essential findings implicate carotid stenosis as having a pivotal role in the multifactorial etiology of stroke after coronary bypass. In one of the few randomized trials, Gold et al[16] assigned 124 patients to a low mean arterial pressure group (50-60 mm Hg) and 124 patients to a high mean arterial pressure group (80-100 mm Hg) during cardiopulmonary bypass. Those in the high-pressure group had fewer combined cardiac and neurologic complications (4.8% vs 13%) and fewer strokes (2.4% vs 7.2%). Caplan and Hennerici[15] have suggested that decreased flow may result in reduced washout of microembolic materials from the brain and that the watershed areas are particularly susceptible to this combination. This latter hypothesis thus brings together two of the putative underlying mechanisms for vascular damage during CABG, suggesting that microembolism in the context of hypoperfusion may be associated with a greater risk of ischemic injury. Using single photon-emission computed tomography (SPECT) with acetazolamide to predict the risk of hemodynamic stroke in patients with extracranial artery disease, Kuroda et al[17] demonstrated that cerebral blood flow changes in response to changes in blood pressure. Consequently, asymptomatic patients with reduced cerebral perfusion pressure and impaired reactivity to acetazolamide have been shown to have higher risk for ipsilateral ischemic stroke. Such patients, even when asymptomatic, may tolerate perioperative reductions in cardiac output or blood pressure poorly, with increased risk of cerebral infarction. Nakamura et al[11] described reduced cerebral perfusion reserve in 11 of 40 patients with significant carotid disease, of whom 7 underwent prophylactic cerebrovascular interventions (in the remaining 4 patients prophylactic intervention was technically impossible). Follow-up SPECT studies confirmed improvement of cerebral perfusion reserve in all seven patients, none of

whom sustained a perioperative stroke. In 29 of these 40 patients, normal cerebral perfusion on SPECT was visualized, and no ipsilateral periprocedural stroke was reported. In our opinion, the data of the latter group (29 of 40) demonstrating normal cerebral perfusion could therefore not be brought forward as evidence for isolated CABG, as previously advocated by Naylor et al. In our own experience with computed tomography perfusion technique,[18] more specifically measuring the mean transit time, we observed significant improvement in cerebral perfusion after carotid stenting in asymptomatic patients awaiting cardiac surgery. This suggests a compromised cerebral circulation due to carotid stenosis is reversible with carotid intervention.

Future neurologic protection

Gaudino et al[19] have shown that surgical treatment of severe monolateral asymptomatic carotid artery stenosis in patients at the time of CABG confers substantial neurologic protection in the years after surgery. In fact, during the follow-up periods, the incidence of neurologic events (stroke and transient ischemic attack) was significantly higher in the non-revascularized group. That a different etiology of the event (cardioembolic, hypertensive) was not evident at the time of hospital admission in any of these cases strongly argues in favor of a carotid origin of the strokes. In addition, the need for subsequent carotid endarterectomy and, even more importantly, the asymptomatic progression to carotid occlusion, occurred with a concerning high frequency in patients who underwent isolated CABG.

Clinical perspective

The importance of hemodynamic factors in the pathogenesis and treatment of ischemic cerebrovascular disease in patients undergoing cardiac surgery is a matter of ongoing debate. Stratifying patients based on the degree of carotid stenosis fails to differentiate those with reduced cerebral perfusion pressure from those with noncompromised cerebral hemodynamics. Moreover, it seems hazardous to use the degree of carotid stenosis to decide whether a patient may be at increased risk for stroke on hemodynamic grounds. This implies that the choice of medical therapy or revascularization should not be based on these considerations only. It has been established that the effect of carotid stenosis on cerebral circulation could be more accurately assessed by analysis of arteriographic circulation patterns, depicting the adequacy of collateral circulatory pathways and patterns.[20] Noninvasive measurements

of cerebral perfusion, such as SPECT with acetazolamide or computed tomography perfusion, may become a valuable method to predict the risk of hemodynamic stroke in patients with significant carotid disease scheduled for cardiac surgery and guide clinicians to the judicious use of prophylactic cerebrovascular interventions.

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PART III

Carotid stenting prior to cardiac surgery in neurological asymptomatic and symptomatic patients

Chapter 3.1

Staged carotid angioplasy and stenting followed by cardiac surgery in patients with severe asymptomatic carotid artery stenosis: early and long-term results

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Background The strategy for treating patients with severe asymptomatic carotid artery stenosis and cardiac disease remains unresolved. Staged or combined carotid endarterectomy in these patients offers the potential benefit of decreased neurological morbidity during and after cardiac surgery; however, in high-risk patients with severe coronary artery disease, chronic obstructive pulmonary disease, or renal impairment, the incidence of death and stroke is significantly higher.

Methods and Results We report the results of a prospective, single-center study designed to evaluate the feasibility and safety of carotid artery angioplasty and stenting (CAS) before cardiac surgery in neurologically asymptomatic patients. The periprocedural and long-term outcomes of 356 consecutive patients who underwent CAS before cardiac surgery were analyzed. The procedural success rate of CAS was 97.7%. The death and stroke rate from time of CAS to 30 days after cardiac surgery was 4.8% (n=17). The myocardial infarction rate from time of CAS to 30 days after cardiac surgery was 2.0% (n=7), and the combined death, stroke, and myocardial infarction rate was 6.7% (n=24). Distal embolic protection devices were used in 40% of the cases.

Conclusions This large cohort of asymptomatic patients who underwent staged CAS and cardiac surgery experienced a low periprocedural complication rate. The high rate of freedom from death and stroke during the 5 years of follow-up supports the long-term durability of this approach. Our findings suggest that this new strategy may become a valuable alternative in the treatment of patients with combined carotid and cardiac disease.

Introduction

In the absence of randomized trials, the best management of patients with concomitant severe carotid and coronary artery disease remains in dispute, particularly in asymptomatic patients. The incidence of perioperative stroke that occurs in patients with coexistent asymptomatic carotid disease undergoing cardiac surgery varies from 3% to 11%, depending on the severity of carotid stenosis.[1] The prevalence of significant carotid artery stenosis in patients who undergo coronary artery bypass grafting (CABG) ranges from 3% to 22%.[2-5] This variation depends on the frequency, rigidity of screening, and definition of "significant" carotid artery stenosis used. It has been demonstrated that the presence of severe carotid artery stenosis correlates with the severity of coronary artery disease.[6] The cause of perioperative neurological events during heart surgery is multifactorial; however, evidence suggests that in most patients, hypoperfusion due to a severely stenotic carotid artery or embolization from an ulcerative plaque could be the responsible mechanism.[7,8] Ischemic neurological injury during cardiopulmonary bypass caused by inevitable relative hypotension would be difficult to avoid in patients with severe carotid stenosis. During cardiopulmonary bypass, cerebral autoregulation is severely impaired, which makes cerebral blood flow directly proportional to cerebral perfusion pressure.[8] This finding provided a logical reason for the initial trials of combined or staged carotid endarterectomy (CEA) in these patients in an attempt to reduce perioperative mortality.

Clinical Perspective

Even though we have achieved good results with combined CEA and CABG at our center,[9-12] this approach requires long operative times. Recent studies have shown that carotid angioplasty and stenting (CAS) is a feasible and effective minimally invasive technique.[13-15] The effect of CAS on the incidence of death and stroke after cardiac surgery remains unclear. The expected benefit of a reduction in myocardial infarction (MI) rates is yet to be proved; however, in high-risk CEA patients, carotid stenting has proved superior to CEA.[16] We report the results of CAS and subsequent cardiac surgery in 356 patients with asymptomatic severe carotid artery disease.

Methods

Patient Population

In a prospective, nonrandomized study, we analyzed 364 consecutive patients scheduled for CAS and cardiac surgery from December 1997 to June 2005 at our center. Patients were considered asymptomatic if an ipsilateral cerebrovascular event had not occurred within the prior 4 months. Significant carotid artery disease was defined as luminal diameter reduction of 80%, according to North American Symptomatic Carotid Endarterectomy Trial criteria.[17,18] The indications for cardiac surgery were symptomatic (documented myocardial ischemia) severe coronary artery disease (including bypass failure) not eligible for percutaneous revascularization, symptomatic valve disease, and disease (aneurysm/dissection) of the ascending aorta or arch that demanded reconstructive surgery. Patients were excluded if they had severe renal impairment (serum creatinine 300 mol/L), peripheral vascular disease that precluded femoral artery access, major neurological deficit, or any other illness that impeded their ability to provide informed consent. Patients with severe diffuse atherosclerosis of the common carotid artery, chronic total occlusions, and long preocclusive lesions ("string sign" lesions) were also excluded. All patients gave written informed consent. This registry was approved by the ethics committee of our hospital.

End-Point Definition

The primary end point of the present study was the combined incidence of death and stroke from time of CAS to 30 days after cardiac surgery. Strokes were considered disabling (major) if patients had a modified Rankin score of 3 at 30 days after onset of symptoms. A minor stroke was defined as a Rankin score of 3 or less that resolved completely within 30 days. Transient ischemic attack and amaurosis fugax were diagnosed if the symptoms disappeared within 24 hours. Fatal stroke was defined as death attributed to an ischemic or hemorrhagic stroke. The cause of death was obtained from the death certificate or the postmortem examination report. Secondary end points were MI and combined death, stroke, and MI from time of CAS to 30 days after cardiac surgery. In the long-term outcome, cumulative event rates at 5 years are described. Cardiocerebrovascular mortality was reported separately and was defined as death related to a cardiac or neurological event. The diagnosis of Q-wave MI was based on the presence of new Q waves on the ECG and an elevated creatine kinase at least 2 times the upper limit of the normal range with an elevated

level of MB isoenzyme. In the absence of pathological Q waves, the diagnosis of non–Q-wave MI was based on an increase in the creatine kinase level to more than twice the upper limit of the normal range with an elevated level of MB isoenzyme. After CAS and cardiac surgery, a 12-lead ECG was performed in all patients. After cardiac surgery, the ECG was performed on a daily basis during the first 48 hours; afterward, during the remaining period of hospitalization, ECGs were performed in case of unexplained chest pain.

CAS Procedure

Cervical-cerebral angiography was performed according to the standard technique with intracranial views to determine patency and the completeness of the circle of Willis. Patients were accepted for the percutaneous approach by a consensus decision that involved the neurologist, the cardiovascular surgeon, and the interventional cardiologist. All patients received aspirin and clopidogrel for at least 3 days before the procedure.[19] Initial loading doses were 300 mg for both drugs, followed by 100 and 75 mg daily, respectively. All antihypertensive medication was discontinued 1 day before the procedure to decrease baroreceptor stimulation–related bradycardia and hypotension caused by balloon inflation. Patients were not sedated before or during the procedure. Cerebral blood flow velocities in the ipsilateral middle cerebral artery (if an adequate window was available) were monitored with transcranial Doppler during the procedure.[20] The hemodynamic status and oxygen saturation were monitored continuously. All procedures were performed via femoral access. An 8F short femoral introducer sheath was inserted, and heparin was administered intravenously (10 000 IU). The common carotid artery was engaged selectively with a diagnostic catheter (Sidewinder II, 5F, Cordis, Miami Lakes, Fla), which was exchanged for a long, 0.018-inch, stiff wire (SV-5, 300 cm, Cordis) positioned proximal to the target lesion. After this, an 8F percutaneous coronary angioplasty guiding catheter was placed in position (MP A1 8F, Cordis) and, if required, supported by a telescopic diagnostic catheter (MP A1 5F, 125 cm, Cordis). Selective angiography of the region of interest was performed; since the year 2004, 3D computed rotational angiography has become standard practice.[21] After the lesion was crossed with a flexible coronary wire, a low-profile, undersized angioplasty balloon (3.0 to 3.5 mm) was used to predilate the lesion, followed by placement of an appropriately sized self-expandable stent. To maximize stent deployment and vessel scaffolding, postdilation was performed with a balloon (5.5 to 7.0 mm) after atropine (0.5 mg IV) was administered. In addition to angiography (rotational), duplex ultrasonography was performed to facilitate stent

selection and optimal deployment. A distal cerebral protection device (FilterWire EZ system, Boston Scientific, Natick, Mass) has been available since the year 2002 and was used in every procedure, unless the lesion was considered too tight to allow the passage of the device. On completion of the procedure, ipsilateral carotid and intracranial angiography (rotational) was performed to verify angiographic success and exclude distal embolization. Procedural success was defined as successful stent deployment with a residual diameter stenosis 30%, as determined by postprocedural quantitative carotid angiography. After the procedure, all patients were routinely admitted for 2 to 4 hours to the medium-care or coronary care unit. All patients were evaluated clinically by a neurologist before the procedure, during the procedure, and immediately afterward. In case of a major stroke, the patient was monitored afterwards on the stroke unit.

Subsequent Cardiac Surgery

Cardiac surgery (including coronary artery bypass, valve surgery, or reconstructive surgery of the ascending aorta) was usually scheduled 14 to 30 days after CAS, unless clinical instability dictated otherwise. Aspirin and clopidogrel were discontinued 5 days before surgery, if possible. Our institution is a large cardiovascular referral center. It also operates as a training center for cardiologists and cardiothoracic surgeons. On a yearly basis in our hospital, we perform up to 2000 cardiothoracic surgery procedures and 2800 percutaneous interventions. During the period of enrollment, 618 CAS procedures, 9484 CABGs (1120 off-pump), 2234 valve surgery procedures, 1317 major aortic surgery procedures, and 56 combined CEA/CABG procedures were performed.

Data Collection and Patient Follow-Up

The mean follow-up per patient was 31 months, which resulted in a total follow-up of 910 patient-years. In case of an event, hospital notes or death certificates were consulted when possible. Telephone follow-up interviews were conducted at 1 month and thereafter at 6-month intervals by a dedicated full-time research coordinator. An independent board-certified neurologist graded symptoms according to functional testing with the modified Rankin score if a cerebrovascular event occurred.[22]

Statistical Analysis

Proportions are expressed as percentage and compared between groups by means of the Fisher exact test; continuous data are expressed as meanSD. For right-censored

data (ie, time to event), the Kaplan-Meier method was used to compute the long-term survival, stroke, and MI outcomes with corresponding 95% confidence intervals. The log-rank test was used to compare groups. For all computations, SAS version 8.2 (SAS Corp, Cary, NC) was used. The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

Results

Patient Characteristics

The baseline clinical characteristics of all patients are shown in Table 1.

Angiographic and Stenting Results

CAS was performed predominantly in the proximal internal carotid artery (n=341) but also included the distal (n=6) and proximal (n=9) common carotid artery. The overall procedural success rate was 97.7%. Eight technically unsuccessful procedures were due to inadequate guiding catheter position or wire support. In the data analysis, these patients were excluded. In 5 patients, concomitant left subclavian stenosis or occlusion was treated with angioplasty and stenting. Twenty-two patients (6.2%) underwent staged, bilateral CAS. A distal cerebral protection device was used in 143 patients (40.2%). The mean angiographic degree of stenosis was reduced from 855% (before stenting) to 59%. A variety of cerebral stents were used: Easy Wall stent (Boston Scientific; 3.1%), Carotid Wall stent (Boston Scientific; 75.6%), Acculink (Guidant, Natick, Mass; 18.2%), Precise (Cordis; 2.25%), NexStent (Boston Scientific), Omnilink (Guidant), and Protégé (EV3, Plymouth, Minn).

Table 1. Baseline Clinical Patient Characteristics (n=356 Patients)

Age, meanSD, y	72.9 ± 7.7
Women	104 (28.6)
Hypertension	164 (45.1)
Diabetes mellitus	81 (22.2)
Hypercholesterolemia	157 (43.1)
Smoking	72 (19.8)
History of neurological symptoms*	58 (15.9)
Previous MI	117(32.1)
Valvular heart disease	88 (24.2)
Congestive heart failure	46 (12.6)
Unstable angina pectoris	141 (38.8)
Previous CABG	47 (12.9)
Previous PTCA	47 (12.9)
Previous carotid angioplasty	7 (1.9)
Previous CEA	16 (4.4)
Previous heart/neck radiotherapy	18 (4.9)
Pulmonary disease	39 (10.7)
Renal failure (creatinine 120–300 mol/L)	43 (11.8)
Contralateral severe ACI stenosis	22 (6.1)
Severe stenosis or occlusion of left subclavian artery	5 (1.4)

Except for age, all values are n (%). PTCA indicates percutaneous transluminal coronary angioplasty; ACI, acute coronary insufficiency.
*Stroke or transient ischemic attack 4 months or more before CAS.

Cardiac Surgery Results

The mean time to cardiac surgery after CAS was 22 days, with a range of 1 day to 3 months. In the present study population, 113 patients (31.7%) underwent CABG within 14 days after CAS, 111 (31.1%) after 14 to 30 days, and 132 (37.1%) after 30 days. In the present series, 319 patients (89.6%) underwent CABG, in whom 23 procedures (7.2%) were accomplished without cardiopulmonary bypass (off-pump), 97 patients (27.2%) had valve surgery (the majority of whose procedures were combined with CABG), and 17 (4.8%) underwent reconstructive surgery of the ascending aorta. Forty-seven (13.2%) of the cardiac interventions were redo procedures (second or third). Thirteen patients (3.7%) underwent combined cardiac surgery with contralateral CEA after CAS.

Periprocedural Outcome and 30-Day Follow-Up

Periprocedural event rates after CAS and after cardiac surgery are listed in Table 2. During the period between CAS and surgery, 1 cardiac death (0.3%) occurred due to cardiac arrhythmia, 2 patients (0.6%) had an MI, 5 patients (1.4%) had unstable angina, 1 patient had a major ipsilateral stroke and did not proceed to surgery (0.3%), 4 patients (1.1%) had minor ipsilateral stroke, and 8 patients (2.2%) had a transient ischemic attack. Cardiac surgery was performed in 354 of 356 patients. Thirteen patients (3.7%) died within 30 days after cardiac surgery. The causes of death were cardiac in 8 cases, including 2 patients who could not be weaned off bypass; 4 patients died of septicemia and multiorgan failure, and 1 death was neurologically determined. In those patients in whom a nonfatal neurological event occurred after cardiac surgery, control duplex ultrasonography was performed that showed adequate stent apposition in the treated carotid artery without hemodynamically significant (re)stenosis or stent thrombosis. In the patient in whom death was neurologically determined, the CT scan showed a major cerebral hemorrhage without any carotid stent thrombosis. In patients ≥ 80 years of age (n=70), the cardiac and neurological death rate was significantly higher than in patients < 80 years of age (n= 286; 7.1% versus 1.7%, P=0.03).

Table 2. Periprocedural Event Rate After Staged CAS and Cardiac Surgery

Event	CAS Patients (n=356)	Cardiac Surgery Patients (n=354)	Total (n=356)
All deaths	1 (0.3)	12 (3.4)	13 (3.7)
- Cardiac deaths	1 (0,3)	7 (2.0)	8 (2.2)
- Neurological deaths	0	1 (0.3)	1 (0.3)
- Nonneurological/noncardiovascular deaths	0	4 (1.1)	4 (1.1)
All strokes	5 (1.4)	6 (1.7)	11 (3.1)
- Major ipsilateral nonfatal strokes	1 (0.3)	3 (0.8)	4 (1.1)
- Major contralateral nonfatal strokes	0	2 (0.6)	2 (0.6)
- Minor strokes	4 (1.1)	1 (0.3)	5 (1.4)
Transient ischemic attacks	8 (2.2)	5 (1.4)	13 (3.7)
Nonfatal MIs	2 (0.6)	5 (1.4)	7 (2.0)
All deaths and major strokes	2 (0.6)	15 (4.2)	17 (4.8)
All deaths, major strokes, and MIs	1 (0.3)	20 (5.6)	24 (6.7)

*Value*s are n (%).

All cardiac and neurological deaths occurred in the immediate postoperative period. Three of the octogenarians died from Q-wave MI, 1 patient died from congestive heart failure, and 1 death was neurologically determined. Male and female patients had similar periprocedural complication rates. Although not statistically significant, periprocedural event rates were lower in patients treated with cerebral distal protection (n=143, 40.2%) than in those treated without cerebral protection (n=213, 59.8%; 2.2% versus 3.8%, P= 0.50).

Long-Term Follow-Up

Overall median follow-up was 31 months, with 25% of the patients being followed up for 48 months. Two patients underwent repeat carotid angioplasty for restenosis at 3 and 7 months after the first procedure, respectively. In both patients, subsequent follow-up with duplex ultrasonography at 3 years showed a stabilization of the restenotic process with an estimated in-stent restenosis of 50% to 70%. Fifty-eight deaths (16.3%) occurred; 38 deaths (10.7%) were cardiac related, 4 (1.1%) were neurological, and 16 (4.5%) were of other causes. Fourteen strokes (3.9%) occurred, with 4 (1.1%) major ipsilateral nonfatal strokes, 2 (0.6%) major contralateral nonfatal strokes, 8 (2.2%) minor strokes, and 15 (4.2%) transient ischemic attacks. Seven (2.0%) nonfatal MIs occurred. Survival at 5 years was 75.5% (95% confidence interval 69.0% to 82.0%; Figure 1).

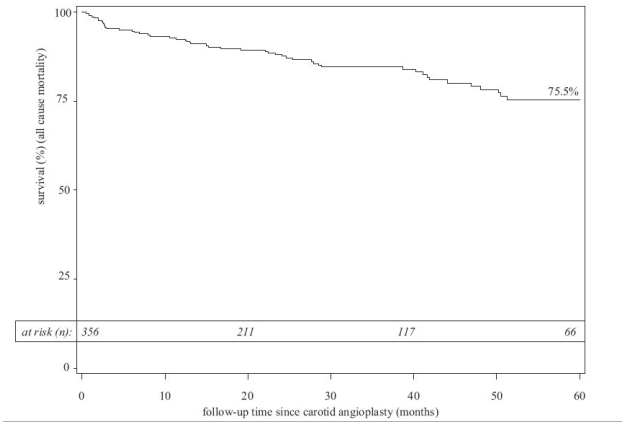

Figure 1. Kaplan-Meier curve: 5-year survival.
n indicates number at risk.

A univariate analysis showing the cumulative 5-year event rates is depicted in Table 3. No differences existed in all-cause mortality between patients ≥ 80 and < 80 years of age or between patients treated with or without distal cerebral protection. However, the 5-year rate of freedom from all-cause mortality was significantly higher in women than in men (Figure 2). Patients ≥ 80 years of age had significantly higher rates of transient ischemic attack than those < 80 years old. The Kaplan-Meier curve for 5-year freedom from all stroke and death is shown in Figure 3.

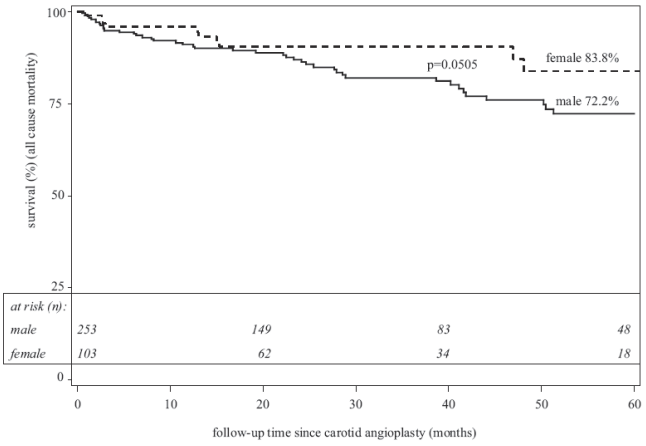

Figure 2. Kaplan–Meier curve: 5-year survival for men and women.
n Indicates number at risk; solid line, males; and dashed line, females.

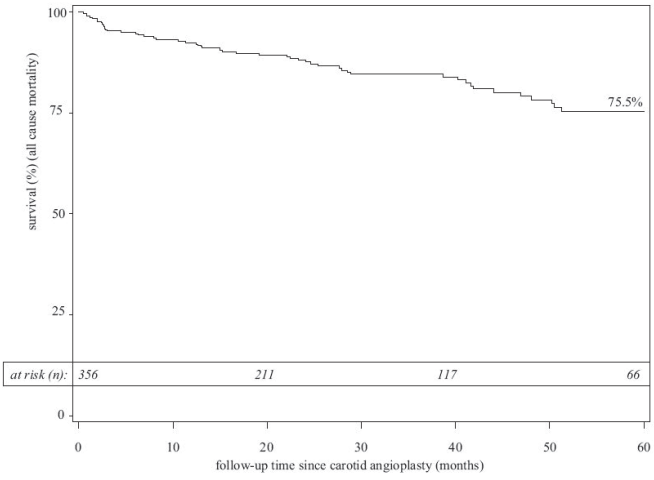

Figure 3. Kaplan–Meier curve: 5-year freedom from all stroke and death.
n indicates number at risk.

Table 3. Cumulative 5-Year Event Rates (Univariate Analysis)

	Cumulative Event Rate at 5 Years, % (95% CI)	*P*
All cause mortality	24.5 (18.0–31.0)	...
Cardiocerebrovascular mortality	16.6 (11.2–22.0)	...
MI	2.0 (0.5–3.5)	...
Major stroke	3.1 (0.1–6.0)	...
Minor stroke	2.9 (0.8–5.0)	...
Transient ischemic attack	5.6 (2.3–8.9)	...
All-cause mortality + minor stroke + major stroke	28.6 (21.8–35.3)	...
Cardiocerebrovascular mortality + major stroke + MI	20.5 (14.6–26.3)	0.7713
Age < 80 y	20.0 (13.5–26.4)	...
Age ≥ 80 y	23.0 (8.5–37.4)	...
All-cause mortality by sex		0.0505
Men	27.8 (19.9–35.6)	...
Women	16.2 (5.5–26.9)	...
All-cause mortality by age		0.5404
Age < 80 y	23.9 (16.7–31.1)	...
Age ≥ 80 y	27.3 (12.1–42.4)	...
All-cause mortality by use of distal protection device		0.7654
No distal protection device used*	15.5 (10.3–20.8)	...
Distal protection device used*	17.5 (7.3–27.6)	...
Transient ischemic attack by age		0.0377
Age < 80 y	3.7 (1.2–6.2)	...
Age ≥ 80 y	13.5 (0.5–26.6)	...

CI indicates confidence interval.
*Denotes event rates at 3-year follow-up.

Discussion

CAS followed by cardiac surgery may provide a valuable treatment for patients with combined carotid and cardiac disease, given the low periprocedural complication rates observed in the present study. The high rate of freedom from death and stroke during the 5 years of follow-up supports the long-term durability of this approach. The ideal strategy for treating patients with severe asymptomatic carotid artery stenosis and cardiac disease remains unclear.[23] Perioperative stroke risk is thought to be <2% when carotid stenoses are <50%, 10% when stenoses are 50% to 80%, and 11% to 19% in patients with stenoses >80%. Patients with untreated bilateral, high-grade stenoses or occlusions have a 20% chance of stroke (American Heart Association/American

College of Cardiology guidelines).[24,25] Das et al[26] observed a risk of 11.5% for stroke and death in patients with severe carotid disease undergoing isolated CABG,with an undetermined incidence of nonfatal MI. Naylor et al[23] reported a 10% to 12% risk of death, stroke, or MI for staged or combined operations and concluded that staged or synchronous operations might be able to reduce the death or stroke rate. Ziada et al[27] described significantly fewer adverse events in patients who underwent CAS and cardiac surgery, despite a higher baseline risk profile, than in those undergoing combined CEA and CABG. Our strategy demonstrates a favorable stroke and death risk of 4.8% and a combined risk of 6.7% for death, stroke, and MI. The reported total periprocedural MI rate of 2.0% is in contrast to observational studies of CEA and CABG, in which the rate varies from 3.6% (synchronous) to 6.5% (staged), especially when one bears in mind that in the present study population, 13% of cardiac surgical procedures were redo procedures. This new approach demonstrates a low rate of ipsilateral major stroke (1.1%), especially in view of the fact that 13 patients (3.7%) underwent CAS and cardiac surgery combined with contralateral CEA. The periprocedural cardiac and neurological death rate was higher for patients ≥ 80 years than for those < 80 years of age. The immediate postoperative period was crucial for these octogenarians, with all fatal events occurring within 2 days of cardiac surgery. Approximately 60% of the procedures included in the present study were performed before the availability of embolic distal protection devices in our institution. The need for repeated intervention was low in the present group of patients. This low rate is consistent with the low angiographic restenosis rate in other studies, although those studies reported on CAS of the extracranial arteries without concomitant cardiac surgery.[13,14,28,29] An optimal strategy for the discontinuation of antiplatelet agents, which takes into account both adequate timing for complete carotid stent endothelialization with decreased platelet activation and a brief waiting period for cardiac surgery to reduce the incidence of cardiac events, is inconceivable.[30-32]
Inevitably, a compromise is required. The minimum delay between CAS and cardiac surgery should be determined by the extensiveness of the cardiac disease. In those patients who require urgent cardiac surgery, the operation should be performed without discontinuation of dual-antiplatelet therapy. If the cardiac condition warrants a prolonged delay, the optimal timing, derived from our own experience, would be between 2 and 3 weeks, and the antiplatelet drug regimen should be continued until 5 days before surgery. In the present study, 31.7% of patients underwent CABG within 14 days after CAS, 32.2% after 14 to 30 days, and 37.1% after 30 days. Because neither

stent thrombosis nor increased perioperative bleeding complications were observed in these patients, this clinical practice may be the most achievable compromise. This new approach provides a less radical intervention from the patient's point of view and therefore might reduce psychological trauma and improve the patient's quality of life.

Study Limitations

This prospective, nonrandomized study cannot be compared with other trials and series of CEA because of the different composition of patient populations, especially with the inclusion in the present study of high-risk patients with severe cardiac disease. A large prospective trial with randomization either to staged CAS-CABG, combined CEA-CABG, or isolated CABG in a study population similar to ours would demonstrate the optimal therapeutic strategy.

Conclusion

In this large group of patients with no neurological symptoms who underwent staged CAS and cardiac surgery, a low periprocedural complication rate was found. The high rate of freedom from death and stroke during the 5 years of follow-up supports the long-term durability of this approach. These findings suggest that CAS before cardiac surgery may be a valuable alternative to the entirely surgical approach. These 2 strategies should be compared in an adequately powered randomized trial.

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Chapter 3.2

Editorial comment Management of Patients With concomitant Severe Coronary and Carotid Artery Disease: Is There a Perfect Solution?

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Despite limited evidence of the benefit of carotid revascularization before or together with coronary artery bypass grafting (CABG), patients with advanced carotid and coronary disease are frequently treated by a combined or staged carotid/coronary surgical revascularization. In the present issue of Circulation,[1] investigators from Nieuwegein in the Netherlands describe in a large group of patients (n=356) an alternative revascularization approach: carotid artery stenting (CAS) followed by CABG. The rate of death, stroke, or myocardial infarction (MI) from the time of CAS to 30 days after cardiac surgery (6.8%) compares well with previous surgical series[2-21] (Table). The associated neurological complication rates were low both at 30 days (major ipsilateral stroke 1.1%) and at a mean follow-up of 31 months (neurological death 1.1% and major ipsilateral stroke 1.1%). The carotid restenosis rate was negligible. The authors must be commended for the favorable patient outcomes and for the volume of procedures performed (47 per year), which are superior to most, if not all, recent surgical series of combined coronary-carotid revascularization (Table). Additional important aspects of the study were that patients were accepted for CAS by a consensus decision that involved neurologists, surgeons, and interventionists and that neurologists were deeply involved in the care of those patients throughout the hospital stay.

With respect to the surgical management of concomitant coronary and carotid disease, a systematic review of the studies published up to 2002 showed that the overall 30-day rate of death, stroke, or MI was 11%.[2] Several single-center experiences have followed, documenting a death rate ranging between 3.6% and 6.1% and a stroke rate between 2.8% and 5.5% up to 30 days (Table). A population-based analysis performed in the United States detected a combined death and stroke rate of 17.7% among 226 procedures.[5] Among 744 patients extracted from the New York Cardiac Database, the combined death and stroke rate was 8.1%.[11] An analysis of all combined surgical procedures performed in Canada, with the exception of the province of Quebec, detected an in-hospital mortality rate of 4.9% and a postoperative stroke rate of 8.5%.[4] Finally, using the Nationwide Inpatient Sample, an in-hospital death or stroke rate of 9.7% was reported among 7073 patients treated with carotid endarterectomy (CEA) and CABG.[6] According to the American Heart Association, the decision to perform CEA in patients with asymptomatic carotid stenosis 70% that requires CABG is "uncertain."[17] The recent American Academy of Neurology recommendations on CEA stated that "the available data are insufficient to declare either CEA before or simultaneous with CABG as superior [to a conservative carotid management] in

patients with concomitant carotid and coronary occlusive disease."[18] The concept of performing CAS before open heart surgery is not novel. In a retrospective analysis, investigators at the Cleveland Clinic in Ohio compared the outcomes of patients undergoing CAS before open heart surgery (n=56) and those undergoing a combined surgical approach (n=111) and showed favorable results for the partially endovascular approach.[12] The analysis was limited by imbalances among the groups: more unstable/severe angina, severe left ventricular dysfunction, symptomatic carotid disease, and need for repeat open heart surgery in the CAS group; more severe contralateral carotid disease in the group treated only surgically. The incidence of death, stroke, or MI 30 days after open heart surgery was 10.7% in the CAS group and 21.6% in the surgical group (P=0.08; Table).

Table Outcomes up to 30 Days for Patients Undergoing CEA and CABG or CAS followed by CABG

Study	N	Patients per Year,n	Death, %	Stroke, %	MI, %	Death/ Stroke, %	Death/Stroke/ MI, %
CEA-CABG							
Systematic review 1972-2002[2]	8972	N/A	4.5	4.5	3.9	8.4	11.0
Liège, Belgium[3]	311	22	6.1	5.5	2.2	11.6	13.8
Canada[4]	669	N/A	4.9	8.5	N/A	13.0	N/A
Medicare[5]	226	N/A	6.6	12.0	N/A	17.7	N/A
US nationwide inpatient sample[6]	7073	N/A	5.6	4.9	N/A	9.7	N/A
Albany, NY[7]	702	28	N/A	N/A	N/A	4.4	N/A
Houstan, Tex[8]	227	12	3.6	2.8	0.7	N/A	N/A
Stony Brook, NY[9]	154	26	3.9	3.9	N/A	7.8	N/A
Cleveland, Ohio[10]	272	25	5.2	5.2	2.9	N/A	N/A
New York State Cardiac Database[11]	744	N/A	4.4	5.1	N/A	8.1	N/A
CAS-CABG							
Cleveland, Ohio[12]	56	10	5.4	1.8	3.3	7.1	10.7
Sydney, Australia[13]	20	N/A	0	5.0	5.0	5.0	10.0
Sheffield, United Kingdom[14]	52	7	13.5	5.8	N/A	19.2	N/A
Buenos Aires, Argentina[15]	30	3	10.0	0	3.3	10.0	13.3
Rome, Italy[16]	10	N/A	0	0	0	0	0
Nieuwegein, the Netherlands[1]	356	47	3.7	3.1	2.0	4.8	6.8

N/A indicates not appplicable; MI myocardial infarction

Investigators in Sheffield, United Kingdom, performed a prospective study on 52 patients undergoing CAS followed by open heart surgery. Despite the lack of periprocedural neurological events after CAS, 3 patients died of cardiac causes while awaiting surgery, and 6 had complications related to surgery, for a total death or stroke rate at 30 days after CABG of 19.2%.[14] A group from Sydney, Australia, reported a death, stroke, or MI rate of 10% among 20 patients undergoing staged CAS-CABG.[13] Unresolved issues include the minimal delay required between CAS and open heart surgery and the antiplatelet regimen at the time of CABG. Although the need for urgent cardiac surgery was not an exclusion criteria in the present study, and approximately one third of the patients had unstable angina, the patients were "planned for CAS and cardiac surgery." Individuals with uncontrolled cardiac symptoms may have undergone urgent combined surgery. Therefore, the described strategy may not apply to those patients. In the study, all patients received dual-antiplatelet therapy at the time of CAS, and "aspirin and clopidogrel were discontinued 5 days before surgery, if possible." Although it is unclear why aspirin discontinuation was recommended, the antiplatelet regimen at the time of CABG was not detailed. The authors described that the mean time to cardiac surgery was 22 days and that approximately one third of patients underwent CABG within 14 days, one third between 14 days and 1 month, and one third after 1 month. Encouraging in this respect was the lack of carotid stent thrombosis reported. A group in Chicago, Ill, reported no deaths or neurological events among 37 patients treated with CAS who underwent CABG within 48 hours.[19] The antithrombotic regimen during and after CAS consisted of unfractionated heparin and the glycoprotein IIb/IIIa receptor antagonist eptifibatide, the latter for up to 6 hours before CABG. A recent study from Buenos Aires, Argentina, showed the feasibility of another approach, namely, concurrent CAS and open heart surgery.[15] The endovascular procedure was performed after the administration of aspirin and unfractionated heparin, and patients (n=30) were transferred from the catheterization laboratories to the operating room. Clopidogrel was added after surgery if the patient had no postoperative bleeding. No strokes or neurological deaths were observed. The same strategy was also associated with no strokes or deaths among 10 patients treated in Rome, Italy.[16] The role of best medical treatment as an alternative to revascularization in patients with asymptomatic carotid stenosis, as well as secondary prevention after carotid revascularization, needs to be elucidated. A broad diseasemanagement approach based on lifestyle modification, statin therapy, and optimal blood pressure control,

preferably with an angiotensin-converting–enzyme inhibitor, is more likely to affect both the quality and duration of life than carotid revascularization itself. This aspect is critical, because after CEA, patients remain at a higher long-term risk of (cardiac) death.[20] The differential role of carotid disease and ascending aorta atherosclerosis as underlying mechanisms of stroke among patients with advanced carotid and coronary disease who are undergoing cardiac surgery needs to be elucidated. The question is whether the focus is on the wrong culprit (carotid stenosis) instead of addressing the true (and difficult to treat) source of embolism, namely, the ascending aorta.[21] Although stroke risk during CABG has been related to the degree of carotid stenosis, it has been estimated that more than half of all territorial infarctions on CT scan or autopsy are not related to carotid disease alone.[22] Unfortunately, despite the increasing amount of evidence in the literature that points to ascending aorta atherosclerosis as a critical culprit in the pathogenesis of post-CABG stroke, most cardiac surgery databases do not track prospectively the extent of atherosclerotic disease in the ascending aorta.[23] How can we identify the best management strategy (optimal medical therapy, endarterectomy, or stent) for patients with severe asymptomatic carotid stenosis that requires open heart surgery? The perfect but unrealistic solution would be a randomized trial; however, the target population is too small. In a nationwide US survey, among the population of patients undergoing CABG, those undergoing combined CEA-CABG accounted for only 1.1% in 1993 and 1.6% in 2002.[6] Even lower was the proportion of combined CEA-CABG compared with CABG in a recent Canadian survey (0.5%).[4] Finally, high-volume centers report between 13 and 30 combined surgical procedures per year (Table). A randomized trial testing noninferiority between CABG only, CEA-CABG, and CAS followed by CABG would be relevant clinically. However, given the assumption of a 30-day death, stroke, or MI rate in the CEA-CABG group of 12% and a noninferiority boundary of 3%, such a study would require an enrollment of 4000 patients to be adequately powered. It is unlikely that this will ever take place, because even CEA versus CAS trials, which address a much broader patient population, have had to be stopped recently because of slow enrollment and lack of funding.[24] In the absence of a perfect solution, a realistic way of improving the evidence base would be to perform small, randomized studies focusing on surrogate end points, such as the occurrence of new lesions on magnetic resonance imaging or postoperative cognitive deficits. In the meantime, the best revascularization strategy for patients with advanced coronary and carotid disease should be suggested on a case-by case basis by a multidisciplinary team

that includes neurologists, surgeons, and interventionists who take into account the comorbidities of the patient, the degree of urgency of cardiac surgery, and local expertise. It would be in the best interest of these high-risk patients to be treated in high-volume centers like that in Nieuwegein.

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Chapter 4.1

Carotid artery stenting and cardiac surgery in symptomatic patients.

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Objectives The purpose of this study was to evaluate the feasibility and safety of the combined outcome of carotid artery stenting (CAS) and coronary artery bypass graft (CABG) surgery in neurologically symptomatic patients.

Background The risk of perioperative stroke in patients undergoing CABG who report a prior history of transient ischemic attack or stroke has been associated with a 4-fold increased risk as compared to the risk for neurologically asymptomatic patients. It seems appropriate to offer prophylactic carotid endarterectomy to neurologically symptomatic patients who have significant carotid artery disease and are scheduled for CABG. The CAS-CABG outcome for symptomatic patients remains underreported, notwithstanding randomized data supporting CAS for high-risk patients.

Methods In a prospective, single-center study, the periprocedural and long-term outcomes of 57 consecutive patients who underwent CAS before cardiac surgery were analyzed.

Results The procedural success rate of CAS was 98%. The combined death, stroke, and myocardial infarction rate was 12.3%. The death and major stroke rate from time of CAS to 30 days after cardiac surgery was 3.5%. The myocardial infarction rate from time of CAS to 30 days after cardiac surgery was 1.5%.

Conclusions This is the first single-center study reporting the combined outcome of CAS-CABG in symptomatic patients. The periprocedural complication rate and long-term results of the CAS-CABG strategy in this high-risk population support the reliability of this approach. In such a high-risk population, this strategy might offer a valuable alternative to the combined surgical approach; however, a large randomized trial is clearly warranted.

Introduction

Optimal treatment of patients with concurrent carotid and coronary artery disease remains debatable despite more than 100 publications during the last 30 years.[1-3] Stroke is still a major noncardiac complication of coronary artery bypass graft (CABG) surgery, with an absolute incidence of 2%. Carotid artery disease has been associated with an increased risk of perioperative stroke after CABG, rising from 3% in predominantly asymptomatic patients with unilateral 50% to 99% stenosis, to 5% in those with bilateral 50% to 99% stenosis, and 7% to 11% in patients with carotid occlusion.[1,4,5] Moreover, the risk of perioperative stroke in CABGpatients who report a prior history of transient ischemic attack (TIA) or stroke has been associated with a 4-fold increased risk as compared to the risk for neurologically asymptomatic patients (8.5% [95% confidence interval (CI): 4.9 to 12.1] versus 2.2% [95% CI: 1.4 to 3.1]).[1] Therefore, it seems appropriate to offer prophylactic carotid endarterectomy (CEA) to neurologically symptomatic patients undergoing CABG who have significant carotid artery disease.[2,6-8] The findings from the SAPPHIRE (Stenting and Angioplasty With Protection in Patients at High Risk for Endarterectomy) trial, including patients with significant cardiac disease, showed that among high-risk patients with severe carotid artery stenosis and coexisting conditions, carotid artery stenting (CAS) using an emboliprotection device is not inferior to CEA.[9,10] The CAS-CABG outcome for symptomatic patients remains underreported, notwithstanding these randomized data supporting CAS for high-risk patients. In the available data describing the CAS or CEA-CABG strategy, periprocedural event rates of the symptomatic and the asymptomatic patients are scarcely reported separately. We report the results of CAS and subsequent cardiac surgery in 57 patients with symptomatic carotid artery disease.

Methods

Patient population

In a prospective, nonrandomized study, we entered 57 consecutive symptomatic patients scheduled for CAS and cardiac surgery between December 1998 and January 2008. Patients were considered symptomatic if an ipsilateral carotid territory stroke or TIA had occurred within 4 months before the procedure. A carotid artery stenosis was considered significant when a diameter reduction of at least 70% on duplex and an angiographic stenosis of more than 50% (using the quantitative coronary

analysis technique) of the luminal diameter was measured in the common carotid artery, internal carotid artery, or at the bifurcation according to the NASCET (North American Symptomatic Carotid Endarterectomy Trial) criteria.[11,12] The indications for cardiac surgery were symptomatic (documented myocardial ischemia) severe coronary artery disease (including bypass failure) not eligible for percutaneous revascularization, symptomatic valve disease, and disease (aneurysm or dissection) of the ascending aorta or arch that demanded reconstructive surgery. Exclusion criteria included: severe renal impairment (serum creatinine 300 mol/l), peripheral vascular disease precluding femoral artery access, major neurological deficit or any other illness impeding informed consent, severe diffuse atherosclerosis of the common carotid artery, chronic total occlusions, long re-occlusive lesions ("string sign" lesions). All patients gave written informed consent. This registry was approved by the ethical committee of our hospital.

Endpoint definition

The primary endpoint of the present study was the combined incidence of death, all strokes, and myocardial infarction (MI) from time of CAS to 30 days after cardiac surgery. Secondary endpoints were MI rate and death and major stroke rate from time of CAS to 30 days after cardiac surgery. In the long-term outcome, cumulative event rates at 5 years are reported. Strokes were considered disabling (major) if patients had a modified Rankin score of more than 3 at 30 days after onset of symptoms. A minor stroke was defined as a Rankin score of 3 or less that resolved completely within 30 days.[13] The diagnosis of Q-wave MI, evaluated by an independent cardiologist, was based on the presence of acute chest pain, new Q waves on the electrocardiogram, and an elevated creatine kinase to at least 2 the upper limit of the normal range with an elevated level of MB isoenzyme. In the absence of pathological Q waves, the diagnosis of non–Q-wave MI was based on the increase of creatine kinase level to more than twice the upper limit of the normal range with an elevated level of MB isoenzyme. In our institution, cardiac enzymes are drawn routinely every 8 h during the first 24 h after each procedure. A 12-lead electrocardiogram was performed in all patients following CAS and cardiac surgery. The electrocardiogram was performed daily during the first 48 h following cardiac surgery and in case of unexplained chest pain during the remaining period of hospitalization. Cardio-cerebrovascular mortality was reported separately and was defined as death related to a cardiac or neurological event.[14]

CAS procedure and subsequent cardiac surgery

Carotid stenting has been performed following the highest standard of care using a distal embolic protection device since 2002. Cardiac surgery (including coronary artery bypass, valve, or reconstructive surgery of the ascending aorta) was usually scheduled at least 3 weeks after CAS, unless clinical instability dictated otherwise. The approach in our institution for this staged strategy has been described earlier.[14] All patients were clinically evaluated before the procedure, during the procedure, and immediately afterward by an impartial neurologist. Before and after CABG, the same neurologist examined the patients once more. In case of a major stroke, the patient was monitored afterward in the stroke unit. All patients were evaluated by this neurologist at an outpatient clinic after 1 and 3 months. It is our practice to perform CAS (with dual antiplatelet therapy) and then to stop the clopidogrel 7 days before CABG (aspirin continued). Clopidogrel is restarted (mean time of 2 days) after recovery from surgery. In those patients requiring urgent cardiac surgery, CAS is performed using dual antiplatelet therapy, which is not stopped before the cardiac procedure.

Statistical analysis

Proportions are expressed as percentage and continuous data are expressed as mean SD. For right-censored data (i.e., time to event), the Kaplan-Meier method was used to compute the long-term survival, stroke, and MI outcomes with corresponding 95% CI. The log-rank test was used to compare groups. For 95% CI, exact calculations are used (no asymptotic approximations). For all computations, R (version 2.12, the R Foundation for Statistical Computing, Vienna, Austria) was used. The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agreed to the manuscript as written.

Results

Patient characteristics

The baseline clinical characteristics of all patients are shown in Table 1. The median waiting time between the last neurological event and the CAS procedure was 36 days (interquartile range: 6 to 90 days).

Angiographic and stenting results.

CAS was performed predominantly in the proximal internal carotid artery (n 52), but it also included the distal (n=3) and proximal (without involvement of the ostium)

(n=2) common carotid artery. In 2 patients, concomitant left subclavian stenosis or occlusion was treated with angioplasty and stenting. A distal cerebral protection device was used in 29 patients (50.9%) before 2002, and since 2002, in all patients. The mean angiographic degree of stenosis was reduced from 86±4% to 4±9%. We used a variety of peripheral or carotid stents: 5 Carotid Wall (Boston Scientific, Natick, Massachusetts), 48 Acculink (Guidant/Abbott, Natick, Massachusetts), 3 NexStent (Boston Scientific), and 1 Omnilink (Guidant/Abbott).

Table 1. Baseline Clinical Patient Characteristics

	Patients n=57
Age, yrs	69.7±8.4
Female	19 (33.3)
Hypertesion	36(62)
Diabetes Mellitus	8 (14)
Hypercholesterolemia	31 (54.4)
Smoking	11 (19.3)
Previous myocardial infarction	16 (28.1)
Valvular heart disease	14 (24.6)
Congestive heart failure	3 (5.4)
Unstable angina pectoris	21 (36.8)
Previous CABG	8 (14)
Previous PCI	7 (12.3)
Previous CEA	1 (1.8)
Major stroke	3 (5.3)
Minor stroke	12 (21.1)
TIA	42 (73.7)

Values are mean ± SD or n(%).
CABG = coronary artery bypass graft; CEA = carotid endarterectomy; PCI = percutaneous coronary intervention; TIA = transient ischemic attack.

Cardiac surgery results

The median time interval between CAS and cardiac surgery was 28 days (interquartile range 12 to 58 days). In the present series, 52 patients (91.2%) underwent CABG, in whom 4 procedures (7%) were accomplished without cardiopulmonary bypass,

3 patients (5%) had valve surgery combined with CABG, and 2(3.5%) underwent reconstructive surgery of the ascending aorta. Eight (14%) of the cardiac interventions were redo procedures (second or third). Although the latter group is exposed to a higher risk for cardiovascular complications, we included these patients because they represent a substantial group of patients treated in our daily practice. No major bleeding requiring rethoracotomy was reported in those patients on dual antiplatelet therapy versus those on acetylsalicylic acid alone during surgery.

Periprocedural outcome and 30-day follow-up

Periprocedural event rates after CAS and after cardiac surgery are listed in Table 2. During the period between CAS and surgery, 1 patient suffered a MI and 4 patients had a minor stroke of which one was contralateral. Cardiac surgery was performed in 57 patients. One patient who suffered from a MI while waiting for CABG died 3 months after CABG. One patient died (cardiac-related) and 1 patient suffered a major stroke within 30 days after cardiac surgery. In the latter patient, post-procedural duplex ultrasonography was performed and showed adequate stent apposition in the treated carotid artery without hemodynamically significant restenosis or stent thrombosis. Male and female patients had similar periprocedural complication rates.

Table 2. Periprocedural Outcome After Staged CAS and Cardiac Surgery

Event	CAS Patients (n = 57)	Cardiac Surgery Patients (n = 57)	Total (n = 57)
All deaths	0	1 (1.5)	1 (1.5)
Cardiac deaths	0	1 (1.5)	1. (1.5)
Neurological deaths	0	0	0
Non neurological/ noncardiovascular deaths	0	0	0
All strokes*	4 (7.0)	1 (1.5)	5 (8.8)
Major strokes	0	1 (1.5)	1 (1.5)
Minor strokes	4*(7.0)	1 (1.5)	4 (7.0)
All MIs	1 (1.5)	0	1 (1.5)
All deaths and major strokes	0	2 (3.5)	2 (3.5)
All deaths, all strokes, and MIs	5(8.8)	2 (3.5)	7 (12.3)

Values are n (%). *Three ipsilateral and 1 contralateral strokes.
MI = myocardal infarction

Long-term follow-up

Overall median follow-up was 50 months, with 33% of the patients being followed for 60 months. There were 18 deaths (31.6%): 8 (14%) were cardiac-related (2 unknown deaths were considered as cardiac); 2 (3.5%) were neurological deaths; and 8 (11.8%) died of other causes. No repeat carotid intervention for restenosis was necessary. On duplex follow-up in 50 patients (between 3 and 6 months), 4 moderate restenoses (50% to 65%) were detected. None of these patients had symptoms related to the treated hemisphere. There was 1 late minor stroke and 1 late major stroke. No MI occurred. A univariate analysis showing the cumulative 5-year event rates is depicted in Table 3. The survival at 5 years was 63.7% (95% CI: 51.3% to 79.1%). The freedom from all deaths, all strokes, or MI is 56.7% (see Kaplan-Meier curve in Fig. 1). The all-cause mortality and the all-death, all-stroke, and MI rates were significantly higher in patients ≥ 75 years of age than in those < 75 years old.

Table 3. Cumulative 5-Year Event Rates (Univariate Analysis)

	Cumulative event Rate at 5 Years(%)	95% CI	p value
All-cause mortality	36.3	(20.9–48.7)	
Cardio-cerebrovascular mortality	21.0	(7.9–32.2)	
MI	1.8	(0.0–5.3)	
Major stroke	6.1	(0.0–14.5)	
Minor stroke	9.0	(1.1–16.2)	
All-cause mortality + minor + major stroke	43.3	(27.4–55.7)	
Cardio-cerebrovascular mortality (unknown included) major stroke	22.5	(9.2–33.8)	
All-cause mortality + all strokes + MIs:			
Age < 75 yrs	35.4	16.9–49.9	0.02
Age ≥ 75 yrs	56.9	25.0–75.3	
Symptoms ≤ 30 days	45.6	16.6–64.5	0.97
Symptoms > 30 days	42.8	21.9–58.1	
Without distal protection device	32.6	11.2–48.9	0.12
With distal protection device	55.4	28.0–72.3	
All-cause mortality: men	37.2	(18.6–51.5)	0.88
All-cause mortality: women	31.6	(4.2–51.1)	
All-cause mortality: age < 75 yrs	27.3	(10.0–41.2)	0.01
All-cause mortality: age ≥ 75 yrs	53.9	(21.1–73.1)	
All-cause mortality: without distal protection device	32.6	(11.2–48.9)	0.49
All-cause mortality: with distal protection device	39.6	(14.5–57.3)	

CI confidence interval; MI myocardial infarction.

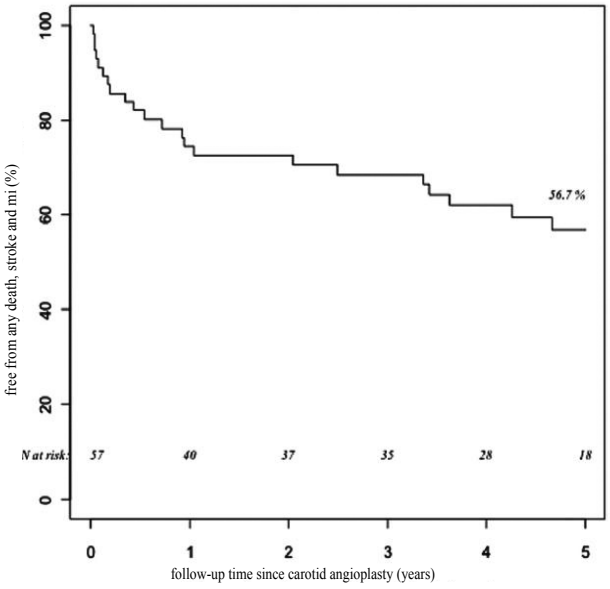

Figure 1. Kaplan-Meier Curve: 5-Year Freedom From All Deaths, All Strokes, and MIs

n indicates number at risk. Data represent Kaplan-Meier curve for patients free from any death, stroke, and myocardial infarction (MI) during followup. Percentage on the right of the black line represent the freedom from all deaths, all strokes, or MI at 5 years.

Discussion

It is considered appropriate to offer prophylactic CEA to CABG patients who have unilateral or bilateral significant carotid artery stenosis if they describe a history of TIA or stroke, especially if the index event was within the preceding 6 months. D'Agostino et al.[8] reported a periprocedural stroke rate of 17.9% in patients with unilateral carotid disease and 26.3% in those with bilateral disease undergoing isolated CABG. These patients have a very high risk of stroke during CABG, and prophylactic intervention can be justified. In the present study, we report the periprocedural complication rates and long-term results of the CAS-CABG strategy in symptomatic patients.In some systematic reviews, the 30-day stroke rates have

been evaluated and varied from 2.7% after staged CEA-CABG (57% asymptomatic) to 4.2% after staged CAS-CABG (87% asymptomatic), 4.6% after synchronous CEA-CABG (59% asymptomatic) and 6.3% after reverse staged CABG-CEA (no detailed data available describing the neurological status).[2,6,7] It is difficult to compare the outcome insymptomatic patients to such data. However, Timaran et al.[15] described the outcome for the symptomatic subpopulation in a large study based on the NIS (Nationwide Inpatient Sample) databases of 27,084 patients undergoing either synchronous CEA-CABG or staged CAS-CABG in the United States between 2000 and 2004. Stratified analyses according to the symptomatic status and type of carotid revascularization revealed that among 973 patients with symptomatic carotid stenosis, 96.4% underwent CEA-CABG, and post-operative stroke occurred in 14.2%. Only 25 patients with symptomatic carotid stenosis in this series underwent CAS-CABG, and the post-operative stroke rate was 44%. As expected, this reported event rate after CEA-CABG (14.1%) for the symptomatic subpopulation is higher than for the above-mentioned group of mainly asymptomatic patients.[2,6,7] However, the 5-fold increased risk of post-operative stroke (44%) for the CASCABG approach compared with those undergoing CEA-CABG (odds ratio: 4.7; 95% CI: 2.1 to 10.6; p < 001) is striking. Given the small number of patients undergoing CAS-CABG, this comparison should be interpreted cautiously. In contrast to these findings, we report a favorable 30-day all-stroke rate of 8.8% and a combined risk for death, all strokes, and MI of 12.3% for the CAS-CABG approach. One possible explanation for the lower periprocedural combined risk in the present study compared with the Timaran data may be related to the fact that patients underwent cardiac surgery without discontinuation of aspirin, whereas clopidogrel was administered until 7 days before the operations. The balance between the optimal antiplatelet therapy required for CAS and not postponing CABG seems to influence this outcome favorably.[16]

Furthermore, the high volume of CAS procedures in our center could account for these favorable short-term results of the combined procedure. The low periprocedural MI rate of 1.5% emphasizes the reduced invasiveness of this approach, which is especially important for these high-risk patients. No statistical difference was found when these CAS results before CABG are compared with the cumulative incidence of the primary endpoint at 30 days in the SAPPHIRE trial for the symptomatic patients (8.8% vs. 2.1% SAPPHIRE CAS, p= 0.212 and 9.3% SAPPHIRE CEA, p= 0.18). The long-term follow-up showed a survival rate of 63.7% with a significantly higher all-cause mortality rate and all-death, stroke, and MI rate for patients 75 years. We report a

12.3% stroke rate at 3 years, which was not statistically different from the subgroup analyses for symptomatic patients in the SAPPHIRE study (12.3% [7 of 57 patients] vs. 6.0% [3 of 50 patients] in the SAPPHIRE CAS group (p= 0.331) and vs. 8.7% [4 of 46 patients] in the SAPPHIRE CEA group, p= 0.751), taking into account that in our study, all patients underwent CABG, whereas in the SAPPHIRE population, only a minority had coexisting severe coronary artery disease.[9,10] Whether or not the 3% rule for isolated CEA can be achieved in such a high-risk population remains uncertain. However, undertaking a CAS procedure with a ≤ 3% complication rate in asymptomatic patients and < 6% in symptomatic patients should remain the goal of all interventionists.[17,18] Patients with recent onset neurological symptoms may pose an additional problem. They face the highest risk of stroke in the first few weeks of the index event, and CAS or CEA may have to be performed with the acceptance that the procedural risk will be higher.[19] Delaying the intervention might reduce the procedural risk, but it lessens the benefit of intervening because of the number of strokes that occur while waiting.

Finally, we conducted both crude and propensity score–adjusted comparisons for the periprocedural outcome between this patient group and the asymptomatic population planned for CABG in our center. When analyzing the baseline clinical patient characteristics from this study and the asymptomatic population, we found clinically comparable groups (Table 4). The periprocedural outcome for both groups is shown in Table 5. The stroke rate, as expected, is lower for the asymptomatic patients (3.1% vs. 8.8%, p=0.05). A short-term propensity score weighting was not applicable due to a low periprocedural event rate. To adjust long-term survival for symptomatic versus asymptomatic patients for differences in baseline characteristics, we used propensity score–weighted Cox proportional hazards modeling. Long-term survival depends on being symptomatic or not. The crude hazard ratio for death is 1.62 (95% CI: 0.94 to 2.77) on average for the first 5 years after CABG for symptomatic patients versus asymptomatic patients. After propensity score–weighting (accounting for sex, age, hypertension, diabetes, smoking, hypercholesterolemia, prior valve disease, prior MI, prior congestive heart failure, and prior CEA), the adjusted hazard ratio is 1.65 (95% CI: 1.17 to 2.33). Therefore, symptomatic patients have worse longterm survival with a hazard ratio of 1.65, which cannot be explained by difference in baseline characteristics.

Table 4. Single-Center Baseline Clinical Patient Characteristics for Symptomatic and Asymptomatic Patients Planned for CAS-CABG

	Asymptomatic Patients n = 356	Symptomatic Patients n = 57	p Value
Age, yrs, mean SD	72.97±7.7	69.7±8.4	0.01
Female	104 (28.6)	19 (33.3)	0.53
Hypertension	164 (45.1)	36 (62)	0.02
Diabetes mellitus	81 (22.2)	8(14)	0.17
Hypercholesterolemia	157 (43.1)	31 (54.4)	0.15
Smoking	72 (19.8)	11 (19.3)	0.99
History of neurological symptoms	58 (15.9)		
Previous MI	177 (32.1)	16 (28.1)	0.54
Valvular heart disease	88 (24.2)	14 (24.6)	0.99
Congestive heart failure	46 (12.6)	3 (5.4)	0.12
Unstable angina pectoris	141 (38.8)	21 (36.8)	0.77
Previous CABG	47 (12.9)	8 (14)	0.83
Previous PTCA	47 (12.9)	7 (12.3)	0.99
Previous carotid angioplasty	7 (1.9)		
Previous CEA	16 (4.4)	1 (1.8)	0.49

Data are n (%) unless otherwise indicated.
CAS = carotid artery stenting; PTC Apercutaneous transluminal coronary angioplasty; other abbreviations as in Tables 1 and 2.

Table 5. Comparison of 30-Day Outcome Between Symptomatic and Asymptomatic Patients Undergoing CAS and CABG at St.-Antonius Hospital

	Asymptomatic CAS-CABG (n = 356)	Symptomatic CAS-CABG (n = 57)	p Value
Death	13 (3.6)	1 (1.7)	0.70
Stroke	11 (3.1)	5 (8.8)	0.05
MI	7 (2)	1 (1.7)	0.99

Data presented as n (%).
Abbreviations as in Tables 1, 2, and 4.

Study limitations

Only 4 patients underwent off-pump CABG. Therefore, a meaningful comparison with onpump CABG or CEA–off-pump CABG could not be made.[20] Analyzing the latest natural history data, it becomes clear that about 40% of all strokes occur within the first 24 h after the index event. Therefore, a much earlier carotid intervention should be planned after symptoms.[21] Current guideline documents from the American Heart Association/American Stroke Association recommend surgery within 2 weeks of symptom onset.[22] These assumptions were not taken into account in our institution until recently. It might also be expected that the periprocedural CAS complication rates will rise when intervening in an earlier phase. When interpreting the data from Timaran et al.[15], one should take into account the ascertainment bias in the NIS database for strokes after CAS. In the United States, reimbursement for CAS depends on being enrolled in a study. Therefore, all patients are carefully examined before and after therapy by a neurologist. Very few CEA patients are examined by an independent neurologist. Thus, the reporting may not be equal and could make CAS look worse than CEA.

Conclusions

We report the outcome of CAS-CABG in symptomatic patients. The periprocedural complication rate and long-term results of the CAS-CABG strategy in this high-risk population support the reliability of this approach. In such a high-risk population, this strategy might offer a valuable alternative to the combined surgical approach; however, a large randomized trial is clearly warranted.

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Chapter 4.2

Editorial comment Carotid artery stenting before cardiac surgery: a promising path down a muddy road?

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The management of synchronous carotid disease and coronary or valvular disease requiring surgical repair has been a constant challenge to clinicians for decades and for a variety of reasons. First, although it is a vexing problem, it is relatively infrequent, such that any single institution/operator experience in management will always be clouded by "the last case I did" syndrome, more reflective than definitive. Second, even in patients without carotid stenosis, the risk of stroke inherent in cardiac surgery from other sources (atheroembolic from aortic manipulation, air emboli, and so on) clouds the assessment of the neurological "natural" history of the unoperated carotid stenosis in this setting. However, it seems clear enough that the patient with symptomatic carotid disease is at most risk and requires further management consideration, but that most asymptomatic patients with unilateral disease can withstand a cardiac operation with little increase in overall stroke risk and, therefore, should not be subjected to carotid revascularization risks.[2] Next, the published database that generally helps guide such decisions in practice comprises largely single-center reports, and usually retrospectively analyzed. A recent Cochrane attempt to review all the published randomized data on the subject could not be completed, because there were no such studies in existence.[3] Further complicating matters, the therapeutic approaches are multiple—carotid endarterectomy (CEA) can be done either before, after, or combined with cardiac surgery, which might be on- or off-pump and this further dilutes an already shallow pool of data. And lastly, the data that are available are of mixed quality with regard to ascertainment of important clinical events (always an issue in retrospective assessments), selection of patients for any given approach (such bias is inherent in the practice of medicine absent the "guidance" of an investigational protocol), and almost uniformly lack a control group (even nonrandomized).

Into this tar pit wades the relative newcomer on the block, carotid artery stenting (CAS). The appeal of CAS as an alternative to CEA is obvious in patients with cardiac disease: the lack of anesthesia and physiological surgical "stress" in an obviously vulnerable population, often with multiple comorbidities and organ involvement. In support of this speculative advantage, periprocedural outcomes from the randomized SAPPHIRE (Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy) trial in symptomatic high surgical risk patients trended better in CAS compared with CEA, 2.1% versus 9.3% ($p = 0.18$).[4] In addition, the recent National Institutes of Health CREST (Carotid Revascularization Endarterectomy versus Stenting Trial) randomized trial results, representing standard surgical risk

patients enrolled from 2000 to 2008, demonstrated no differences between CEA and CAS in 1,321 symptomatic patients for the primary endpoint of death, stroke, and myocardial infarction (MI), 5.4 ± 0.9% versus 6.7 ± 1.0% (p= 0. 57), respectively.[5]

On this encouraging background, in this issue of JACC: Cardiovascular Interventions, Van der Heyden et al.[6] report the outcomes of patients with strictly symptomatic carotid stenosis requiring cardiac surgery, the first prospective study to singularly address the critical group in question. We must be mindful that, although it spanned 10 years, it is nevertheless a small study and therefore subject to the statistical vagaries that can confound results, so conclusions drawn should be appropriately circumspect. Consecutive patient outcomes were prospectively gathered from 1998 to 2008 in this single-arm study at an expert high-volume center, and both MIs and strokes appear to be appropriately ascertained. An embolic protection device (EPD) was used when available after 2002, but representative of only one half of the treated population-important because metaanalyses have suggested that stroke outcomes are likely better with EPD use in CAS, although no large-scale randomized data exist.[7] Specific to this analysis was the helpful reporting of events temporally and specifically related either to the CAS or to the cardiac surgery, most of which was done on-pump. Employing CAS, the authors demonstrated a remarkably low rate (1.5%) of MI in this group of patients with high-risk coronary anatomy and an acceptable rate of stroke (7.0%), all of which were minor (and 1 of which was contralateral, presumably due to aortic arch source during access attempts). There were only 2 additional events occurring after surgery—a death and a major stroke—for a combined rate of death, stroke, and myocardial infarction of 12.3%. Not surprisingly, the 5-year morbidity and mortality in this group was substantial, most of it vascular, and worse in elderly patients.

Do these results reflect the current outcomes expected from high-surgical-risk populations undergoing CAS? A fair question, because results in the United States for CAS have shown a dramatic improvement over the past decade, and complications have more than halved since the initial SAPPHIRE[4] and ARCHeR (ACCULINK for Revascularization of Carotids in High Risk Patients) studies.[8] The death and stroke rate of 7.0% reported here is higher than the 2 most recent and largest prospective multicenter experiences with CAS in symptomatic patients: the combined CAPTURE 2 (Carotid ACCULINK/ACCUNET Post-approval Trial to Uncover Rare Events)/EXACT (Emboshield and Xact Post Approval Carotid Stent Trial) single-arm study outcomes in high surgical risk patients, and the CREST study in standard surgical risk patients,

which were 5.7% and 6.0%, respectively. This might be related to the lack of EPD in the first one-half of the patients, an evolving technique over 10 years in a novel therapy, and the small numbers of subjects (i.e., 1 less stroke event and the rate becomes more contemporary). To the positive, all CAS-related strokes were minor, and it has been observed that most of these will resolve significantly and leave little if any residual neurological deficit.[9,10]

That proviso aside, some answers to important questions might be forthcoming after considering this well-collected and clinically relevant data in the clinical management of the patient with symptomatic carotid disease requiring cardiac surgery. Is CAS better than no carotid intervention at all (i.e., have we satisfied Bacon's imperative to have "altered for the better designedly?"). What is the relative value of CAS versus CEA in the management of these patients? Before making any comparison of these data with historical unoperated or CEA outcomes, 2 important caveats must be considered. First, there are very limited data with regard to prophylactic CEA in a purely symptomatic population, and to compare mixed populations that include significant numbers of asymptomatic patients is not a sound approach, because results would be expected to differ between these populations. Second, most prior studies have not been as vigilant about ascertaining related events as Van der Heyden et al.[6], specifically assessing with neurological evaluation before and after the procedures or documenting MI by prospectively checking enzyme and electrocardiograms. It has been amply demonstrated that the prospective evaluation of stroke in patients undergoing isolated CEA results in the trebling of strokes reported, mostly by picking up the minor strokes that otherwise go unnoticed by operators.[11,12] Furthermore, the distinction between major and minor stroke has not typically been made in prior published reports on the subject. It is noteworthy that in the present study there was only 1 major stroke (after cardiac surgery), making the combined major stroke rate and death approximately 1.8% and comparing exceptionally well to the rate of 14.2% in historical/retrospective data, which presumably reported primarily major strokes.[13] It has also been recently shown that CEA and CAS perioperative MI is a predictor of long-term mortality, regardless of size of the event[10], so that this is an important but generally undercounted/reported outcome. With regard to the outcomes with staged CAS and cardiac surgery seen here, they do in fact seem to be at least comparable to the stroke rate of 8.5% in unoperated symptomatic carotid disease undergoing cardiac surgery and to the rate of death and stroke in staged CEA and cardiac surgery, both of which might be underestimated for the reasons given previously.[14,15]

It is tempting to suggest that CAS might be the preferred treatment in these cases, given the previously enumerated problems in comparisons with historical CEA outcomes, with the observed improvements in CAS outcomes over time and with routine EPD availability, and with the lack of associated major stroke in CAS. However, lacking a direct randomized comparison and given the difficult-to-compare historical data, it is not possible to make any definitive statements about the relative merits of 1 approach over the other. On the basis of the results reported by Van der Heyden et al.[6], we can conclude that a well-performed CAS by experienced operators is likely to be at least on par with CEA as a staged pre-treatment strategy and likely better than nothing at all, for managing symptomatic patients with carotid disease undergoing cardiac surgery. Perhaps even Bacon would be satisfied.

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PART IV

Cerebral perfusion

Chapter 5

CT measurement of changes in cerebral perfusion in patients with asymptomatic carotid artery stenosis undergoing carotid stenting prior to cardiac surgery: "Proof of Principle"

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Aims: To identify asymptomatic patients with impaired cerebral perfusion using CT perfusion (CTP) technique during staged carotid stenting (CAS) and cardiac surgery.

Methods and Results: This is a prospective, non-randomized study in 16 neurologically asymptomatic patients designed to analyse cerebral perfusion using CTP before and after CAS. Mean transit time (MTT) was significant lower and cerebral blood flow (CBF) was significantly higher in the non-target hemisphere compared to the target hemisphere before treatment (4.64 ± 1.08 s vs 5.67 ± 1.29 and 57.37 ± 24.90 s vs 48.19 ± 13.02 respectively). Mean dMTT (absolute difference in MTT values between treated and untreated hemisphere) decreased from 0.92 ± 1.08s before to 0.04 ±0.30s after carotid revascularization ($p<0.05$) and mean relative CBF (ratios of the treated to the untreated hemisphere) increased from 0.92 ± 0.12 to 1.04 ± 0.12 after revascularization ($p<0.05$). Subgroup analysis based on pre- treatment dMTT showed significant changes in 50% of the patients with larger dMTT. There was 1 transient ischemic attack reported 30 days after combined procedure.

Conclusion: A significant improvement of cerebral perfusion after carotid stenting is shown in about 50% of the asymptomatic patients in this study. This suggests the potential presence of a compromised cerebral circulation in asymptomatic patients with severe carotid artery disease scheduled for cardiac surgery.

Introduction

The management of concomitant severe carotid and coronary artery disease is controversial. The incidence of perioperative stroke during cardiac surgery is 2%, however in the presence of severe carotid disease a fourfold increased risk has been described.[1,2] The initial studies of combined or staged carotid endarterectomy (CEA) in these patients were conceived in an attempt to reduce perioperative morbidity and mortality. In the presence of concurrent carotid and coronary artery disease, carotid stenting (CAS) now offers an alternate means of carotid revascularization and seems to pose less risk of myocardial ischemia than CEA.

Evidence suggests that hypoperfusion due to a severely stenotic carotid artery or micro-embolisation from an ulcerative plaque form part of the different mechanisms for peri-operative neurological events during open heart surgery.[3,4] Hypotension induced ischaemic neurological injury during cardiopulmonary bypass is hard to avoid in patients with severe carotid stenosis. During cardiopulmonary bypass cerebral autoregulation is severely impaired, making cerebral blood flow directly proportional to cerebral perfusion pressure.[5] This finding provided a logical reason for carotid revascularization prior to or in combination with cardiac surgery.

In patients with isolated carotid disease, hemodynamic factors have long been associated with the symptomatic status of stenosis.[6] Also, the importance of cerebral hemodynamics in association with the risk of stroke in patients with severe carotid stenosis (CS) and occlusion has been described.[7-10] In asymptomatic subjects with severe CS however, little or no proof of the above is available. Only a paucity of literature is available elucidating the hemodynamics in asymptomatic patients with CS undergoing cardiac surgery.[6] It has been published recently, that CT perfusion (CTP) technique is able to show impairment of cerebral perfusion in a subgroup of patients with unilateral symptomatic carotid artery stenosis.[11] This study concluded that relative pre-treatment CT perfusion values can identify symptomatic patients in whom carotid revascularization would most likely lead to an improvement in cerebral hemodynamics after treatment.

We hypothesized that in asymptomatic patients CTP analysis before CAS can be used to allow identification of those patients who benefit the most of carotid revascularization through protection against hemodynamic changes during cardiopulmonary bypass.

Methods

Patients

We analysed 56 consecutive patients planned for CAS and cardiac surgery from may 2005 to October 2009 at our centre in a prospective, non-randomized study. Patients were considered asymptomatic if an ipsilateral cerebrovascular event had not occurred 4 months prior to cardiac surgery. Significant carotid artery stenosis was defined as a luminal diameter reduction of more than 80%, according to NASCET criteria.[12,13] The indications for cardiac surgery included symptomatic (documented myocardial ischemia) severe coronary artery disease (including bypass failure) not eligible for percutaneous revascularization, symptomatic valve disease and disease (aneurysm/dissection) of the ascending aorta or arch requiring reconstructive surgery, following institutional guidelines.[14,15]. We included patients with bilateral carotid atherosclerosis, patients who agreed undergoing CTP before and after CAS and patients without contraindication for CT scan. Patients were excluded if they had severe renal impairment (eGFR < 35 ml/min), peripheral vascular disease that precluded femoral artery access, major neurological deficit, or any other illness that impeded their ability to provide informed consent. Patients with severe diffuse atherosclerosis of the common carotid artery, chronic total occlusions, and long preocclusive lesions ("string sign" lesions) were also excluded. Sixteen patients met the inclusion criteria for the current study. All patients were scanned within 3 days prior to the treatment and the majority one month after stent placement. The degree of stenosis in the treated carotid artery (target) was assessed before revascularization and at one month follow-up in all patients using duplex ultrasound. The study was approved by the medical ethics committee of our hospital and written informed consent was obtained from all patients.

End-point Definition

Primary endpoint were absolute and relative measurements of cerebral blood volume (CBV), cerebral blood flow (CBF) and mean transit time (MTT), comparing CT perfusion parameters of both hemispheres before and after revascularization.

Secondary endpoints were the incidence of death, stroke or myocardial infarction (MI) at 6 months after the CAS and cardiac surgery.

CT perfusion scanning

Dynamic CTP source images were acquired using a 16-detector-row scanner (MX8000 IDT, Philips Medical Systems, Cleveland, OH). A bolus injection of 40 ml contrast with an iodine concentration of 300 mg I/ml (Ultravist 300, Schering AG, Berlin, Germany) was administered at 5 ml/s followed by a 40 ml-saline chaser bolus at 5 ml/s using a power injector with a dual head system (Stellant Dual CT injector, Medrad Europe BV, Beek, The Netherlands) for all perfusion scans. CTP data were transferred to a post-processing workstation (Philips Medical Systems, Best, the Netherlands) on which CBV, MTT, and CBF were calculated. Time-enhancement curves derived from contrast passage through the anterior cerebral artery and the superior sagittal sinus provided the arterial input function (AIF) and venous output function (VOF) respectively. For AIF, an operator placed a region of interest (ROI) over the both anterior cerebral arteries at each slab. Hereafter the computer selected the optimum curve, based on height of the peak and the size of the area under the curve. The same was done for VOF within the superior sagittal sinus. Visual inspection was always performed to assure that the complete AIF and at least three points of the down slope of the VOF were included. The CBV was calculated as the ratio of the area under the time concentration curve of the first bolus passage through the tissue to that of the area under the curve of the VOF. The MTT, the average time required by the blood to cross the capillary network, was calculated by a deconvolution operation.[16] According to the central volume principle, CBF was calculated from measured CBV and MTT values: CBF = CBV/ MTT.[17] This method has shown to be most accurate at lower injection rates.[18,19] The same operator always chose AIF and VOF, visually controlled the curves, and performed the subsequent post-processing of the ROIs for quantitative measurements. Imaging protocol and post-processing have been extensively described in a previous manuscript.[11]

CAS procedure and Subsequent Cardiac Surgery

Carotid stenting was performed following the highest standard of care using a distal embolic protection device. Cardiac surgery (including coronary artery bypass, valve or reconstructive surgery of the ascending aorta) was scheduled 4 weeks after CAS, unless clinical instability required earlier intervention. This in accordance with our institutional policy of staged strategy, which has been described earlier.[14] Patients were examined by a neurologist prior to CAS and before discharge.

Data Collection and Patient Follow-Up

Telephonic follow-up interviews were conducted at 1 month and thereafter 6 monthly intervals by a dedicated full time research coordinator. In case of an event, hospital notes or death certificate were consulted when possible. An independent board-certified neurologist graded symptoms according to functional testing using the modified Rankin score if a cerebrovascular event occurred.[20]

Statistical Analysis

CT perfusion analysis provides absolute perfusion data for each pixel in the target and non-target hemispheres; CBV expressed as ml/100 g tissue, MTT expressed in seconds and CBF expressed in ml/100 g tissue/min. We chose to include relative perfusion data in our analysis by normalizing measured values in the target hemisphere to those in the non-target hemisphere because brain perfusion measurements are subject to high inter-subject variation and influenced by physiologic stimuli.[21,22] As a relative measure for MTT we chose the absolute difference in MTT values between the target and the non-target hemisphere (dMTT) because MTT itself is derived from the difference between the width of the curves (AIF and voxel of interest). The ratios of target to non-target hemisphere were calculated for relative CBF (rCBF) and relative CBV (rCBV) because these parameters are derived from the ratio of the areas under the attenuation curves (VOF and voxel of interest). The mean of measurements in the two evaluated slabs was calculated for both absolute and relative data for each CTP scan.

We first analyzed the total group of patients and compared absolute pre- and post treatment values and target versus non-target hemispheres using a paired t-test. Subsequently, we analyzed the relative data and compared pre- and post treatment dMTT, rCBF and rCBV. Finally, we split our study population into two equal groups based on the baseline dMTT: in group 1 we analysed 8 patients with lower dMTT, in group 2 8 patients with higher dMTT. The MTT was chosen because it is least affected by the differences between grey and white matter and because it has shown to be significantly correlated with cerebral perfusion pressure (CPP) and is therefore considered to be a sensitive index of CPP.[23-25] Pre-treatment and post-treatment values for rCBV, dMTT and rCBF were compared using the Wilcoxon signed ranks test in each group. Statistical analysis was performed using statistical package SPSS version 15.0. A p-value <0.05 was considered statistically significant.

Results

Patient Characteristics

The baseline clinical characteristics of all patients are shown in Table 1. No patient had undergone a previous carotid endarterectomy or carotid angioplasty or stenting. Adequate stent-apposition without hemodynamic significant (re)stenosis or stent thrombosis was seen in all patients on control duplex examination. Mean arterial blood pressure during pre- and post-treatment CT was not statistically significant. In the majority of patients the post-treatment CT was performed before cardiac surgery. Pre- and post-treatment CT were performed in 16 patients.

Table 1. Baseline Clinical Patient Characteristics

	Patients n=16
Age (mean ± SD),y	72.9±7.7
Female, n (%)	2 (12.5)
Hypertesion, n (%)	15 (93.7)
Diabetes Mellitus, n (%)	4 (25)
Hypercholesterolemia, n (%)	15 (93.7)
Smoking, n (%)	6 (37.5)
Previous myocardial infarction, n (%)	4 (25)
Previous CABG, n (%)	2 (12.5)
Previous PTCA, n (%)	7 (43.7)
Renal failure (creatinine 120-300 μmol/l), n (%)	1 (6.2)
Mean carotid stenosis stented side (%), range	89,5 (75,99)
Mean carotid stenosis other side, range	50 (30,55)
Left side stented, n (%)	9 (56)

Angiographic/Stenting and Cardiac Surgery Results

One patient reported a transient ischemic attack (TIA) following CAS. None of the included patients had symptoms between pre- and post-treatment CT. The mean angiographic degree of stenosis was reduced from 89,5% ± 5% (before stenting) to 5% ± 9%. In all patients the same type of stent (Acculink, Abbott) was implanted successfully, using only one type of distal protection device (Emboshield filter, Abbott). The mean time interval to cardiac surgery after CAS was 24 days, with

a range of 1 day to 3 months. In 4 patients coronary artery bypass grafting was combined with valve replacement. There was no minor or major stroke or myocardial infarction reported within 30 days of the combined procedure. One patient died of documented pneumonia 1 month after cardiac surgery.

Perfusion Parameters

Absolute Perfusion Parameters

When comparing CT perfusion parameters of both hemispheres before and after revascularization, we found a significant lower MTT and higher CBF in the non-target hemisphere compared to the target hemisphere before treatment (4.64 ± 1.08 s vs 5.67 ± 1.29 and 57.37 ± 24.90 s vs 48.19 ± 13.02 respectively). There were no significant changes after revascularization in both hemispheres (Table 2).

Table 2. Comparison of absolute values in pre- and post-treatment CT perfusion data for the target and non-target hemisphere

Absolute data			
	CBV (ml/100 g) mean±SD	**CBF (ml/100g/min mean±SD**	**MTT (s) mean±SD**
Non-target hemisphere, before treatment	4.06±0.84	57.37±24.90*	4.64±1.08*
Non-target hemisphere, after treatment	3.99±0,71	48.98±15.01	5.04±1.10
Target hemisphere, before treatment	4.38±0,98	48.19±13,02*	5.67±1,29*
Target hemisphere, after treatment	4,03±0,60	47,74±12,83	5,00±0,88

* before treatment: significant difference between ipsilateral and contralateral hemisphere ($p<0.05$)

Relative Perfusion Parameters

The mean dMTT decreased from 0.92 ± 1.08s before to 0.04 ± 0.30s after carotid revascularization ($p<0.05$) and mean rCBF increased from 0.92 ± 0.12 to 1.04 ± 0.12 after revascularization ($p<0.05$). The rCBV did not change significantly (Table 3 and Figure 1).

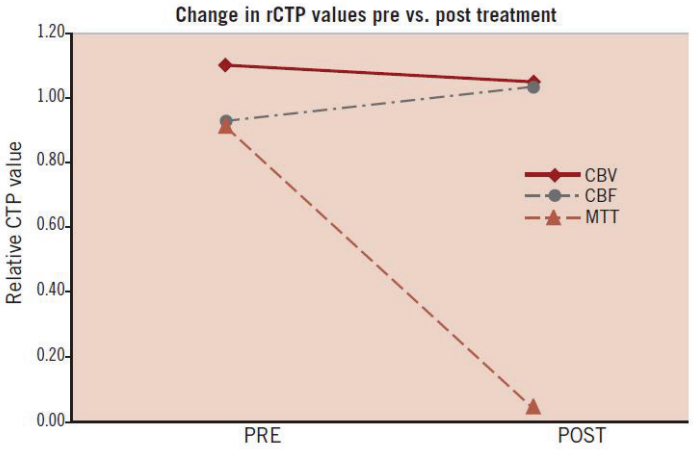

Figure 1. Changes in relative cerebral perfusion values before/after carotid artery stenting.

Table 3. Relative perfusion values before and after treatment

Relative data			
	rCBV (ml/100 g) mean±SD	**rCBF (ml/100g/min mean±SD**	**dMTT (s) mean±SD**
Before treatment	1.10±0.14	0.92±0.12*	0.92±1.08*
After treatment	1.05±0.11	1.04±0.12*	0,04±0.30*

* before treatment: significant difference between ipsilateral and contralateral hemisphere ($p<0.05$)

Subgroup Analysis based on dMTT

In the first 8 patients baseline dMTT was <0.7s, in the second half baseline dMTT was >0.7s. The effect of carotid revascularization on cerebral perfusion parameters was dependent on the baseline dMTT (Table 4). In the 8 patients of group 1, no significant change in any of the relative CT perfusion values was detected. In the patients of group 2, mean dMTT decreased from 1.67 ± 1.06s to -0.03 ± 0.33s s ($p<0.05$) and rCBF increased from 0.86 ± 0.09 to 1.1 ± 0.14 ($p<0.05$) but no significant changes in rCBV occurred (Figure 2).

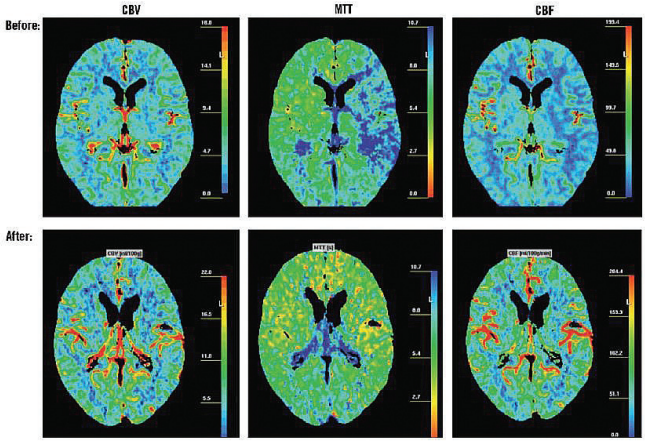

Figure 2. An illustration of CT perfusion images: the mean transit time (MTT), cerebral blood volume (CBV), and cerebral blood flow (CBF) maps are shown before and after CS.

Table 4. Comparison of relative CTP perfusion paramaters for groups based on pre-treatment dMTT (group 1, dMTT<0.7s, group 2 dMTT>0.7s). Significance of difference between relative perfusion parameters and after treatment was tested using the Wilcoxon signed ranks test.

	Group 1 n=8 mean± SD	***p-value***	**Group 2 n=8 mean ± SD**	***p-value***
rCBV				
Pre-treatment	1.03±0.10		1.18±0.13	
Post-treatment	1.02±0.09	*0.888*	1.08±0.13	*0.075*
dMTT				
Pre-treatment	0.17±0.29		1.67±1.06	
Post-treatment	0.11±0.27	*0.933*	-0.03±0.33	***<0.05***
rCBF				
Pre-treatment	0.99±0.11		0.86±0.09	
Post-treatment	0.99±0.06	*0.674*	1.10±0.14	***<0.05***

Discussion

It is well recognized that there are a number of potential etiologies for perioperative stroke in the cardiac surgical patient, including embolization of atherosclerotic debris or thrombus from the aortic cannulation site, air embolus, left ventricular thrombus, aortic dissection, low cardiac output, and intracerebral disease, in addition to extracranial significant carotid artery disease. While clinically significant carotid disease may be responsible for only a minority of perioperative strokes in this patient population, it is the one etiology that can be identified preoperatively and noninvasively and can be prevented by timely intervention.[26]

The importance of hemodynamic factors in the pathogenesis and treatment of ischemic cerebrovascular disease in patients undergoing cardiac surgery is a matter of ongoing debate. Stratifying patients based on the degree of CS fails to differentiate those with reduced cerebral perfusion pressure from those with non-compromised cerebral hemodynamics. Moreover, it seems hazardous to use the degree of CS to decide whether a patient may be at increased risk for stroke on hemodynamic grounds. This implies that choice of medical therapy or revascularization should not be based on these considerations. It has been established that the effect of CS on cerebral circulation could be more accurately assessed by analysis of arteriographic circulation patterns, depicting the adequacy of collateral circulatory pathways and patterns.[27] It remains to be determined whether the patients with true cerebral circulatory compromise are at an increased risk for stroke, either spontaneously or during cardiopulmonary bypass. Among others, thrombo-embolization plays a role in the origin of perioperative stroke in patients undergoing cardiac surgery. However, it seems likely that the effects of thrombo-embolic particles are influenced by the presence of perfusion deficits.[28]

The increasing number of endovascular procedures for the treatment of CS performed during the last decade has intensified the need for monitoring the outcome of these procedure. The semi-quantitative evaluation of cerebral perfusion makes it a reliable tool for the follow-up of patients who undergo CAS. CTP before and after CAS has shown to allow for assessment of pre-treatment interhemispheric differences, which may or may not resolve after treatment.

The first finding of this study is that there is significant improvement of cerebral perfusion after carotid stenting even in this selected group of asymptomatic patients. This suggests the presence of a compromised cerebral circulation due to

carotid stenosis, even though these patients have never been aware of this. The second finding is, that not all patients have shown such an improvement. Based on pre-treatment dMTT, in about 50% of the patients improvement is seen, while in the others no significant reduction of mean transit time or any other perfusion parameter was observed.

Gaudiello et al. demonstrated that the normalization of the perfusion parameters occurs in all patients as soon as 1 week after the stent-placement procedure.[29]

A recent study published by Trojanowska et al. showed a trend toward hemodynamic normalization at 3 days poststenting but an incomplete normalization in a small percentage of patients at 6 months.[30] The selection of patients, the interventional procedure performed, and the volume of study could all account for the differences. Most interesting, Sanchez-Arjona et al. have shown, with a different method of study, significant hemodynamic changes in the anterior brain circulation, ipsilateral to CAS at 6 hours after the procedure.[31]

The neuropsychologic consequences of an ischemic event are well known, though generally neglected because the attention of the physician is driven toward the more striking and invalidating motor deficits.[32] However, recent articles have demonstrated that even asymptomatic patients with an elevated ICA luminal narrowing show higher depression scores or reduced neuropsychologic test performances that seem to be reversed by CAS.[33-35]. Notwithstanding the fact that only an improved cerebral perfusion has been demonstrated in this study, a lesser stroke risk or improvement in neurocognitive functioning during cardiac surgery might be considered as potential benefits after CAS.

Study limitations

Although CT perfusion analysis yields absolute quantitative data, several studies have shown that values obtained with this technique are subject to physiological variations and are influenced by post-processing steps.[24,36] Some of these limitations, intrinsic to absolute perfusion values, are overcome by using relative perfusion parameters, relating the absolute perfusion data in the target hemisphere to the contralateral hemisphere. The advantage of this approach is the elimination of physiological variations and inter-patient differences in total cerebral perfusion but the disadvantage is that results will be more difficult to interpret when significant

stenoses are present in both carotid arteries. Also, the presence of a carotid stenosis influences the AIF and may result in overestimation of absolute MTT and underestimation of absolute CBF. However, the use of relative data largely eliminates these effects.[11]

Secondly, we did not compare CT perfusion values to a reference standard such as PET or Xe-CT. However, previous studies have already shown that CBF measured with CT perfusion correlates well tot these established techniques.[18]

Third, we did not evaluate the effects of the configuration of the circle of Willis nor the presence of (irregular) plaques, because for such a multi-factorial analysis much more patients are needed and the purpose of this study was to evaluate whether it is possible to discriminate patients with different response to carotid intervention based on cerebral perfusion at baseline.

Fourth, some patients had cardiac surgery before the post-treatment perfusion scan, which may have influenced cerebral perfusion pressure. How much this pressure is influenced in patients with compromised cerebral autoregulation remains unclear, but is not inconceivable.

Conclusion

The management of concomitant severe carotid and coronary artery disease is controversial. Limited data are available on cerebral hemodynamics in association with the risk of stroke in asymptomatic patients with severe carotid stenosis undergoing cardiac surgery. Using CT perfusion technique, more specifically the mean transit time, a significant improvement of cerebral perfusion after carotid stenting is shown in about 50% of the asymptomatic patients in this study. This suggests the presence of a compromised cerebral circulation due to carotid stenosis, even though these patients are asymptomatic. The impaired perfusion observed in this patient population can be reversed. CAS prior to cardiac surgery might thereby positively influence the reduced neuropsychological functioning which has been described in asymptomatic patients with an elevated ICA luminal narrowing.

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Chapter 6

Effect of stenting on cerebral CT perfusion in symptomatic and asymptomatic patients with carotid artery stenosis

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Background and purpose: The introduction of CAS has led to increased treatment of both symptomatic and asymptomatic patients with internal carotid stenosis. This study was performed to compare the effect of stent placement on cerebral perfusion in symptomatic and asymptomatic patients using CT perfusion.

Materials en methods: We included 45 patients with carotid artery stenosis of 70% who underwent arterial stent placement. Thirty-one patients were treated because of symptoms; 14 symptomatic patients were treated before coronary artery bypass grafting. Patients underwent CTP before and after stent placement. We calculated MTT, CBV, and CBF, and derived relative numbers that compared treated with untreated hemispheres: ratios of CBV and CBF and difference in MTT. We compared the effect of carotid stent placement on cerebral perfusion in symptomatic and asymptomatic patients.

Results: All perfusion parameters changed significantly after treatment in symptomatic patients: rCBF increased from 0.81 to 0.93 ($P < .001$), rCBV decreased from 1.02 to 0.95 ($P < .05$), and dMTT decreased from 1.29 to 0.14 ($P < .001$). In asymptomatic patients only, rCBF changed significantly with an increase from 0.92 to 1.03 ($P < .05$). When we compared symptomatic and asymptomatic patients before treatment, rCBF in symptomatic patients was significantly lower. The decrease of rCBV after treatment in symptomatic patients resulted in a significantly lower value than in asymptomatic patients.

Conclusions: Carotid artery stent placement improves blood flow in the affected hemisphere in symptomatic and asymptomatic patients. CBF before treatment is more strongly impaired in patients with symptomatic carotid stenosis. Compensatory hyperemia on the symptomatic side before treatment (rCBV > 1) turns into hypoxemia after treatment, suggesting impaired autoregulation in these patients.

Introduction

Risk of ischemic stroke increases with the severity of stenosis in both symptomatic and asymptomatic patients with internal carotid artery stenosis.[1] The introduction of CAS as an alternative to surgery has led to a renewed search for risk factors of stroke to improve the selection of patients who would profit most from such an intervention. Several studies compared carotid plaque composition from symptomatic and asymptomatic patients to understand the underlying mechanisms.[2]

A severe carotid artery stenosis may cause reduced perfusion pressure and will, therefore, influence cerebral hemodynamics. Collateral circulation, on the other hand, can maintain normal cerebral perfusion pressure and normal flow in many patients with carotid artery stenosis.[3] In symptomatic patients with severe carotid stenosis and occlusion,[4-6] the association of cerebral hemodynamics with the risk of stroke has been described. In asymptomatic patients with severe carotid stenosis, less proof of this association is available. However, Silvestrini et al[7] showed that patients with severe asymptomatic carotid artery stenosis might be hemodynamically compromised. Furthermore, Soinne et al[8] showed that early and late CBF post-operatively are slightly higher than preoperative values in the ipsilateral and contralateral arteries in asymptomatic patients, though the differences before and after treatment were minor.

Treatment of internal carotid artery stenosis of 70% in symptomatic patients is generally accepted, but on average, 6 patients have to undergo CEA to prevent 1 stroke.[9] The benefit of treatment in asymptomatic patients is still controversial because substantially more patients need to be treated to prevent 1 stroke. The annual risk of stroke in asymptomatic patients with a stenosis of 60%–99% is estimated to be 3.2%.[10] Despite this low annual risk, several trials indicate the benefit of treatment in asymptomatic patients.[11-13]

The introduction of CAS has led to increased treatment of both symptomatic and asymptomatic patients, though the benefit of stent placement has not been proved for all indications. CTP has been used to evaluate the effect of stent placement in symptomatic patients with carotid artery stenosis of ≥ 50%, showing significant improvement of CTP parameters.[14,15] Currently, however, it is not completely clear whether perfusion will also improve in asymptomatic patients after CAS.

Therefore, in this study, we compare the effect of stent placement on cerebral perfusion in symptomatic and asymptomatic patients with internal carotid artery stenosis by using CTP analysis.

Materials and Methods

Patients

All symptomatic patients were participants of the International Carotid Stenting Study, a randomized controlled trial in which CEA and stent placement are compared in patients with a symptomatic stenosis (www.cavatas.com, ISRCTN 25337470). Patients with an asymptomatic stenosis were diagnosed and treated during the work-up for CABG. Inclusion of all patients was based on the presence of carotid artery stenosis of 65% measured on duplex or CTA according to the North American Symptomatic Carotid Endarterectomy Trial criteria, accessible for carotid stent placement (ie, tortuous anatomy proximal or distal to stenosis). Subjects had to be independent in daily life (modified Rankin Scale score of 3), with no history of previous ipsilateral CEA or radiation therapy.

Both symptomatic and asymptomatic patients were clinically evaluated by an independent neurologist before the procedure, during the procedure, and immediately afterward. The mean time from symptom onset to treatment was 44.3 days in symptomatic patients. All included patients underwent CAS. Exclusion criteria were a contralateral stenosis of 50% and the presence of contraindications for CTA, such as renal failure or contrast allergy. The degree of stenosis was measured with duplex sonography in combination with CTA for symptomatic patients. In asymptomatic patients, it was assessed by using duplex sonography. None of the patients had significant stenoses in the intracranial vasculature on CTA.

From October 2003 until April 2006, a CTP study was performed in 59 symptomatic patients who underwent CAS. Twenty-eight patients were excluded from analysis: Nineteen patients had a contralateral stenosis of 50%. Another 9 patients were excluded due to a missing pre- or post-treatment scan or technical problems with contrast administration, motion artifacts, or problems during postprocessing. Consequently, our selection process yielded 31 symptomatic patients for further analysis.

From October 2006 till January 2009, a CTP study was performed in 27 asymptomatic patients. Thirteen patients were excluded from the analysis: Six patients had a contralateral stenosis of 50% and 7 patients were excluded due to a missing pre- or post-treatment scan or technical problems with contrast administration, motion artifacts, or problems during postprocessing. Consequently, this process yielded 14 asymptomatic patients for further analysis.

In both groups, we strived for a scan within 1 week before treatment and 1 month after CAS. The medical ethics committee of the 2 hospitals participating in this study had given approval for this study. Written informed consent was obtained from all patients.

CAS Procedure

Stents and other devices used for CAS were chosen at the discretion of the interventionist but had to have a CE mark. The protocol recommended that a cerebral protection device be used, but this was not mandatory. On the basis of the degree and shape of the stenosis, it was decided whether pre- and postdilatation was required. Acombination of aspirin and clopidogrel to cover stent-placement procedures was recommended.[16]

CTP

Imaging Protocol

In both institutions, a Philips Healthcare (Best, the Netherlands) multisection CT scanner was used. CTP data were acquired at the level of the basal ganglia: 30 data sets with a cycle time of 2 seconds by using a 16-section scanner, 40-section scanner or a 64-section scanner (Philips Healthcare). The cycle time was 2 seconds, resulting in 30 images acquired during 60 seconds, which has shown to result in accurate perfusion data.[17] For an optimum signalintensity-to-noise ratio, we used a low-kilovolt(peak) technique in combination with 150 mAs.[18] For the 16-detector row scanner, we had 2.4-cm coverage (collimation 8 x 3 mm, reconstructed in two 12-mm slabs). With the introduction of 40-detector row and 64-detector row, this improved to 4-cm coverage (collimation of 32x1.25 mm, images were reconstructed in 4 adjacent slabs of 10mmor 64x0.625 mm collimation reconstructed in 8 slabs of 5 mm). For all perfusion scans, a bolus injection of 40 mL of contrast with an iodine concentration of 300 mg I/mL iopromide (Ultravist 300, Schering, Berlin, Germany) was administered at 5 mL/s, followed by a 40-mL saline chaser bolus at 5 mL/s by using a power injector with a dualhead system. The scans were obtained at the level of the basal ganglia, 3 cm above the dorsum sellae, with the scan angle set parallel to the orbitomeatal line to avoid direct radiation exposure to the eye lens. Although symptomatic and asymptomatic patients were scanned in different hospitals, imaging protocols of all scans were equal.

Data Analysis

CTP data were transferred to a postprocessing workstation (Extended Brilliance Workspace, Philips Healthcare), on which CBV, MTT, and CBF were calculated by using a deconvolution technique.[19] Postprocessing of CTP data was performed in a standardized way. The arteria cerebri anterior was used as the arterial input function; the sinus sagittalis superior was used as the venous output function. Regions of interest were drawn according to a standardized method and guided by an expert opinion for each patient individually. A vascular pixel elimination method was used to exclude vascular pixels and, therefore, avoid over- or underestimation of perfusion data. We excluded regions of prior infarction in regions of interest. To quantify changes in perfusion parameters before and after stent placement, we matched 2 slabs close to the level of the basal ganglia of the pretreatment CTP examination to 2 corresponding slabs at the same level on the post-treatment CTP examination. A region of interest corresponding to the cortical flow territory of the middle cerebral artery of both hemispheres according to the maps of Damasio[20] was manually outlined on each slab (Figure 1).

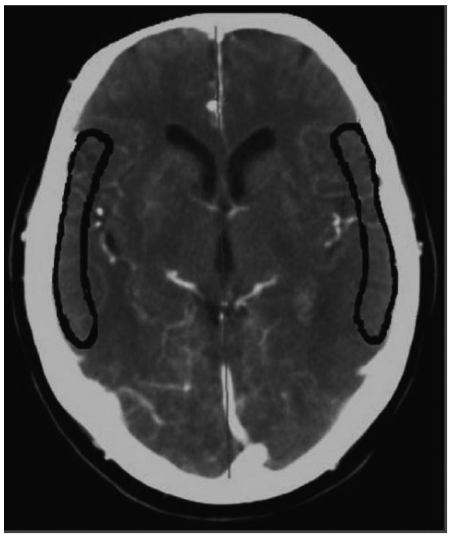

Figure 1. Manual outlining of middle cerebral artery territory on transverse CT sections, according to the maps of Damasio.[20]

The deconvolution technique used provides estimates of absolute perfusion data for each pixel in treated and untreated hemispheres; CBV expressed as milliliter/100 g tissue, MTT expressed in seconds, and CBF expressed in milliliters/100 g tissue/ min. Because absolute cerebral perfusion is known to depend also on extracerebral factors as well,[21] we chose to normalize measured values in the treated hemisphere to those in the untreated hemisphere. As a relative measure for MTT, we chose the absolute difference in MTT values between the treated and untreated hemispheres. For relative CBV and relative CBF, the ratios of the treated to the untreated hemispheres were calculated. For each CTP examination, the relative CTP data were averaged over the 2 adjacent slabs included in the evaluation. Data collection was blinded to all other clinical data. First, we analyzed symptomatic and asymptomatic patients separately, comparing relative pre- and post-treatment values by using a paired t test and the Wilcoxon signed ranks test for 2 related samples. Subsequently, we analyzed differences between symptomatic and asymptomatic patients for both pre- and post-treatment values by using the Mann-Whitney U-test for 2 independent samples. Statistical analysis was performed by using the Statistical Package for the Social Sciences, Version 15.0 (SPSS Inc, Chicago, Illinois). A P value < .05 was considered statistically significant.

Results

Finally, we analyzed 31 symptomatic and 14 asymptomatic patients with both pre- and post-treatment CTP scans. Patient characteristics are shown in Table 1.

Change of CTP after Treatment

In symptomatic patients, rCBF increased from 0.81 to 0.93 (P< .001), rCBV decreased from 1.02 to 0.95 (P< .05), and dMTT decreased from 1.29 to 0.14 (P< .001) after treatment. In asymptomatic patients, only rCBF changed significantly after treatment: It increased from 0.92 to 1.03 (P< .05). The decrease in dMTT from 0.56 to 0.06 did not reach significance (P= .081). There was no significant change in rCBV (Table 2 and Fig 2).

Table 1. Patient Characteristics (n = 45)

Patient Demographics	Symptomatic Patients (n=31)	Asymptomatic Patients (n=14)	*P* Value[a]
Age (yr) (mean) (range)	67.0 10.4 (43–82)	69.6 9.0 (56–82)	.43[b]
Male (No.) (%)	21 (67.7)	13 (92.9)	.13[c]
Carotid arteries			
Left side treated (No.) (%)	15 (48.4)	9 (64.3)	.32
Stenosis grade(%), mean SD (range)	89.5 9.4 (65–99)	88.95.8 (75–99)	.32[b]
Symptoms			
Stroke (No.) (%)	11 (35.5)	None	N.A.
TIA (No.) (%)	13 (41.9)	None	N.A.
AF (No.) (%)	7 (22.6)	None	N.A.
Interval in days			
Pretreatment CTP to treatment (mean) (range)	3.2 6.4 (0–35)	3.5 1.9 (3–10)	.03[b]
Treatment to post-treatment CTP (mean) (range)	33.9 4.8 (22–44)	71.9 82.6 (8–263)	.84[b]
Medical history			
Hypertension (No.) (%)	25 (80.6)	13 (92.9)	.41[c]
Diabetes mellitus (No.) (%)	3 (9.7)	3 (21.4)	.36[c]
Hypercholesterolemia (No.) (%)	12 (38.7)	12 (85.7)	.008
Smoking (No.) (%)	10 (32.3)	6 (42.9)	.52[c]
Previous myocardial infarction (No.) (%)	4 (12.9)	3 (21.4)	.66[c]
Previous CABG (No.) (%)	2 (6.5)	1 (7.1)	1.00[c]

Note:—N.A. indicates not applicable.
a P values analyzed with the Pearson 2 test.
b Mann-Whitney U test for 2 independent samples.
c Fisher exact test.

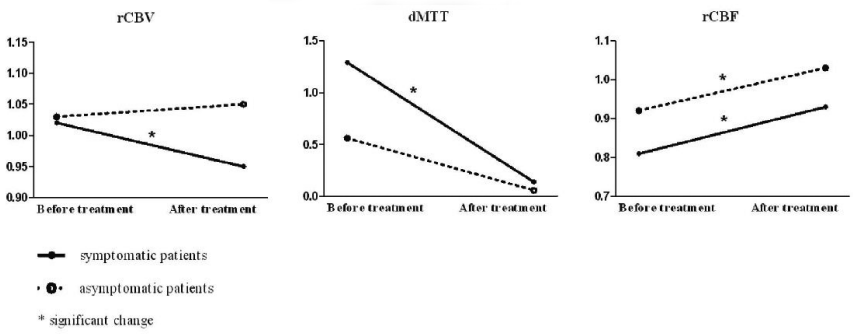

Figure 2. A-C, Relative CTP values measured before and after treatment in symptomatic and asymptomatic patients: ratio of rCBV, dMTT, and rCBF.

Table 2. Comparison of pre- and post-treatment CTP data for symptomatic and asymptomatic patients[a]

Pre- and Post Post-treatment	rCBV (ml./100 g) (mean)	P Value	dMTT (s) (mean)	P Value	rCBF (ml./100g/min) (mean)	P Value
Symptomatic patients before treatment (*n*=31)	1.02 ± 0.13		1.29 ± 1.21		0.81 ± 0.14	
Symptomatic patients after treatment (*n*=31)	0.95 ± 0.14	.036[b]	0.14 ± 1.08	<.001[b]	0.93 ± 0.17	<.001[b]
Asymptomatic patients before treatment (*n*=14)	1.03 ± 0.08		0.56 ± 0.66		0.92 ± 0.12	
Asymptomatic patients after treatment (*n*=14)	1.05 ± 0.13	.221	0.06 ± 0.55	0.081	1.03 ± 0.14	.026[b]

a The significance of the difference between relative perfusion parameters was tested using the paired-samples t test in symptomatic patients and the Wilcoxon signed ranks test in asymptomatic patients
b significant difference with a P-value < .05

Comparison of Symptomatic and Asymptomatic Patients

Before treatment, we found a significantly lower rCBF (0.81 versus 0.92, P< .005) in symptomatic patients. dMTT was almost significantly higher in symptomatic patients (1.29 versus 0.56, P= .061), and rCBV showed no significant difference before treatment. After treatment, only rCBV showed a significant difference: rCBV was significantly lower in symptomatic patients (0.95 versus 1.05, P< .005). The difference in dMTT was not significant (0.14 versus 0.06, P= .57), while rCBF was almost significantly lower in symptomatic patients (0.93 versus 1.03, P= .056) (Table 3).

Table 3. Comparison between symptomatic and asymptomatic patients in pre- and post-treatment values[a]

Pre- and Post Post-treatment	rCBV (ml./100 g) (mean)	p Value	dMTT (s) (mean)	p Value	rCBF (ml./100g/min) (mean)	P Value
Symptomatic patients before treatment (*n*=31)	1.02 ± 0.13		1.29 ± 1.21		0.81 ± 0.14	
Symptomatic patients after treatment (*n*=31)	1.03 ± 0.08	.902	0.56 ± 0,66	0.61	0.92 ± 0.12	.009[b]
Asymptomatic patients before treatment (*n*=14)	0.95 ± 0.14		0.14 ± 1.08		0.93 ± 0.17	
Asymptomatic patients after treatment (*n*=14)	1.05 ± 0.13	.009[b]	0.06 ± 0.55	.573	1.03 ± 0.14	.056

a The significance of the difference between relative perfusion parameters was tested using the Mann-Whitney U test.
b Significant difference with P-value < .05

Discussion

The purpose of this study was to compare how cerebral perfusion is affected by CAS in patients with symptomatic and asymptomatic carotid artery stenosis. First, our results showed a significant improvement after CAS of all 3 perfusion parameters in symptomatic patients, while in asymptomatic, patients only rCBF showed a significant increase. So despite the small number of patients in our study, both symptomatic and asymptomatic patients showed significant improvement of cerebral perfusion parameters after stent placement (Figure 3).

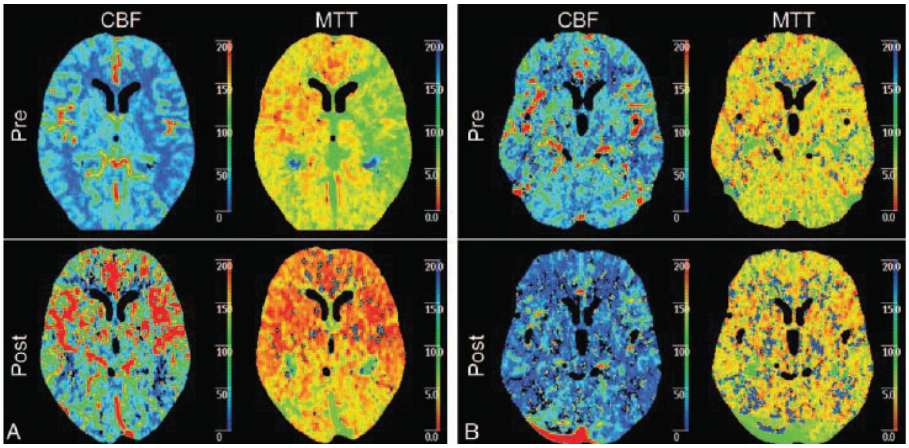

Fig 3. A, Example of an symptomatic patient with a left-sided carotid artery stenosis of 99%. Before treatment, CBF and MTT show explicit differences between the right and left hemispheres with a higher CBF and a higher MTT in the right hemisphere in comparison with the left hemisphere. After CAS, both CBF and MTT show a symmetric pattern of perfusion.
B, An example of an asymptomatic patient with a left-sided carotid artery stenosis of 95%. Before treatment, CBF and MTT show differences between the right and left hemisphere with a higher CBF and a higher MTT in the right hemisphere in comparison with the left hemisphere. However, this difference is not as clear as in the symptomatic patient. After CAS, both CBF and MTT show a symmetric pattern of perfusion.

When we compared symptomatic and asymptomatic patients before stent placement, rCBF was significantly lower in symptomatic patients. This indicates the presence of more hemodynamic compromise in these patients before treatment of carotid artery stenosis. Finally, rCBV after stent placement was significantly lower in symptomatic patients. In these patients, the compensatory hyperemia on the symptomatic side before treatment (rCBV>1) turned into hypoxemia after treatment, suggesting impaired autoregulation. These differences in perfusion parameters between both

groups of patients before and after stent placement are suggestive of the existence of a different hemodynamic status in symptomatic and asymptomatic patients. Previous studies have shown differences in hemodynamic status between symptomatic and asymptomatic patients.[22,23] Sivlestrini et al[23] described a significant improvement of cerebral hemodynamics in symptomatic patients after CEA by measuring cerebrovascular reactivity. Furthermore, this article reports significant differences in the cerebral hemodynamic perfusion pattern after CEA between symptomatic and asymptomatic patients.[23] Soinne et al[8] investigated patients with asymptomatic and symptomatic stenosis by means of dynamic susceptibility contrast MR imaging and transcranial Doppler sonography. They found a significant difference between symptomatic and asymptomatic patients both before as well in response to CEA. However, it is not yet clear if cerebral perfusion re-establishes equally in surgical patients and those with CAS. To our knowledge, our study is the first comparing symptomatic and asymptomatic patients with a carotid artery stenosis by using CTP. Our results are in agreement with these above-mentioned previous studies, but we think our study provides additional evidence for the benefit of stent placement in patients with an asymptomatic carotid artery stenosis by showing improvement in both rCBF and dMTT. In the first stage of hemodynamic compromise, collaterals of the brain are not able to maintain normal cerebral perfusion, which leads to reflex vasodilatation and subsequently elevation of intravascular CBV. CBF is still preserved at this stage of hemodynamic compromise. When further reductions in perfusion pressure take place with concurrent increasing MTT, CBV reaches its maximum and cerebrovascular autoregulation is not sufficient to maintain normal perfusion. Stage II hemodynamic failure occurs when CBF declines and oxygen extraction increases. Several studies have tried to determine the association between stage I or II hemodynamic compromise and the risk of stroke. Contradicting results concerning the association between stage I hemodynamic compromise and cerebrovascular events have been reported.[3] However, stage II hemodynamic compromise has been shown to be an independent predictor of stroke in patients with symptomatic carotid occlusion.[24] Also patients with symptomatic stenosis and ipsilateral hemodynamic compromise are at higher risk of disabling stroke than patients with normal cerebral perfusion.[4] It is important to evaluate individual perfusion parameters and relate these to the different stages of hemodynamic compromise. MTT is considered the most sensitive perfusion parameter because it directly relates to cerebral perfusion pressure.[21] Before treatment, dMTT was higher in symptomatic patients, though

this difference was not significant. dMTT changed significantly after treatment in symptomatic patients, while it did not change significantly in asymptomatic patients. Both findings confirm the presence of differences in cerebral hemodynamics between symptomatic and asymptomatic patients. Also, it implies that symptomatic patients are more hemodynamically compromised. CBV remains a parameter that is difficult to interpret, despite extensive studies analyzing it.[25] It might reflect autoregulatory capacity, because it represents the vasodilatatory and vasoconstrictive capacity of the brain. One could expect to observe normalization and symmetry of CBV after treatment, though it is not clear when vasodilatation turns into vasoconstriction. Also, it is possible that autoregulation takes more time to recover. The significantly lower rCBV in symptomatic patients might suggest irreversible impaired autoregulation in this group of patients, though a CTP scan should be repeated after 1 year to provide definite conclusions.

Thus, we can explain the higher dMTT and lower rCBF in symptomatic patients before treatment by the known hemodynamic responses in the presence of carotid artery stenosis. The increase in perfusion can be a result of loss of normal vasoconstriction secondary to chronic dilatation of resistant vessels and impaired cerebral vasoreactivity. The reduced rCBV in symptomatic patients after treatment is a new finding, which might represent disturbed autoregulatory capacity.

The presence of a hemodynamically significant carotid artery lesion is regarded as one of the possible causes of an impaired cerebral circulation. A stenosis itself, however, is a poor indicator of the hemodynamic status of the cerebral circulation in the ipsilateral hemisphere.[26] Several important mechanisms are known to maintain normal cerebral perfusion pressure via collaterals of the circle of Willis, ophthalmic collaterals, and leptomeningeal arteries. This study, showing differences of cerebral perfusion between asymptomatic and symptomatic patients, supports the relation between symptoms and impaired cerebral hemodynamics. Van der Heyden et al[27] recently showed that cerebral perfusion parameters improve after carotid stent placement in 50% of asymptomatic patients. This indicates the presence of a compromised cerebral circulation due to a carotid artery stenosis. CTP analysis can contribute to the selection of patients with a compromised cerebral circulation who would benefit from CAS. One of the limitations of our study is that we did not compare CTP values to a reference standard, though previous studies have shown that CBF measured with CTP correlates well to PET or xenon-enhanced CT.[28] Second, we did not evaluate the effects of the configuration of the circle

of Willis on perfusion, because for such a multifactorial analysis, more patients are needed. Previous studies have reported conflicting results with regard to the relation between the presence of collaterals and cerebral hemodynamics. Jongen et al[29] reported that the presence or absence of collateral pathways in the circle of Willis did not affect perfusion in the ipsilateral MCA territory. Third, symptomatic and asymptomatic patients underwent CTP in a different hospital, though always in multislice CT scanners. To eliminate physiologic variation and interpatient differences, we compared relative values, relating absolute perfusion data in the treated hemisphere to the contralateral and untreated side. A fourth drawback of this study is a methodologic problem with the deconvolution algorithm. We used a delay-sensitive algorithm, which may underestimate blood flow and overestimate MTT.[30] However, at this time, clinical experience by using these algorithms is not yet available. Another limitation of this study is that arterial input function can have a significant impact on the perfusion parameters. Finally, we could not include as many patients with symptomatic as with asymptomatic carotid stenosis. However, because treatment of asymptomatic stenosis is still controversial, inclusion of asymptomatic patients for CTP analysis is limited, and these data provide a representative sample of patients with asymptomatic carotid artery stenosis.

Conclusions

CTP analysis can be used to identify differences between patients with symptomatic and asymptomatic carotid stenosis before revascularization, as well as differences in their response to treatment. Before treatment, symptomatic patients had significantly lower rCBF. After treatment, rCBV was significantly lower in symptomatic patients. Carotid artery stent placement improves cerebral perfusion in symptomatic and asymptomatic patients. However, cerebral blood flow before treatment is more strongly impaired in patients with symptomatic carotid stenosis. In these patients, the compensatory hyperemia on the symptomatic side before treatment (rCBV 1) turns into hypoxemia after treatment, suggesting severely impaired autoregulation. CTP analysis can contribute to the selection of asymptomatic patients with a compromised cerebral circulation who would benefit from CAS.

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PART V

Embolic protection devices and antiplatelet therapy

Chapter 7

The role of embolic protection devices during carotid stenting prior to cardiac surgery in asymptomatic patients: empty filters?

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Objectives: The purpose of this study was to analyze the debris captured in the distal protection filters used during carotid artery stenting (CAS). Background: CAS is an option available to high-risk patients requiring revascularization. Filters are suggested for optimal stroke prevention during CAS.

Methods: From May 2005 to June 2007, filters from 59 asymptomatic patients who underwent CAS were collected and sent to a specialized laboratory for light-microscope and histological analysis. Peri- and postprocedural outcomes were assessed during 1-year follow-up.

Results: On the basis of biomedical imaging of the filter debris, the captured material could not be identified as embolized particles from the carotid plaque. On histological analysis the debris consisted mainly of red blood cell aggregates and/ or platelets, occasionally accompanied by granulocytes. We found no consistent histological evidence of embolized particles originating from atherosclerotic plaques. Post-procedure, three neurological events were reported: two (3.4%) transient ischemic attacks (TIA) and one (1.7%) ipsilateral minor stroke.

Conclusion: The filters used during CAS in asymptomatic patients planned for cardiac surgery often remained empty. These findings may be explained by assuming that asymptomatic patients feature a different atherosclerotic plaque composition or stabilization through antiplatelet medication. Larger, randomized trials are clearly warranted, especially in the asymptomatic population.

Introduction

Optimal management of patients with concomitant carotid and coronary artery disease who are scheduled to undergo coronary bypass (CABG) remains controversial. The heterogeneity of this subset of patients, who present with generalized atherosclerosis, is key to understanding this controversy. Despite the limited available evidence regarding the benefit of prophylactic carotid revascularisation, many cardiac surgery patients with advanced carotid and coronary disease are currently treated with staged or synchronous carotid/coronary interventions. In this case, the rationale is that such a strategy will reduce perioperative mortality and neurological morbidity. However, the overall effectiveness of this approach ultimately depends on the procedural risk. If it is too high, it is unlikely to confer benefit.[1] During the last decade, there has been considerable interest in establishing whether carotid artery stenting (CAS) might be a safer, better alternative. CAS is less invasive, it does not require a neck incision, it does not cause cranial nerve injury, and it involves shorter hospital stays.[2-6] In studies of patients considered ''high risk'' for carotid endarterectomy (CEA), CAS was considered at least ''as good as'' CEA.[2] In search of a safer, less invasive method, CAS has emerged in recent years as an alternative approach for CEA in patients with significant stenosis.[7] Even though the safety of the procedure is debated in terms of complication rates, experienced centers manage to report excellent figures from carefully monitored procedures,[8-16] whereas the CAS versus CEA debate is ongoing, the need to fine-tune technique in the former is evident. Taking this into account, the role of the embolic protection device (EPD) has been evaluated many times, though only twice by means of a prospective, randomized controlled studies.[17-20] This probably evolves from the common sense view that a filter, per definition, captures debris and therefore protects brain. The purpose of this study was to analyze the captured debris of filters retrieved after CAS in asymptomatic patients with significant bilateral carotid artery disease who had cardiac surgery planned.

Materials and Methods

Study Population

From May 2005 to June 2007, filters from 59 consecutive patients who underwent CAS were collected and sent to the ISREC (Institut Suisse de Recherche Experimentale sur le Cancer) in Lausanne, Switzerland for light-microscope and histological analysis.

CAS procedures were conducted in asymptomatic patients with identified, significant stenosis (>90% ascertained by duplex ultrasound and >80 % on angiography) prior to cardiac surgery. All patients gave written informed consent. This observational study was approved by the ethical committee of our hospital.

Carotid Stenting Procedure and Subsequent Cardiac Surgery

Patients who fulfilled the duplex thresholds then underwent diagnostic cervical-cerebral angiography, which also included intracranial views to determine patency and completeness of the circle of Willis. Three-dimensional rotational angiography was performed to obtain detailed information on the target stenosis.[21]

Significant carotid artery disease was defined as a target lesion in the common carotid artery, internal carotid artery, or at the bifurcation with an angiographic stenosis severity of >80% according to NASCET criteria.[22,23] Patients were accepted for CAS by a consensus decision involving a neurologist, cardiovascular surgeon, and interventional cardiologist. When the aortic arch was markedly unfolded and peripheral vascular disease or severe tortuosity made an endovascular procedure more hazardous, the patient was referred for combined CEA-CABG. Furthermore, patients with allergy and/or insensitivity to acetylsalicylic acid, heparin, or clopidogrel and severe renal insufficiency were also not suited for CAS. During the procedure the hemodynamic status and oxygen saturation were continuously monitored. All procedures were performed via femoral access. An 8-French short femoral introducer sheath was inserted, and heparin was administered intravenously to maintain the activated clotting time (ACT) between 250 and 300 sec. The common carotid artery was selectively engaged with a diagnostic catheter (Sidewinder II, 5 Fr, Cordis J&J) and exchanged for a long 0.018-inch stiff wire (SV-5, 300 cm, Cordis J&J) positioned proximal to the target lesion. Following this, a 8-French percutaneous coronary angioplasty guiding catheter was placed in position (MP A1, 8-French Cordis J&J), if required supported by a telescopic diagnostic catheter (MP A1 5-French, 125 cm, Cordis J&J). After the lesion was crossed with the premounted filter system and deployment in the minimum landing zone was performed, a low-profile undersized angioplasty balloon (3.0–3.5 20 mm) was used to predilate the lesion, followed by the placement of an appropriately sized self-expandable stent. To maximize stent deployment and vessel scaffolding, postdilatation was performed with an appriopriately sized balloon (varying from 5.0 to 7.0 20 mm, dependent on the reference diameter) after administering intravenous Atropine (0.5 mg). Finally, the

filter was retrieved using a dedicated sheath and a closure device (Angioseal; St-Jude Medical) was used to obtain hemostasis in the groin.[24] All procedures were performed under transcranial Doppler monitoring. All patients were clinically evaluated by a neurologist before, during and immediately after the procedure. Following CABG the patient was examined by the same neurologist. In the event of major stroke, the patient was monitored afterwards on the stroke-unit. It is our practice to perform CAS on dual antiplatelet therapy and then to withhold clopidogrel starting 7 days prior to CABG, while continuing aspirin. Clopidogrel is readministered after recovery from surgery. In those patients requiring urgent cardiac surgery, CAS is performed using dual antiplatelet therapy, which is not stopped prior to the cardiac procedure.

TCD Monitoring

The TCD monitoring of the ipsilateral middle cerebral artery (MCA) was performed during the CAS, using a 2-MHz pulsed Doppler transducer (Pioneer TC4040, EME, Madison, WI), gated at a focal depth of 45–60 mm. The transducer was placed over the temporal bone to insontate the main stem of the ipsilateral MCA and was fixed with a head strap. The number of isolated microembolic signals (MES) in the MCA was registered according to the criteria described by the consensus committee.[25] If the number of MES was too high to be counted separately, heartbeats with microemboli were counted as microembolic showers. During the procedure the MES and the showers were counted and presented as totals or as numbers during the different phases of the procedure: spontaneous, wire manipulation, deployment of the protection filter, predilation, stentdeployment, stent postdilation, and retrievement of the filter. The Doppler spectra were observed on-line and the audio-Doppler signal were made audible in the angiography suite. For off-line analysis, the audio Doppler signals were recorded on CD ROM. Analysis of recordings were performed by an observer blinded to the clinical details.

Filter Analysis

In the post-procedure, filters were cut loose from the guidewire with sterilized scissors and instantly immersed in an O.C.T.(Tissue TekVR) compound (polyvinyl alcohol < 11%, Carbowax < 5%, nonreactive ingredients > 85%) for preservation. This compound typically surrounds and covers the tissue specimen to avoid accidental loss of material. Immediately afterwards, these small containers were frozen at -80^{0}C.
An international express service (FedEx) shipped the samples to Switzerland every 2

weeks in a mobile freezer, where they were analyzed by an experienced pathologist after extensive biomedical imaging. To perform biomedical imaging, the filters were opened and flattened on a slide coated with a pad of agarose. Images were taken with an upright microscope using a differential interference contrast (Leica DM5500, camera DFC320 colour, objective HCX PL Fluotar 5/0.15). To view the entire filter, mosaics were acquired. The final image is a reconstruction, edge by edge, of all individual images. After acquisition, the filters containing all the materials were immediately fixed in 10% formalin, then processed for histological analysis. The samples were analyzed by conventional light microscopy on both H&E (hematoxylin-eosin) and VGEL (Van Giesen elastin) stained cytopsins, to provide information on the amount of detected material typically identifiable in an atheromatous plaque.

Results

Patient Characteristics

Baseline clinical characteristics of all patients are shown in Table I.

Table 1. Baseline Clinical Patient Characteristics

	Patients *(n = 59)*
Age (mean ± SD), years	69.3 ± 8.5
Female, *n (%)*	17 (28.8)
Hypertension, *n (%)*	38 (64.4)
Diabetes mellitus, n (%)	9 (15.2)
Hypercholesterolemia, n (%)	43 (72.9)
Smoking, n (%)	13 (22.1)
Average degree of stenosis (%)	88.1 ± 8.8
Previous myocardial infarction, n (%)	18 (30.5)
Valvular heart disease, n (%)	15 (25.4)
Congestive heart failure, n (%)	6 (10.2)
Unstable angina pectoris, n (%)	28 (47.5)
Previous CABG, n (%)	8 (13.5)
Previous PCI, n (%)	9 (15.2)
Previous CEA, n (%)	1 (1.7)

CAS and Cardiac Surgery Results

CAS was performed predominantly in the proximal internal carotid artery (n = 54) but also included the distal (n = 3) and proximal (n = 2) common carotid artery. The overall procedural success rate was 98%. One procedure was unsuccessful due to inadequate guiding catheter positioning. This patient was excluded from data analysis. The mean angiographic degree of stenosis was reduced from 88.1% ± 8.8% to 4% ± 9%. A variety of peripheral or carotid stents was used: 49 Acculink stents (Abbott), 6 Nex stents (Boston Scientific), 2 Precise stents (Cordis), and 2 Protege RX stents (ev3). Two types of filter protection devices were used: the FilterWire EZ (Boston Scientific) (radiopaque Nitinol Loop and a polyurethane filter) in 46 procedures (77.9%) and the SpideRX (ev3) (Nitinol mesh filter) in 13 procedures (22.0%). Specifically, all filters were deployed before predilatation of the culprit lesion and in all cases a postdilatation was performed. All patients underwent surgery within one month after CAS. In the present series, 41 patients (69.5%) underwent CABG, 10 patients (21%) had valve surgery combined with CABG, and 2 patients (3.4%) underwent reconstructive surgery of the ascending aorta. Five (8.5%) patients underwent isolated aortic valve replacement. Eight (13.5%) of the cardiac interventions were redo procedures (second or third).

Periprocedural Outcome and 1-year Follow-Up

Three neurological events were reported: two (3.4%) transient ischemic attacks (TIA) and one (1.7%) ipsilateral minor stroke. One patient died prior to surgery due to dialysis complications. One patient died after CABG due to a persistent ventricular tachycardia. At 1-year follow-up, one patient reported a major hemorrhagic stroke while using anticoagulation. Carotid duplex 3 months after the procedure showed no cases of restenosis. Repetition of this examination at 1 year after CAS presented no patients with significant restenosis, 2 patients with 50–65% restenosis, and one with <50%. The stents were all well-apposed.

Biomedical Imaging

Although the images were of high definition and exposed magnificent quality (Figure 1), it remained hazardous to perform any quantification of the visualized material (Figure 2): when an image of the complete filter was enhanced, unidentified debris appeared captured in most of the filters, together with material corresponding with (histological recognized) red blood cell aggregates and/ or platelets (Figure 3).

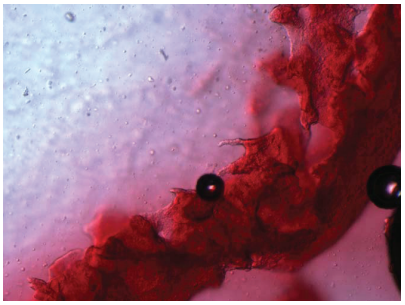

Fig. 1 Uncut filter. Picture taken with upright microscope using a differential interference contrast of an uncut filter within red an enlarged "clump" of red blood cell aggregates and/or platelets.

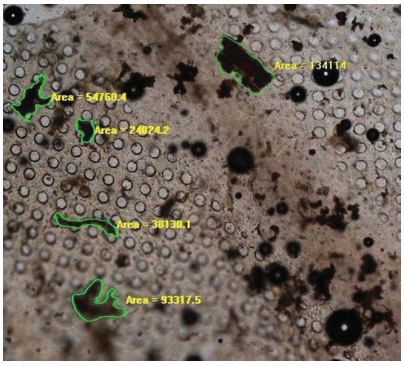

Fig. 2 Automatic contour detection. Automatic contour detection of the material on the filter.

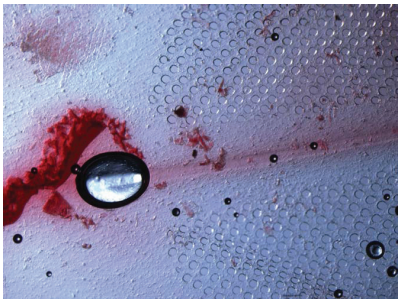

Fig. 3. Spread out filter. Filter cut and spread out, where red material is corresponding with histological recognized red blood cell aggregates and/ or platelets.

In the majority of filters, reproducible images of this unidentified material was seen, mainly consisting of irregular-shaped (Figure 4a),"french fries"-shaped (Figures 4b and 5b) or square-shaped particles (Figure 4c). Differentiation and definition of this material was difficult. However, the "french fries"-shaped particles (Figure 5b) were encountered on images of unused (sterile) filters (Figure 5a–c). Therefore, the origin of this material should not be considered as embolized particles from the carotid plaque. The "square" particles (Figure 4c) could be identified as fibers of a sterile swab, used to clean the angioplasty wire during the procedure.[26,27]

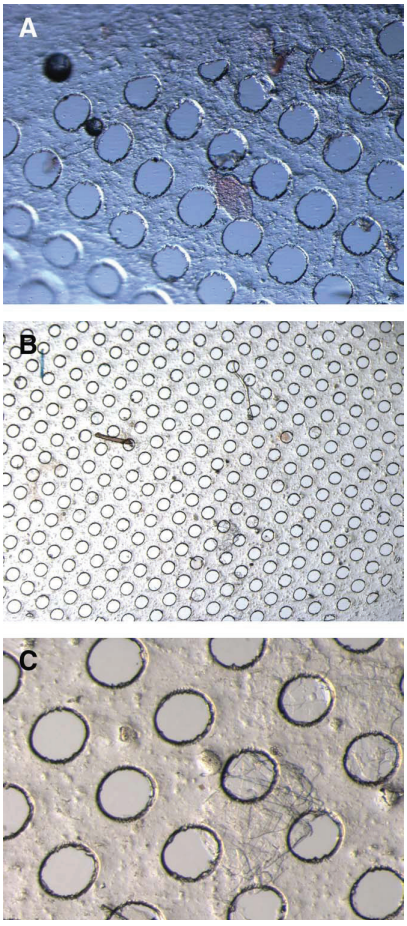

Fig. 4. (a–c) Exogenous debris. Exogenous material: irregular shaped particles (a) and particles shaped like ‘‘french fries’’ (b); square particles (c) most probably, introduced over the wire during the stent procedure and might be fibers of a sterile swab, used to clean the angioplasty wire during the procedure.

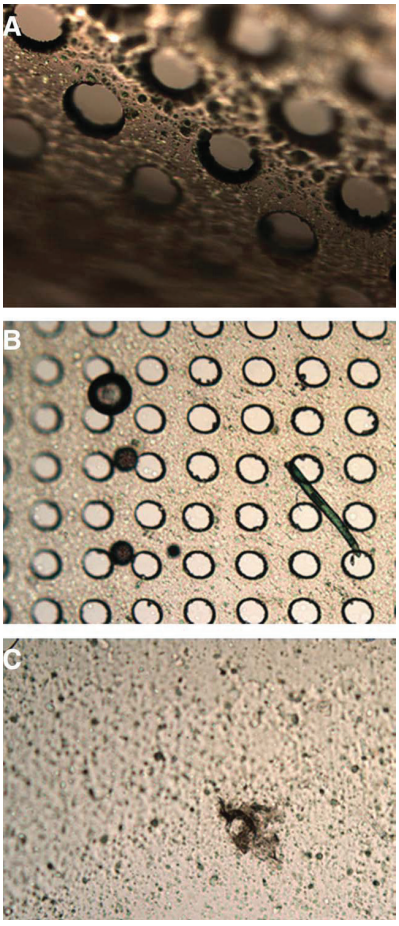

Fig. 5. (a–c) Sterile unused filter. Unidentified, anorganic substances were encountered on images of unused (sterile) filters; (a) filter with micropores (80–100 lm); (b) particle ‘‘french fries’’ shaped; (c) unidentified exogenous particle.

Histological Analysis

The quantities of material were comparable among different samples. The material mainly consisted of aggregates of red blood cells, and/or platelets (both probably hemolysed), occasionally accompanied by white blood cells (granulocytes). Other particles observed relatively frequently (up to 40%) comprised acellular and amor

phous material of exogenous origin, probably debris introduced over the wire during the stent procedure. However, there was no consistent evidence of fibrin or cholesterol deposits (suggestive of thrombotic events or atherosclerotic plaques), lipid-rich macrophages, endothelial cells, or collagen fibers in any other sample analyzed.

Discussion

Until now, no level-1 evidence based on clinical outcome data exists in support of EPDs. Surrogate markers such as magnetic-resonance diffusion-weighted imaging of brain, procedural transcranial Doppler, or biochemical markers of neurological injury have failed to provide evidence in favor of CAS with EPD.[28] Furthermore, the available data pertain predominantly to a majority symptomatic population.

With the use of biomedical imaging and histological analysis of debris captured in embolic protection filters retrieved after CAS in asymptomatic patients prior to CABG, we were unable to detect material or deposits suggesting recurrent thromboembotic events originating from an atherosclerotic plaque. The obtained material corresponds essentially to aggregates or isolated blood cells and material of exogenous origin. To explain these findings, we refer to virtual histology intravascular ultrasound (VH IVUS) assessment studies of carotid plaque, in which it was shown that patients on aspirin had significantly less necrotic lipid core plaque than patients not taking aspirin.[29] In addition to its antiplatelet properties, aspirin may have an anti-inflammatory effect that stabilizes plaque in these patients.[30] Also, it was noted that patients with calcified nodules protruding into the lumen of the carotid artery on VH IVUS had a higher incidence of previous neurological symptoms. It has been demonstrated that the necrotic core, especially when superficial and surrounded by a thin fibrous cap, is the predominant histological finding in carotid plaques that cause cerebrovascular thrombotic and embolic events.[31,32] However, a prevalence of features of instability has been reported as being low in plaques from patients suffering stroke on whom CEA was performed >180 days after the event. Furthermore, these plaques were no more unstable than plaques that were studied from patients who underwent surgery for asymptomatic stenosis. Therefore, the fact that all patients in this study were on dual antiplatelet therapy (aspirin and clopidogrel) and were neurologically asymptomatic might explain the ''empty'' filters. An interesting finding, when comparing the histological findings of the captured debris of this study with other reports, was that the presence of platelet aggregates is consistent in all

analysis.[33-38] It has been described that these aggregates could cause pore obstruction resulting in transient flow impairment while others found a correlation between filter occlusion and ACT.[34,24] Moreover, it has been shown on electron microscopy by DeRubertis et al.[36] that besides the fact that the most prevalent finding in embolic debris was the presence of individual platelet or platelet aggregates, there is an increased incidence of platelet activation in the debris contained within the filters of symptomatic patients relative to asymptomatics. Furthermore the variance in the amount of the captured material also seemed to be influenced by the preoperative symptom status, where in symptomatic patients in contrast to asymptomatics more debris was captured, emphasizing the different pathophysiology. Among other variables, a significant relationship between the presence of cell debris and age older than 65 years and the number of balloon dilatations performed have been described.[34,37,38] A similar correlation could not be demonstrated in this study.

Although we used several stent types with different scaffolding properties and free cell areas, varying from 4.7 to 11.48 mm2, there was no distinction in clinical outcomes.[39] Similarly, no differences were observed between patients treated with open-cell versus closedcell stent designs. The latter confirms previous reports rom a large multicenter European study, whereby no indication was shown for the specific use of open-cell or closed-cell stents in terms of neurologic complications, stroke, or mortality risk.[40] Two types of filters were used: the FilterWire EZ, which is a perforated membrane filter, and the Spider, which is a wire mesh filter. In an in-vitro study, the occurrence of a pressure gradient and blood flow obstruction were more profound in perforated membrane filters as compared to wire mesh filters.[41] However, evaluation of clinical data from 3,160 procedures with nine different EPDs did not show significant differences in risks of procedural adverse events.[42] Analysis of the two types of filters used in this study did not reveal any diversity. TCD off-line analysis revealed no significant correlation between the captured amount of debris and the occurrence of MES or showers during the different phases. It has been described previously that MES is less common in the asymptomatic patients compared to the symptomatics.[43] Several limitations of this study should be taken into account. Preparation of the filter after the procedure is crucial and could have influenced our findings. Therefore, the filters were fixed gently immediately after retrieval, optimizing chances for excellent recovery of the filtered particles. Coagulation immediately after retrieval and before stabilization of the filter might disturb later histological analysis, but the ‘‘clumping’’ and ‘‘clogging’’ that can be

seen on images of the filter debris are not to be confused with ‘‘thrombi.’’ They are best described as ‘‘aggregates’’ of red corpuscles, and of no significance. Destruction of the captured debris through the freezing process to minus 80°C is not completelyruled out; however, this potential destruction has not been described yet. Long distance shipment of the samples in a mobile freezer proved feasible and, on arrival, the samples were still frozen. The cutting process might have led to disruption of particles, but the intact filter with attached particles was soaked in a plastic monomer and polymerized to be able to cut the filter in its plastic matrix. All further processing (staining, etc.) was carried out without removal of the plastic, thus eliminating disruption. Furthermore, all readings indicated that the immersed particles in the fixative were minimal and that most particles were attached to the filter and the wire scaffolding. The small study size does not allow conclusions regarding the clinical efficacy of protection filters. Larger evaluations are warranted.

Conclusion

Altogether, controversy persists. Besides the fact that there is no level-1 evidence based on clinical outcome data to support EPDs, a new enigma has been added to the list of unknowns: empty filters used during CAS in asymptomatic patients with significant carotid artery disease planned for cardiac surgery. Varying composition of the atherosclerotic plaque in asymptomatic patients and stabilization through antiplatelet medication may explain these findings. Larger randomized trails are clearly warranted, especially in the asymptomatic population.

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Chapter 8

High versus standard clopidogrel loading in patients undergoing carotid artery stenting prior to cardiac surgery to asses the number of microemboli detected with transcranial Doppler: results of the randomized IMPACT trial

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Purpose: To compare the effects of 300mg or 600mg clopidogrel loading dose, prior to carotid artery stenting (CAS) on the number of transcranial Doppler (TCD)-detected microembolic signals (MES) and to investigate the relationship between the magnitude of platelet reactivity and MES.

Materials and Methods: In this prospective randomized, double-blind study, 35 consecutive asymptomatic patients (17.1% females), scheduled for CAS and cardiac surgery were included. The primary endpoint was the number of TCD-detected MES. The secondary endpoints were the absolute magnitude of on-treatment platelet reactivity and the adverse cerebral events. Negative binomial regression to find predictors for sum of single emboli, the student's t-test to assess the association between platelet function tests and randomized dose of 300 or 600mg clopidogrel, and the R2 calculation for the assessment of the association between platelet function tests and embolic load, were used.

Results: No statistically significant difference in the number of TCD-detected MES, in the sum of all the single emboli or showers and platelet aggregation measurements between the two groups was observed. (aggregometry: 21.7 ± 18.3 versus 23.0 ± 18%, p=0.8499 and 45.8 ± 17.5 versus 46.5 ± 14.5%, p=0.9003) (verifyNow P2Y12 assay: 231 ± 93 PRU versus 222 ± 86 PRU, p=0.7704). In one patient a transient ischemic attack occurred.

Conclusion: A loading dose of 300 mg of clopidogrel in combination with aspirin is as effective as 600 mg of clopidogrel in achieving adequate platelet inhibition and preventing periprocedural events in asymptomatic patients undergoing CAS prior to cardiac surgery.

Introduction

Carotid artery stenting (CAS) has emerged in recent years as a valuable alternative approach for carotid endarterectomy (CEA) in patients with significant carotid artery disease. Even though the safety of CAS is debated in terms of complication rates, experienced centres produce excellent figures from carefully monitored procedures and therefore CAS could be considered in selected patients in which the peri-operative risk of CEA is increased as compared to CAS due to coexisting conditions.[1-9] Whereas the CAS versus CEA debate is ongoing, the role of concomitant antithrombotic therapy prior to, during and following CAS has not been established. During carotid stent implantation, the endothelial barrier becomes injured with the subsequent adhesion and activation of circulating platelets.[10] Adequate antithrombotic therapy is therefore of utmost importance. Based on promising data on the use of aspirin plus clopidogrel in the setting of coronary artery stenting this adjunctive dual antiplatelet regimen is currently also the treatment of choice in CAS, but no strict recommendations with regard to the dosage and timing of the initial loading dose of clopidogrel are available.[11-13] In addition, multiple studies have reported a wide interindividual variability in the response to a 300 mg loading dose of clopidogrel with a subsequent substantial proportion of patients not receiving the optimal benefits.[14-16] Therefore, it has been recently demonstrated that a 600 mg loading dose of clopidogrel induces a faster onset of action resulting in a significant reduction in atherothrombotic events without a significant increase in major "Thrombolysis In Myocardial Infarction" (TIMI) bleeding complication in patients undergoing coronary artery stenting.[17] As a result, the interventional cardiology community has already adopted the 600 mg loading dose regimen as standard of care in the setting of early invasive percutaneous coronary interventions (PCI). However, in the setting of CAS, there is no randomized controlled trial available that compared the effects of different loading doses of clopidogrel.

By using transcranial Doppler (TCD) monitoring during CAS, it is possible to detect the number of microembolic signals (MES) throughout the different phases of CAS .[18,19] Post-CAS TCD-monitoring has not been performed systematically in the past and thus could reveal valuable information helpful to the understanding of postprocedural cerebral complications and risk stratification. The primary aim of the present study was to compare the effects of a high versus standard clopidogrel loading dose prior to CAS on the number of TCD-detected microemboli. In a prespecified secondary

analysis, the relationship between the magnitude of on-treatment platelet reactivity and TCD-detected microemboli was investigated to quantify the possible role of platelets in the pathophysiology of TCD-detected micro-emboli.

Materials and Methods

Patient Population

This is a prospective randomized, double-blind, single center study. All patients gave written informed consent. This study was approved by the ethical committee of our hospital and by the central committee on research involving human subjects in The Netherlands. The local institutional review board approved the study.

Consecutive patients who were scheduled for coronary artery bypass grafting (CABG) with established asymptomatic significant carotid artery disease were included in this study from March 2008 to April 2010. Our institutional guidelines prescribe a duplex ultrasound in case of a previous cerebral ischemic event, the presence of a carotid bruit, combined coronary artery or aortic disease with aortic valve stenosis, mitral valve insufficiency or severe peripheral artery disease.[20] Patients were considered asymptomatic if an ipsilateral cerebrovascular event had not occurred within the prior 4 months. Carotid artery stenosis was considered "significant" when a diameter reduction of more than 90% was measured by duplex ultrasonography.[21,22]

Patients fulfilling these stenosis thresholds then underwent diagnostic cervical-cerebral angiography which also includes intracranial views to determine the patency and completeness of the circle of Willis. Three-dimensional rotational angiography was performed in order to obtain detailed information about the target stenosis, including high-quality 3D images of the contrasted vasculature, juxtaluminal calcification and absolute lumen area and other absolute vessel dimensions.[23] Significant carotid artery disease was defined as a target lesion in the common carotid artery, internal carotid artery, or at the bifurcation with a angiographic stenosis severity of more than 80% according to NASCET criteria in asymptomatic patients.[21,22] A different threshold for the degree of artery stenosis is maintained for each diagnostic imaging tool. This might be related to the difference in sensitivity and specificity to detect a significant stenosis using various diagnostics: for duplex ultrasonography the sensitivity is 67% and the specificity 87%; for angiography the sensitivity is 95% and the specificity 99%.[24,25] Patients could be included if they were clopidogrel naive patients and > 18 years of age, with an appropriate temporal bone

window for TCD. Exclusion criteria were: severe renal impairment (serum creatinine ≥ 0.0113mg/dl), malignancy, febrile disorder, any diseases influencing platelet reactivity, concomitant medication known to affect platelet function other than aspirin, known platelet function disorder or a whole blood platelet count of less than 150x103/μL, peripheral vascular disease precluding femoral artery access, major neurological deficit or any other illness impeding informed consent, severe diffuse atherosclerosis of the common carotid artery, chronic total occlusions, "string sign" lesions, contraindication to study drugs, patients with uncontrolled hypertension despite optimal medication and pregnancy.

Randomization procedure

Four days prior to CAS, eligible patients were randomly assigned in a double-blinded fashion to a high clopidogrel loading dose (600 mg) or to a standard loading dose regimen (300 mg). In addition, all patients were pretreated with 100mg aspirine daily. The method used to implement the random allocation sequence was numbered in sealed envelopes. An independent statistician prepared the sequence generation, which was blinded to the enrolling patients and to those performing platelet function testing and the carotid intervention.

Patients randomized to a dose of 300 mg received 4 clopidogrel tablets of 75 mg each and one double blind capsule containing 4 placebo tablets. Patients randomized to a dose of 600 mg received 4 clopidogrel tablets of 75 mg each and one double blind capsule containing 4 clopidogrel tablets of 75 mg each. For clopidogrel, commercially available Plavix tablets (Bristol-Myers Squibb, New York, NY) were used. Placebo tablets, i.e. Albochin FNA tablets, were obtained from Interpharm B.V.(Den Bosch, The Netherlands). For blinding, placebo tablets and clopidogrel tablets were packed as intact tablets in DBcaps® size AA, colour caramel opaque, obtained from Capsugel® (Pfizer, New York, NY). Study medication was packed by the Department of Clinical Pharmacy, St. Antonius Hospital, Nieuwegein. The day after randomization , all patients received a clopidogrel maintenance daily dose of 75 mg on days 2 through 4. On the fourth day, CAS was scheduled.

End-Point Definitions

The primary endpoints were the number of TCD-detected MES during CAS (spontaneous, wire manipulation, deployment of the protection filter, predilation, stentdeployment, stent post-dilation and retrieval the filter) and immediately after

the CAS procedure (in the recovery room for 60 minutes). Secondary endpoints included the absolute magnitude of on-treatment platelet reactivity as measured with the different platelet function assays in both groups and the adverse cerebral events during CAS and after CAS (in the recovery room for 60 minutes and during further follow-up). All patients were physically examined prior to treatment, at discharge and prior to CABG by an independent neurologist. Strokes were considered disabling (major), if patients had a modified Rankin score of more than 3, at 30 days after onset of symptoms. A minor stroke was defined as a Rankin score of 3 or less, or that resolved completely within 30 days.[26] Fatal stroke was defined as death attributed to an ischemic or hemorrhagic stroke. Minor bleeding was defined as the need for transfusion of 1 unit of packed cells (PC). Major bleeding was defined as the need for transfusion of ≥ 2 units of PC or vascular surgery of the access site.

CAS-CABG procedure and Follow-up

CAS was performed in the proximal internal carotid artery. One type of distal cerebral protection device (Emboshield Embolic Protection System, Abbott) was used in all patients.

Procedures are performed via femoral access. An 8 French short femoral introducer sheath is inserted and heparin is administered intravenously to maintain the activated clotting time (ACT) between 250-300 seconds. The common carotid artery is selectively engaged with a diagnostic catheter (Sidewinder II, 5 Fr, Cordis J&J) and exchanged for a long 0.018 inch stiff wire (SV-5, 300cm, Cordis J&J) positioned proximal to the target lesion. Following this an 8 French percutaneous coronary angioplasty guiding catheter is placed in position (MP A1, 8 French Cordis J&J), if required supported by a telescopic diagnostic catheter (MP A1 5 French, 125cm, Cordis J&J). After the lesion is crossed with the premounted filter system and deployment in the minimum landing zone is performed, a low-profile undersized angioplasty balloon (3.0-3.5x20 mm) is used to predilate the lesion, followed by the placement of an appropriately sized self-expandable stent. In order to maximize stent deployment and vessel scaffolding, post-dilatation is performed with an appropriately sized balloon (varying from 5.0 to7.0x20 mm, dependent on the reference diameter) after administering intravenous Atropine (0.5 mg). Finally, the filter is retrieved using a dedicated sheath.[27] Cardiac surgery (including CABG, valve or reconstructive surgery of the ascending aorta) was usually scheduled at least 3 weeks after CAS, unless clinical instability dictated otherwise. According to institutional common practice,

dual antiplatelet therapy was prescribed for 3 weeks and patients were instructed to stop the clopidogrel 7 days prior to cardio-thoracic surgery (with continued aspirin (100 mg) therapy). The mean hospital stay following cardiac surgery was 10 days. In our institution, cardiac enzymes are drawn routinely every 8 h during the first 24 h after each procedure. After CAS and cardiac surgery, a 12-lead ECG was performed in all patients. After cardiac surgery, the ECG was performed on a daily basis during the first 48 hours; afterward, during the remaining period of hospitalization, ECGs were performed in case of unexplained chest pain. All patients were clinically evaluated before the procedure, during the procedure, and immediately afterward by an impartial neurologist. Before and after CABG, the same neurologist examined the patients once more. In case of a major stroke, the patient was monitored afterward in the stroke unit. All patients were evaluated by this neurologist at an outpatient clinic after 1 and 3 months. During follow up, in case of an event, hospital notes or death certificates were consulted when possible. Telephone follow-up interviews were conducted at 1 month and thereafter at 6-month intervals by a dedicated full-time research coordinator.

TCD- monitoring

The TCD monitoring of the ipsilateral middle cerebral artery (MCA) was performed during the CAS procedure and immediately afterwards in the recovery room for 60 minutes, using a 2 MHz pulsed Doppler transducer (Pioneer TC4040, EME, Madison, WI), gated at a focal depth of 45 to 60 mm. The transducer was placed over the temporal bone to insonate the main stem of the ipsilateral MCA and was fixed with a head strap. The number of isolated microembolic signals (MES) in the MCA was registered according to the criteria described by the consensus committee.[28] If the number of MES was too high to be counted separately, heartbeats with microemboli were counted as microembolic showers. During the procedure the MES and the showers were counted and presented as totals or as numbers during the different phases of the procedure: spontaneous, wire manipulation, deployment of the protection filter, predilation, stentdeployment, stent post-dilation and retrieval the filter. The Doppler spectra were observed on-line and the audio-Doppler signals were made audible in the angiography suite. For off-line analysis, the audio Doppler signals were recorded on CD ROM. Analysis of recordings were performed by an observer blinded to the clinical details, the results of platelet function testing and study groups.

Platelet function Testing

Blood samples for platelet function testing were drawn at two different time-points: before the administration of the study medication (baseline value) and just before the CAS-procedure. The absolute level of platelet reactivity before and after clopidogrel treatment (i.e. on-treatment platelet reactivity) was quantified using adenosine diphosphate (ADP)-induced classical light transmittance aggregometry and the VerifyNow P2Y12 assay (Accumetrics, San Diego, USA)

Classical light transmittance aggregometry

Citrated whole-blood samples were centrifuged at 120g for 10 minutes to obtain platelet-rich plasma (PRP) and further centrifuged at 1500g for 15 minutes to obtain platelet-poor plasma (PPP). Maximal aggregation was measured in non-adjusted platelet-rich-plasma after stimulation with different concentrations of ADP (final concentrations: 5 and 20 µmol/L). An APACT 4004 aggregometer (LABiTec, Arensburg, Germany) was used and PPP served as the reference for 100% aggregation (see appendix).[29,30]

The VerifyNow P2Y12 assay

The VerifyNow system is a whole blood assay designed to measure agonist-induced platelet aggregation. It is a rapid cartridge-based method to determine the response to clopidogrel (using 20 µmol/LADP as the agonist and 22 nmol/L prostaglandin E1 (PGE1)). Results of the VerifyNow□P2Y12-assay are reported in P2Y12 reaction units (PRU) (see appendix).[31,32]

Power calculation and Statistical Analysis

Without the prior knowledge of studies performed in this particular field of asymptomatic carotid stenting, we performed a simple power analysis. We assumed a (near)normal distributed outcome variable and set the minimal difference to be detected equal to one standard deviation. With a power of 80% the study would require 17 patients in each group.

For the descriptive statistics we used number with percentage, mean with standard deviation and median with interquartile range where appropriate. To aid interpretation of baseline differences we computed p-values with Fisher's exact test or Student t-test where appropriate.

The primary endpoint number of TCD-detected MES during and immediately after the CAS procedure difference between the randomised groups was tested with the Mann-Whitney test along with the visual aid of strip chart figures.

For the secondary endpoints the absolute magnitude of on-treatment platelet reactivity as measured with the different platelet function assays was tested with the Student t-test. Next we performed explorative analyses. Negative binomial regression was used to find predictors for sum of single emboli and sum of showers. For the assessment of the association between platelet function tests and embolic load, the R2 was calculated from a linear regression with the sum of single emboli used as measure of embolic load and the two platelet function tests respectively as dependent variable. In addition the R2 from a regression using restricted cubic splines to allow non-linearity was calculated. The R2 can vary from 0 to 1, higher values indicating better correlation; in the linear regression form it can be interpreted as the fraction of variation explained.
For all computations, R (version 2.12, The R Foundation for Statistical Computing, Vienna, Austria) was used.

Results

Patient Characteristics

A total of 64 patients were screened with duplex ultrasonography. The stenosis threshold was fulfilled in 50 patients. Of these 50 eligible patients, 45 were randomized. In 35 patients a significant carotid artery stenosis amendable for stenting was visualized on angiography. In the other 10 patients the stenosis did not meet the 90% stenosis threshold, according to the NASCET criteria. Finally, 35 patients were enrolled: 19 patients were assigned to the 300 mg loading dose group and 16 patients to the 600 mg group (see Figure 1 flowchart). Both treatment groups were well balanced with regard to baseline characteristics and use of non study medication (Table 1). Mean age was 76.4±6.1 years for the patients receiving 300mg clopidogrel loading dose and 69.8±7.3 for those receiving 600mg clopidogrel loading dose. In the former group there were 21.1% females, in the latter 12.5%. For this clinical trial we used the standard method of a case report form (CRF) for all patients included. The baseline characteristics were obtained from the case report form, which was completed by a dedicated research nurse who gathered information prospectively after interviewing the patient and where necessary information was abstracted from the patient's chart. Subsequently source verification was performed by in independent third person.

Figure 1 . Flowchart: Randomization procedure

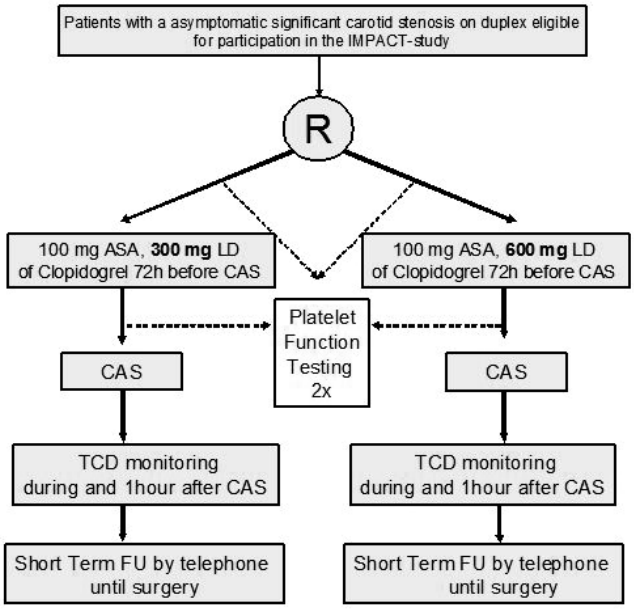


Table 1. Baseline Characteristics of Patients Randomized to Loading dose of 300mg Clopidogrel (+ placebo) or 600mg Clopidogrel

Variables	Clopidogrel 300 mg n=19	Clopidogrel 600 mg n = 16	p-value
Age (mean±SD),y	76.4±6.1	69.8±7.3	0.007
Female, n (%)	4 (21.1)	2 (12.5)	0.666
Hypertension, n (%)	8 (42.1)	5 (31.3)	0.727
Diabetes Mellitus, n (%)	3 (15.8)	3 (18.7)	1.000
Hypercholesterolemia , n (%)	15 (78.9)	13 (81.2)	1.000
Smoking, n (%)	8 (42.1)	6 (37.5)	1.000
Mean BMI	25.7±4	27.8±3.8	0.117
Previous myocardial infarction, n (%)	6 (31.5)	5 (31.3)	1.000
Previous CABG, n (%)	3 (15.8)	2 (12.5)	1.000
Previous PTCA, n (%)	2 (10.5)	2 (12.5)	1.000
Previous CEA, n (%)	1 (5.3)	1 (6.3)	1.000
Aspirin	13 (68.4)	10 (62.5)	0.736
Coumadin	6 (31.6)	4 (25)	0.723
Statin	13 (68.4)	13 (81.2)	0.461

SD:standard deviation; BMI:body mass index; CABG: coronary artery bypass grafting; PTCA: percutaneous transluminal coronary angioplasty; CEA: carotid endarterectomy

Angiographic/ Stenting Results and Short Term Follow Up

The mean angiographic degree of stenosis was reduced from 86±4% to 4±9%. One type of carotid stent (Acculink, Abbott) was used. In one patient a transient ischemic attack (TIA) occurred during CAS. In 3 patients (2 patients from the 300 mg group) a minor groin bleeding was registered. For the overall cohort, the median time interval between CAS and cardiac surgery was 28 days (inter quartile range 12 to 58 days). During CAS and during the period between CAS and surgery no major adverse clinical events occurred.

Platelet Function testing and TCD- detected MES

1. TCD-detected MES

The median number of TCD-detected single emboli for patients with a clopidogrel loading dose of 300 mg or 600 mg for 7 stages of the procedure varied from 10 to 44, the median number of TCD-detected showers of emboli varied from 0 to 40 for both groups in the different stages and the median of the sum of TCD-detected spontaneous single emboli and showers varied from 155 to 180 for the sum of single emboli and from 38 to 52 for he sum of showers. No statistically significant difference in the number of TCD-detected MES between the groups was observed throughout the respective phases of CAS or during the 60 minutes monitoring following the CAS procedure. Plots of individual data points plus median of TCD-detected single emboli and showers for patients with a clopidogrel loading dose of 300 mg or 600 mg for 7 stages of the procedure are shown in Figure 2 and 3. No statistically significant difference was found when all the separate spontaneous emboli or spontaneous embolic showers were summed (Fig. 4).

Figure 2. Plots of individual data points plus median of TCD-detected single emboli for patients with a clopidogrel loading dose of 300 mg or 600 mg for 7 stages of the procedure.

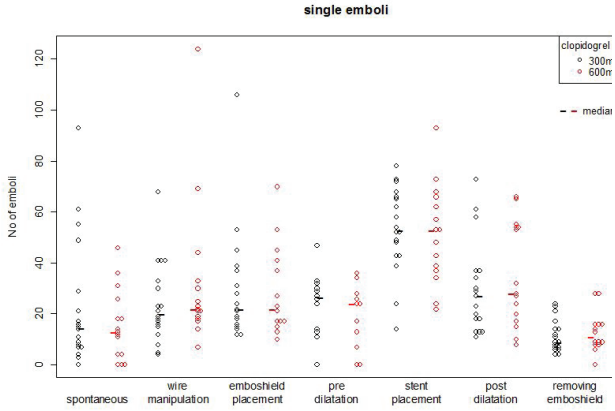


Figure 3. Plots of individual data points plus median of TCD-detected showers of emboli for patients with a clopidogrel loading dose of 300 mg or 600 mg for 7 stages of the procedure.

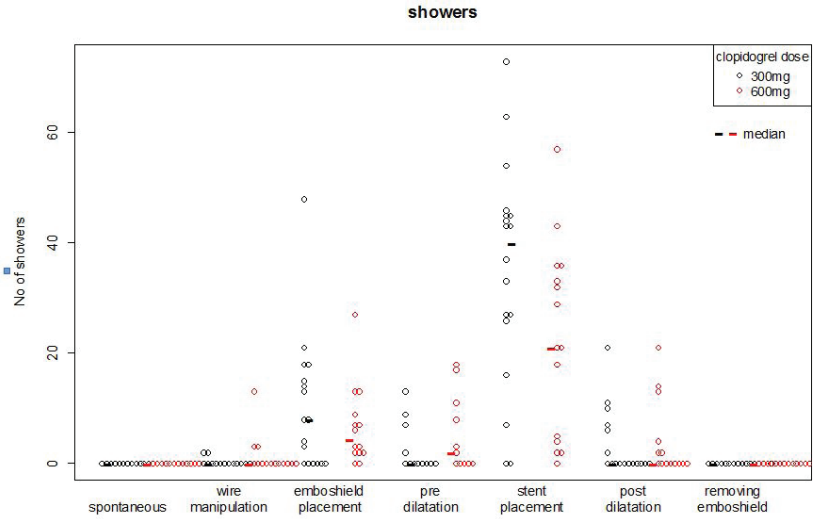
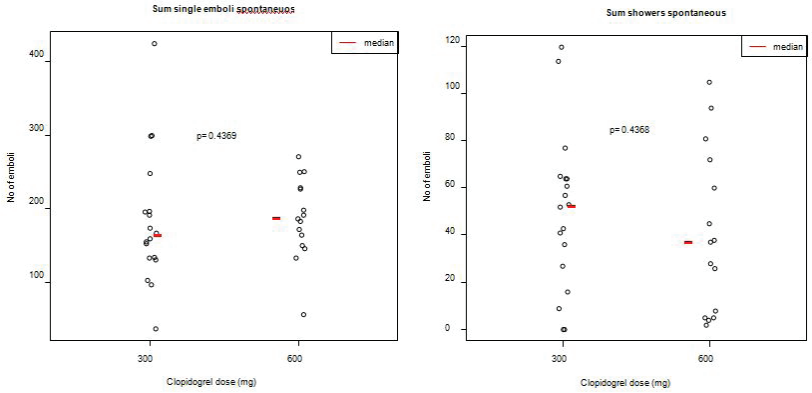


Figure 4. Plots of individual data points plus median of the sum of TCD-detected spontaneous single emboli and showers for patients with a clopidogrel loading dose of 300 mg or 600 mg



2. Platelet function test results

At baseline, there were no statistically significant differences in ADP-induced platelet aggregation profiles between the two groups. After study medication administration, the magnitude of ADP-induced platelet aggregation was not significantly different between the two groups at day 4 (21.7 ± 18.3 versus 23.0 ± 18%, p=0.8499 (5 µmol /L ADP) and 45.8 ± 17.5 versus 46.5 ± 14.5%, p=0.9003 (20 µmol /L ADP) for the 300 mg group and the 600 mg clopidogrel group respectively). Likewise, no significant difference in P2Y12 Reaction units (PRU) as measured with the verifyNow P2Y12 assay was observed (231 ± 93 PRU versus 222 ± 86 PRU for the 300 mg group and 600 mg clopidogrel group respectively, p=0.7704)

3. The association between platelet function tests and MES

No statistically significant associations between the results of platelet function testing (either pre- or post loading dose) and the sum of the single emboli and the sum of the showers were found (Table 2). No predictors for sum of showers from baseline characteristics, medication nor platelet function tests could be identified.

Table 2. Linear and non-linear R2 values of the association of the sum of all single emboli and showers with three platelet function tests

the sum of all single emboli associated with	**linear R^2**	**non-linear R^2**
p2y12 PRU	0.005	0.057
ADP 5	0.046	0.095
ADP 20	0.050	0.106
the sum of all showers associated with		
p2y12 PRU	0.001	0.039
ADP 5	0.044	0.002
ADP 20	0.128	0.097

Discussion

To the best of our knowledge, the present report is the first randomized study aiming to identify the optimal loading dose of clopidogrel in the setting of elective CAS for asymptomatic carotid artery disease prior to cardiothoracic surgery. The principal

finding is that there does not appear to be a significant difference in the number of TCD-detected microemboli during and after CAS between either a 300 mg or a 600 mg loading dose of clopidogrel. Intriguingly, the absolute magnitude of on-treatment platelet reactivity as measured with two platelet function assays was equal in both groups and a predefined exploratory analysis revealed that there is no relationship between the magnitude of platelet reactivity and the number of TCD-detected microemboli. In general, trials of antiplatelet agents in stroke prevention are a major undertaking, requiring thousands of patients to demonstrate significant reductions in well-chosen clinically relevant end points. Therefore, there has been a need for a surrogate marker for stroke that may be used to assess the efficacy of antiplatelet efficacy and optimize choice and dosage of agents before evaluation in large clinical trials. As of yet, accumulating evidence suggests that detection of microemboli using TCD offers such a marker since MES are more common in patient groups known to be at higher risk of recurrent stroke and of even more importance, the number of TCD-detected MES are a strong independent predictor of TIA and stroke risk.[33-36] Kaposzta et al. demonstrated the potential application of ultrasonic emboli detection during CEA to examine the efficacy of new platelet agents in a relatively small number of patients .[37,38]

In contrast to the positive findings reported in medical literature in the setting of CEA we did not observe any statistically significant difference in the number of MES between patients preloaded with 300 and 600 mg of clopidogrel. Although a lower rate of MES was expected in our cohort, because our patients had asymptomatic carotid artery disease, our secondary exploratory analysis did not indicate a possible role for the magnitude of on-treatment platelet reactivity in the pathophysiology of CAS-induced MES.

The occurrence of rapid thrombus formation immediately after arterial injury and stenting, and potential embolization of the thrombus to distal sites, provides the rationale for early antiplatelet therapy.[39] There is clinical evidence supporting the use of antiplatelet therapy after percutaneous coronary intervention.[40] Furthermore, because of the highly diffuse nature of the atherosclerotic disease process, patients undergoing CAS are also at risk of ischemic atherothrombotic events in other vascular beds, expanding the benefits of antiplatelet therapy.[41] In CEA studies the use of clopidogrel has shown to reduce postoperative embolization and did not result into a significant increase of blood loss, although neck closure times were considerably lengthened in several patients taking clopidogrel.[42-43] Bhatt et al. firstly

demonstrated that dual antiplatelet therapy (aspirin in combination with either clopidogrel or ticlopidine) during CAS is associated with a low rate of ischemic events in symptomatic and asymptomatic patients.[44] Dual antiplatelet therapy did not appear to increase the incidence of intracranial hemorrhage. In a randomized trial McKevitt et al demonstrated that dual antiplatelet therapy with clopidogrel and aspirin significantly reduced the 30-day incidence of adverse neurological outcomes after carotid stenting compared with aspirin plus heparin without an additional increase in bleeding complications.[13] In this study, there was no statistically significant difference in platelet inhibition using 2 types of platelet assays between patients receiving a loading dose of 300 or 600 mg of clopidogrel. In particular there was no evidence of a faster onset using a 600mg loading dose, which has been used in the acute coronary setting. Up to the present, there is little knowledge on the optimal loading dose of clopidogrel for asymptomatic patients planned for CAS and CABG. Therefore, the result of this study could be considered as a major contribution, especially because it is shown that there are no clinically significant differences in clopidogrel loading dose for this specific treatment. Therefore, we would not recommend a loading dose of 600 mg of clopidogrel in case of an elective CAS.

The principal limitation of this study is the small sample size. Additionally, microembolization remains a surrogate endpoint, and further studies are needed to determine whether reduction in MES through procedural modifications impacts clinical outcomes associated with CAS.

In conclusion, this double-blind, randomized, placebo-controlled trial demonstrates that a loading dose of 300 mg of clopidogrel in combination with 100 mg of aspirin is as effective as 600 mg of clopidogrel in achieving adequate platelet inhibition and preventing periprocedural adverse events in asymptomatic patients undergoing CAS prior to cardiac surgery.

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Chapter 9

Case report
Acute fracture of Acculink carotid stent during post dilation

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Catheter Cardiovasc Interv. 2009;74(7):1107-9

Introduction

Carotid angioplasty and stenting has become a valuable alternative treatment for carotid endarterectomy, especially in certain high-risk patients. Stent fracture has been described in different arteries. Majority of the studies of stent fractures have been conducted on the femoropopliteal and coronary artery. In these areas, long stent implantation, severe angulations, and overlapping stenting seem to be associated with stent fracture.[1,2] There is no extensive literature available on carotid stent fracture, in particular, not on acute carotid stent fracture. We present a case of acute RX ACCULINK (Abott Vascular) carotid stent fracture following balloon dilation in a patient who underwent carotid artery stenting of a severe asymptomatic carotid artery stenosis before cardiac surgery.

Case report

A 70-year-old man with history of obstructive coronary artery disease, aortic valve stenosis, and significant asymptomatic right internal carotid artery stenosis (Fig. 1) was accepted for coronary bypass grafting and aortic valve replacement. Carotid artery stent placement was performed before cardiac surgery following local institutional guidelines. Through a right transfemoral access, with support of a 8 Fr MPA guiding catheter and after predilation with 3.5 20 mm coronary balloon (10 atm), a 7–10 40 mm Carotid ACCULINK Stent was deployed in the right internal carotid artery under distal protection of an EmboShield PRO (Abott) 4.0–7.0 mm. Standard post dilation was performed successfully, using a 5.5 20 mm Submarine (Invatec) dedicated balloon (pressure at 12 atm with balloon diameter 5.83 mm). On the post procedural angiogram, extravasation of dye was noticed together with fracture of the stent struts (Figs. 2 and 3). Calcification was visible at the site of the fractures. The protection device was retrieved without any resistance. The patient remained hemodynamic and neurologically stable. Physical examination revealed a hematoma of 5 6 cm on the right side of the neck, anterior to the musculus sternocleidomastoideus. Furthermore, patient experienced light swallowing problems during the first 8 hr after the procedure. The hematoma reduced significantly after 24 hr and the swallowing problems resolved. Six weeks later, we performed a duplex ultrasound of the right internal carotid artery, which showed good patency of the stent. Patient underwent successful myocardial revascularization and aortic valve replacement. This patient will be further monitored at our outpatient clinic.

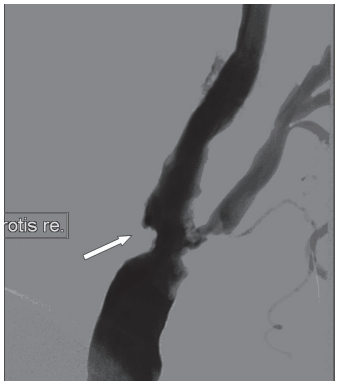

Fig. 1. Right internal carotid artery showed severe stenosis (arrow).

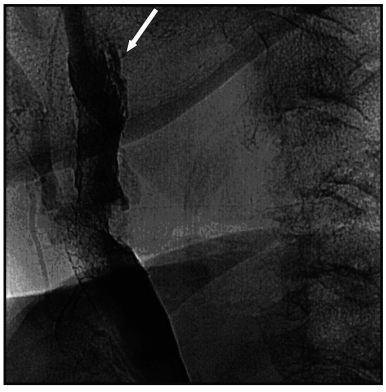

Fig. 2. Post procedural angiogram showed extravasation of dyne (arrow).

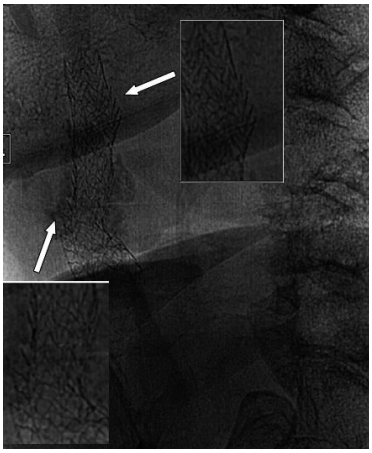

Fig. 3. Post procedural angiogram showed stent struts fracture of an ACCULINK carotid stent.

Discussion

Carotid artery stenting with protection devices is becoming an alternative treatment for symptomatic and asymptomatic patients who are at high risk for carotid endarterectomy.[3,4] Stent fractures have been reported in all of the anatomic territories, such as the coronary arteries, subclavian arteries, aortic artery, pulmonary artery, gastrointestinal artery, kidney artery, and peripheral vasculature, which lead to late complications and an increased rate of restenosis. The underling mechanism leading to stent fracture in femoropopliteal artery has not been completely understood. The superficial course of the artery with crossing of flexion points as well as interaction with the surrounding musculature, potentially exposes the artery to relevant external forces, including compression, torsion, and elongation. This may have a negative impact on vessel patency after both angioplasty and stenting.[1] Late stent fractures have been described as a complication following carotid stenting. De Vries et al. reported a fracture of a covered Symbiot carotid stent 7 months after implantation in a patient with traumatic pseudo aneurysm of the left internal carotid artery.[5] Valibhoy et al. described a fracture of Xact carotid stent in the mid-body of the stent in a noncalcified segment, 6 months after stent deployment with significant restenosis.[6] Similarly, fractures of Xact carotid stent have been reported by Diehm and Surdell and coworkers.[7,8] N' Dandu et al. described a fracture of ACCULINK carotid stent, 6 months after implantation.[9] More recently, Ling et al. showed 14 stent fractures in a registry of 48 deployed stents in the carotid artery. Restenosis

occurred in 21% of those fractured stents, with an average follow-up of 15 months.[10] Multiple mechanisms of stent fractures have been proposed, including overexpansion of the stent with high-pressure inflation, vessel angulations and tortuosity, severe calcification, wall shear stress, head movement.[11,12] and internal stress caused by pulsatile flow.[13] Ling et al. reported a strong association of late stent fracture occurrence with calcified vessel. In a calcified internal carotid artery, a stent fracture is eight times more likely.[10] Heavy calcification of the carotid artery has been reported as a major risk factor and as an important predictor of complication following carotid artery stenting. The calcification impedes complete expansion of the stent and can lead to an acute fracture of the stent, sometimes responsible for in-stent restenosis.[14] In our case, there was no overexpansion of the stent. Post dilation was not excessively high according to our experience. The stent fracture could have been the result of severe tortuosity and calcification of the vessel.

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PART VIII

General Discussion

Chapter 10

General Discussion

This thesis describes the strategy of the management and treatment of patients with concomitant significant carotid and coronary artery disease. The short and long term outcome of a single centre experience is reported and compared with general common practise. The author conducted different observational trials in order to provide more information to justify the institutional policy. More particularly, the use of embolic protection devices in asymptomatic patients is questioned, the optimal antiplatelet therapy is investigated and the use of CT perfusion to better understand individual cerebral hemodynamics is examined.
The concept of performing CAS before cardiac surgery is not novel. A paucity of literature is available describing the effect of CAS on the incidence of death and stroke after cardiac surgery (see Table 1).

Table 1. Clinical Events after Staged CAS and Cardiac Surgery

Reference	year	n	sympt n%	Post CAS-CABG n%			
				Death	Any stroke	MI	Death/Any stroke
Zidia	2005	56	26(46)	3(5.4)	1(1.8)	2(3.6)	4(7.1)
Kovacic	2006	20	8(30.8)	0	1(5)	1(5)	1(4.3)
Randall	2006	52	4(8)	7(13.5)	3(5.8)	n.a.	10(19.2)
Van der Heyden	2007	356	0	13(3.7)	11(3.1)	7(2.0)	24(6.7)
Combined		484	38(7.8)	23(4.7)	16(3.3)	n.a.	39(8)

Present recommendations for asymptomatic and symptomatic patients

Asymptomatic patients

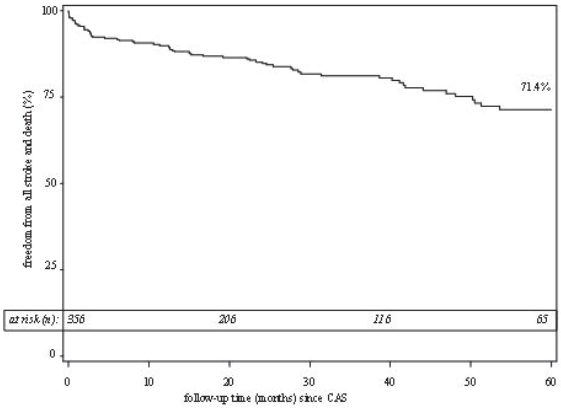
Making a balanced and reasonable recommendation to a patient in the invidious position of having coexistent coronary and carotid atherosclerotic disease is extremely difficult. Possibly due to a greater and more widespread atherosclerotic burden, the operative risk posed by combined CEA-CABG is known to be greater than for CEA and CABG performed as two isolated procedures in patients with disease

restricted to a single territory.[1] In the setting of concurrent carotid and coronary artery disease, CAS now offers an alternate means of carotid revascularization and seem to pose less risk of myocardial ischemia than CEA.[2,3] Therefore, the CAS-CABG approach may be explored as a viable method of combined revascularization strategy in high-risk asymptomatic patients who require CABG, as described in chapter 3.

In most instances in which CAS and CEA before or concomitant with CABG have been compared, results tend to favor CAS. Das et al. observed a risk of 11.5% for stroke and death in patients with severe carotid disease undergoing isolated CABG, with an undetermined incidence of nonfatal MI.[4] Naylor et al. reported a 10% to 12% risk of death, stroke, or MI for staged or combined operations and concluded that staged or synchronous operations might be able to reduce the death or stroke rate.[5] Ziada et al. described significantly fewer adverse events in patients who underwent CAS and cardiac surgery, despite a higher baseline risk profile, than in those undergoing combined CEA and CABG.[6] We demonstrate a favorable stroke and death risk of 4.8% and a combined risk of 6.7% for death, stroke and MI. The latter study showed a low rate of ipsilateral major stroke (1.1%), especially in view of the fact that 13 patients (3.7%) underwent CAS and cardiac surgery combined with contralateral CEA. Also, the periprocedural cardiac and neurological death rate was higher for patients ≥ 80 years than for those < 80 years of age.[1]).

The immediate postoperative period was crucial for these octogenarians, with all fatal events occurring within 2 days of cardiac surgery. Not only short-term but also long-term durable results of 71.4% freedom from all stroke and death at 5 years were described in chapter 3 (see Figure 1).[7]

Figure 1. 5 Years Freedom from All Stroke and Death. n indicates number at risk. (Kaplan-Meier curve)



In a recent large population-based study the safety and efficacy of staged CAS and CABG in terms of perioperative complications among asymptomatic patients has been confirmed and suggests that this approach may be a valuable, if not preferable, alternative to CEA-CABG.[8] However, in those patients with peripheral vascular disease precluding femoral artery access or when the aortic arch is markedly unfolded or severe tortuosity is making an endovascular pathway to the carotid artery hazardous, CEA-CABG remains the first option. Patients with severe renal insufficiency or allergy to antithrombotic medication are not eligible for an endovascular approach.

How can we identify the best management strategy for patients with severe asymptomatic carotid stenosis that requires cardiac surgery? The perfect but unrealistic solution would be a randomized trial; however, the target population is too small. Given the assumption of a 30-day death, stroke or MI rate in the CEA-CABG group of 12% and a noninferiority boundary of 3%, such a study would require an enrolment of ± 4000 patients to be adequately powered. Obviously, such a trial seems inconceivable because of the lack of funding and the awaited slow enrollment.[9]

The 3% Rule

Whether or not the 3 % rule for isolated CEA can be achieved in such a high risk population remains uncertain. However, undertaking a CAS procedure with a <3% complication rate in asymptomatic patients and <6% in symptomatic patient, should remain the goal of all interventionists.[10,11]

Symptomatic patients

The risk of perioperative stroke in CABG patients who report a prior history of TIA or stroke has been associated with a 4-fold increased risk as compared to the risk for neurologically asymptomatic patients (8.5% [95% confidence interval (CI): 4.9 to 12.1] versus 2.2% [95% CI: 1.4 to 3.1]).[12] D'Agostino et al. reported a periprocedural stroke rate of 17.9% in patients with unilateral carotid disease and 26.3% in those with bilateral disease undergoing isolated CABG.[13] These patients have a very high risk of stroke during CABG, and prophylactic intervention can be justified. In the available data describing the CAS or CEA-CABG strategy, periprocedural event rates of the symptomatic and the asymptomatic patients are scarcely reported separately. In some systematic reviews, the 30-day stroke rates have been evaluated and varied from 2.7% after staged CEA-CABG (57% asymptomatic) to 4.2% after staged CAS-CABG (87% asymptomatic), 4.6% after synchronous CEA-CABG (59% asymptomatic) and 6.3% after reverse staged CABG-CEA (no detailed data available describing the neurological

status).[5,14,15] It is difficult to compare the outcome in symptomatic patients to such data. However, Timaran et al. described the outcome for the symptomatic subpopulation in a large study based on the NIS (Nationwide Inpatient Sample) databases of 27,084 patients undergoing either synchronous CEA-CABG or staged CAS-CABG in the United States between 2000 and 2004.[8] Stratified analyses according to the symptomatic status and type of carotid revascularization revealed that among 973 patients with symptomatic carotid stenosis, 96.4% underwent CEA-CABG, and post-operative stroke occurred in 14.2%. Only 25 patients with symptomatic carotid stenosis in this series underwent CAS-CABG, and the post-operative stroke rate was 44%. As expected, this reported event rate after CEA-CABG (14.1%) for the symptomatic subpopulation is higher than for the above-mentioned group of mainly asymptomatic patients.[5,14,15] However, the 5-fold increased risk of post-operative stroke (44%) for the CAS-CABG approach compared with those undergoing CEA-CABG(odds ratio: 4.7; 95% CI: 2.1 to 10.6; p<001) is striking. Given the small number of patients undergoing CAS-CABG, this comparison should be interpreted cautiously.

The findings from the SAPPHIRE trial, including patients with significant cardiac disease, showed that among high-risk patients with severe carotid artery stenosis and coexisting conditions, carotid artery stenting (CAS) using an embolic protection device is not inferior to CEA.[16,17] The CAS-CABG outcome for symptomatic patients remains underreported, notwithstanding these randomized data supporting CAS for high-risk patients.

In chapter 4 we report a favourable 30-day all-stroke rate of 8.8% and a combined risk for death, all strokes and MI of 12.3% for the CAS-CABG approach. One possible explanation for the lower periprocedural combined risk in the present study compared with the Timaran data may be related to the fact that patients underwent cardiac surgery without discontinuation of aspirin, whereas clopidogrel was administered until 7 days before the operations. The balance between the optimal antiplatelet therapy required for CAS and not postponing CABG seems to influence this outcome favorably.[18] Furthermore, the high volume of CAS procedures in our center could account for these favorable short-term results of the combined procedure. No statistical difference was found when these CAS results before CABG are compared with the cumulative incidence of the primary endpoint at 30 days in the SAPPHIRE trial for the symptomatic patients (8.8% vs. 2.1% SAPPHIRE CAS, p=0.212 and 9.3% SAPPHIRE CEA, p=0.18). The long-term follow-up showed a survival rate of 63.7% with a significantly higher all-cause mortality rate and all-death, stroke, and MI

rate for patients ≥75 years. We report a 12.3% stroke rate at 3 years, which was not statistically different from the subgroup analyses for symptomatic patients in the SAPPHIRE study (12.3% [7 of 57 patients] vs. 6.0% [3 of 50 patients] in the SAPPHIRE CAS group (p=0.331) and vs. 8.7% [4 of 46 patients] in the SAPPHIRE CEA group, p=0.751), taking into account that in our study, all patients underwent CABG, whereas in the SAPPHIRE population, only a minority had coexisting severe coronary artery disease.[16,17]

Finally, symptomatic patients may pose an additional problem. They face the highest risk of stroke reoccurrence during the first weeks and therefore "stenting" will have to be performed with the acceptance of higher periprocedural complication rates.[19] However delaying CAS would not really be of any benefit to the patient because of the number of strokes occurring while waiting.

Reduction of Myocardial infarction

The longer operative time and general anaesthesia duration in CEA-CABG patients are probably the most significant contributors of the occurrence of MI during combined surgery. It is also possible that the profound hypotension that frequently follows carotid revascularization due to carotid sinus baroreceptor manipulation results in severe diminution of coronary perfusion, especially with the underlying severe coronary disease. The hemodynamic stress of cardiopulmonary bypass can be detrimental immediately after CEA. Moreover, early postoperative use of additional or larger doses of pressors to treat hypotension after CEA-CABG has been reported.[20,21] In contrast, hypotension after CAS is generally managed with intravenous fluids, and pressor agents are rarely used . The potent antiplatelet treatment used during CAS could have a protective role during the carotid and cardiac revascularization procedures, although clopidogrel is generally stopped 1 week before cardiac surgery. In chapters 3 and 4 we describe the diagnosis of Q wave myocardial infarction in our centre, mainly based on the presence of new Q waves on the electrocardiogram and an elevated creatine kinase to at least two times the upper limit of the normal range with an elevated level of MB isoenzyme. In the absence of pathologic Q waves, the diagnosis of non-Q wave myocardial infarction was based on the increase of creatine kinase level to more than twice the upper limit of the normal range with an elevated level of MB isoenzyme.[7]

From the recent results of the CREST trial, although mainly elucidating on the

overall patient group undergoing carotid revascularization (cardiovascular disease was present in only 49.7% (n=1181) of asymptomatic patients and 37.9% (n=1321) of symptomatics) and therefore not completely representative for the described population, we learned that the rate of MI was lower after CAS versus CEA for symptomatic patients (1.0%±0.4% versus 2.3%±0.6%; HR, 0.45; 95% CI, 0.18 to 1.11; p=0.08) and for asymptomatic patients (1.2%±0.3% versus 2.2%±0.6%; HR, 0.55; 95% CI, 0.22 to 1.38; p=0.20); however not significant, one can assume that the MI rate would increase even more in the CEA group if all patients had concomitant coronary disease.[2,3] Although quality-of-life analyses among survivors at 1 year in the CREST trial indicate that stroke had a greater adverse effect on a broad range of health-status domains than did myocardial infarction, the authors did not take into account the risk of late (>1 year) malign ventricular arrhythmia.

The total periprocedural MI rate of 2.0% reported in chapter 3, is in contrast to observational studies of CEA and CABG, in which the rate varies from 3.6% (synchronous) to 6.5% (staged), especially when one bears in mind that in the present study population, 13% of cardiac surgical procedures were redo procedures.[7] In the symptomatic study, described in chapter 4, one patient who suffered from a MI while waiting for CABG died 3 months after CABG.[24] The low periprocedural MI rate in both groups emphasizes the reduced invasiveness of this approach, which is especially important for these high-risk patients.

Cerebral perfusion

The importance of hemodynamic factors in the pathogenesis and treatment of ischemic cerebrovascular disease in patients undergoing cardiac surgery is a matter of on-going debate. Stratifying patients based on the degree of carotid stenosis (CS) fails to differentiate those with reduced cerebral perfusion pressure from those with noncompromised cerebral hemodynamic.

The increasing number of endovascular procedures for the treatment of CS performed during the last decade has intensified the need for monitoring the outcome of these procedures. In chapters 5 and 6 the semi-quantitative evaluation of cerebral perfusion is studied. Is seems to be a reliable tool for the follow-up of patients who undergo CAS. Computed tomography perfusion (CTP) scanning before and after CAS has shown to allow for assessment of pre-treatment inter-hemispheric differences, which may or may not resolve after treatment. Using CT perfusion technique,[23-25]

more specifically measuring the mean transit time, we encountered a significant improvement of cerebral perfusion after carotid stenting in asymptomatic and symptomatic patients planned for cardiac surgery. Especially, additional evidence for the benefit of stent placement in asymptomatic has been established by demonstrating improvement in both rCBF and dMTT.
In the first stage of hemodynamic compromise, collaterals of the brain are not able to maintain normal cerebral perfusion, which leads to reflex vasodilation and subsequent elevation of intravascular CBV. CBF is still preserved at this stage of hemodynamic compromise. When further reductions in perfusion pressure take place with concurrent increasing MTT, CBV reaches its maximum and cerebrovascular autoregulation is not sufficient to maintain normal perfusion. Stage II hemodynamic failure occurs when CBF declines and oxygen extraction increases.

Distal protection devices

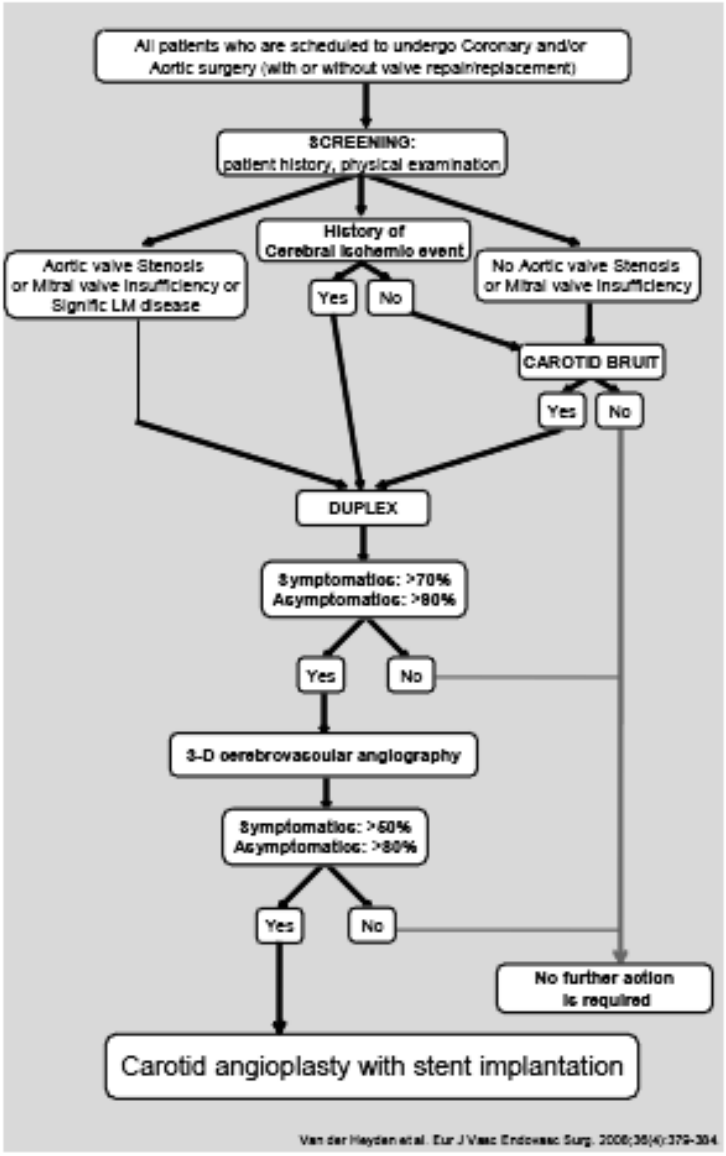
Until now, no level-1 evidence based on clinical outcome data exists in support of embolic protection devices (EPDs). Surrogate markers such as magnetic-resonance diffusion-weighted imaging of brain, procedural transcranial Doppler, or biochemical markers of neurological injury have failed to provide evidence in favor of CAS with EPD.[26] Furthermore, the available data pertain predominantly to a majority symptomatic population.
With the use of biomedical imaging and histological analysis of debris captured in embolic protection filters retrieved, we describe in chapter 7 that we were unable to detect material or deposits suggesting recurrent thromboembotic events originating from an atherosclerotic plaque. The obtained material corresponds essentially to aggregates or isolated blood cells and material of exogenous origin. However, a prevalence of features of instability has been reported as being low in plaques from patients suffering stroke on whom CEA was performed >180 days after the event. Furthermore, these plaques were no more unstable than plaques that were studied from patients who underwent surgery for asymptomatic stenosis. Therefore, the fact that all patients in this study were on dual antiplatelet therapy (aspirin and clopidogrel) and were neurologically asymptomatic might explain the ‘‘empty’’ filters. An interesting finding, when comparing the histological findings of the captured debris of this study with other reports, was that the presence of platelet aggregates is consistent in all analysis.[27-32] It has been described that these

aggregates could cause pore obstruction resulting in transient flow impairment while others found a correlation between filter occlusion and ACT.[7,28] Moreover, it has been shown on electron microscopy by DeRubertis et al. that besides the fact that the most prevalent finding in embolic debris was the presence of individual platelet or platelet aggregates, there is an increased incidence of platelet activation in the debris contained within the filters of symptomatic patients relative to asymptomatics.[30] Furthermore the variance in the amount of the captured material also seemed to be influenced by the preoperative symptom status, where in symptomatic patients in contrast to asymptomatics more debris was captured, emphasizing the different pathophysiology.

Selective preoperative screening

The question of routine carotid evaluation in patients undergoing CABG remains unsettled. Our institutional guidelines prescribe a duplex ultrasound in case of a previous cerebral ischemic event, the presence of a carotid bruit, combined coronary artery or aortic disease with aortic valve stenosis, mitral valve insufficiency or severe peripheral artery disease.[33] We are considering to expand this policy towards patients with diabetes or ≥ 75 years of age.
In figure 2 our institutional screening approach is depicted.

Figure 2. Institutional guidelines for the screening of patients scheduled for cardiac surgery



Timing and medical management

Timing

Different strategies for the administration of the dual antiplatelet therapy have been evaluated, as discussed in the introduction.

In chapter 3 we described our approach in asymptomatic patients, continuing the antiplatelet drug regimen until 5 days before surgery.[7] Consequently 31.7% of patients underwent CABG within 14 days after CAS, 32.2% after 14-30 days and 37.1% after 30 days. They did not report any stent thrombosis or increased perioperative bleeding complications.

In chapter 4 the timing in symptomatic patients, treated in our centre, is evaluated. The median time interval between CAS and cardiac surgery was 28 days (interquartile range: 12 to 58 days).[22] No major bleeding requiring rethoracotomy was reported in those patients on dual antiplatelet therapy versus those on acetylsalicylic acid alone during surgery. One patient suffered a major stroke within 30 days after cardiac surgery. In the latter patient, post procedural duplex ultrasonography was performed and showed adequate stent apposition in the treated carotid artery without hemodynamically significant restenosis or stent thrombosis.

It is our practice to perform CAS (with dual antiplatelet therapy) and then to stop the clopidogrel 7 days before CABG (aspirin continued). Clopidogrel is restarted (mean time of 2 days) after recovery from surgery. In those patients requiring urgent cardiac surgery, CAS is performed using dual antiplatelet therapy, which is not stopped before the cardiac procedure.

Antiplatelet therapy

During carotid stent implantation, the endothelial barrier becomes injured with the subsequent adhesion and activation of circulating platelets.[34] Adequate antithrombotic therapy is therefore of utmost importance. Based on promising data on the use of aspirin plus clopidogrel in the setting of coronary artery stenting this adjunctive dual antiplatelet regimen is currently also the treatment of choice in CAS, but no strict recommendations with regard to the dosage and timing of the initial loading dose of clopidogrel are available.[35-37] By using transcranial Doppler (TCD) monitoring during CAS, it is possible to detect the number of microembolic signals (MES) throughout the different phases of CAS.[38,39] Post-CAS TCD-monitoring has not been performed systematically in the past and thus could reveal valuable

information helpful to the understanding of postprocedural cerebral complications and risk stratification. In chapter 8 the effects of a high versus standard clopidogrel loading dose prior to CAS on the number of TCD-detected microemboli are compared, for the first time in a randomized trial.[40] In a prespecified secondary analysis, the relationship between the magnitude of on-treatment platelet reactivity and TCD-detected microemboli are investigated to quantify the possible role of platelets in the pathophysiology of TCD-detected micro-emboli. The principal finding is that there does not appear to be a significant difference in the number of TCD-detected microemboli during and after CAS between either a 300 mg or a 600 mg loading dose of clopidogrel. Intriguingly, the absolute magnitude of on-treatment platelet reactivity as measured with two platelet function assays was equal in both groups and a predefined exploratory analysis revealed that there is no relationship between the magnitude of platelet reactivity and the number of TCD-detected microemboli. The former is in contrast to the positive findings reported in medical literature in the setting of CEA. Although a lower rate of MES was expected in our cohort, because our patients had asymptomatic carotid artery disease, our secondary exploratory analysis did not indicate a possible role for the magnitude of on-treatment platelet reactivity in the pathophysiology of CAS-induced MES.

Conclusion

Patients with asymptomatic carotid stenosis undergoing CAS-CABG have a decreased stroke and death rate compared to those undergoing isolated CABG or CEA-CABG. CAS may be a safer carotid revascularization option for patients with asymptomatic carotid stenosis requiring CABG in terms of postoperative stroke prevention. In patients with symptomatic carotid stenosis available data are confounding, therefore the preferred strategy remains unclear, however carotid revascularization will result incontestably in higher periprocedural complication rates. Although level I evidence would be ideal to determine the best treatment strategy for patients who require combined treatment of carotid and coronary arterial disease, the design and implementation of a multicenter randomised clinical trial has been proven impractical and unrealistic. The heterogeneity of patients with varying degrees of coronary and carotid artery disease and the preference of carotid intervention are the main limitations for such a trial. Nevertheless, when conceived, such a trial should compare isolated CABG (including on and off pump surgery) with CAS-CABG and CEA-CABG in symptomatic and asymptomatic patients separately.

Optimal treatment of patients with concurrent carotid and coronary artery disease remains unresolved despite extensive publications during the last 30 years. Although only 40% to 50% of strokes after CABG are ipsilateral to an existing carotid lesion, carotid revascularization is one of the few available options to reduce the excessive stroke and death rates in patients with combined disease.

Future perspectives

1. Prevention of cerebrovascular events is the main goal of performing carotid revascularization prior to cardiac surgery. However lack of randomised trials has made it impossible to draw firm conclusions regarding the best management strategy and impedes a shift from the guidelines to a level of evidence A or B.
2. The social and economical consequences of neurological deficits plays a huge role in the field of cardiac surgery. The costs can be estimated to be $2 to $4 billion annually worldwide. The morbidity in survivors of such strokes is likely to remain substantial, particularly in an aging population. Therefore, identification of individuals at high risk for perioperative stroke is increasingly important, not only to accurately assess patient risk for surgery, but also to foster the development of new strategies to reduce the frequency of this complication.[41]
3. The importance of hemodynamic factors in the pathogenesis and treatment of ischemic cerebrovascular disease in patients undergoing cardiac surgery is a matter of ongoing debate. Stratifying patients based on the degree of carotid stenosis fails to differentiate those with reduced cerebral perfusion pressure from those with noncompromised cerebral hemodynamics. Moreover, it seems hazardous to use the degree of carotid stenosis to decide whether a patient may be at increased risk for stroke on hemodynamic grounds. This implies that the choice of medical therapy or revascularization should not be based on these considerations only. Noninvasive measurements of cerebral perfusion, such as SPECT with acetazolamide or CTP, may become a valuable method to predict the risk of hemodynamic stroke in patients with significant carotid disease scheduled for cardiac surgery and guide clinicians to the judicious use of prophylactic cerebrovascular interventions.[42-44]
4. Optimal timing between CAS and CABG needs to be established. In the near future, we aim to investigate the potential benefits of a “real” hybrid procedure, partially based on previous experience of Mendiz and Kramer, where CAS and CABG would be performed in a dedicated hybrid operating room.[45,46] Avoiding the present delay between the 2 procedures could further decrease the periprocedural events, eliminate difficult questions on optimal premedication and could turn out to be more cost-effective.

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Chapter 11

Summary
Samenvatting
Dankwoord
List of publications

Summary

This thesis addresses the outcomes of several clinical aspects in the treatment of patients with significant carotid artery disease undergoing cardiac surgery (CABG). In particular carotid stenting in neurologically asymptomatic and symptomatic patient was described. Also, the cerebral perfusion was studied, the use of a distal protection device and the antiplatelet therapy during carotid artery stenting (CAS) and CABG were examined.

Part I of this thesis, encapsulating **chapter 1**, offers an introduction. An overview of the guidelines, mechanism of stroke during cardiac surgery, techniques of revascularization, screening methods and time management are given.

Part II, **chapter 2** opens the discussion on this controversial subject, giving the pro- and antagonist the opportunity to clarify the evidence to justify their claims. Different assumptions are described and explained: 1. The incidence of significant carotid stenosis (CS) is high, and most perioperative stroke during CABG occurs in the subgroup of patients with CS. 2. The perioperative stroke in patients undergoing CABG occurs primarily in the territory of carotid artery. 3. Although CS could be a small contributor to perioperative stroke risk, preoperative carotid revascularization would eliminate stroke in some of these patients and hence should be offered. 4. CS reduces distal internal carotid blood flow and hence puts the ipsilateral cerebral hemisphere at risk for ischemia during cardiopulmonary bypass. 5. Preoperative carotid endarterectomy (CEA) is necessary to avoid carotid territory stroke in patients undergoing CABG. In conclusion, there seems to be no consensus on the exact influence of impaired cerebral autoregulation in patienst undergoing cardia surgery. Further research on the primary pathophysiological cause of stroke during CABG is warranted.

Part III of the thesis gives a description of a single centre outcome of CAS and CABG in neurological asymptomatic and symptomatic patients. Also, an editorial comment by key opinion leaders on both publications in **chapter 3** and **4** is published.

In **chapter 3** the results of a prospective, single-center study designed to evaluate the feasibility and safety of CAS before cardiac surgery in neurologically asymptomatic

patients is decribed. The periprocedural and long-term outcomes of 356 consecutive patients who underwent CAS before cardiac surgery were analyzed. The procedural success rate of CAS was 97.7%. The death and stroke rate from time of CAS to 30 days after cardiac surgery was 4.8%. The myocardial infarction (MI) rate from time of CAS to 30 days after cardiac surgery was 2.0%, and the combined death, stroke and myocardial infarction rate was 6.7%. Distal embolic protection devices were used in 40% of the cases. In conclusion, this large cohort of asymptomatic patients who underwent staged CAS and cardiac surgery experienced a low periprocedural complication rate. The high rate of freedom from death and stroke during the 5 years of follow-up supports the long-term durability of this approach. These findings suggest that this new strategy may become a valuable alternative in the treatment of patients with combined carotid and cardiac disease.

In **chapter 4** the feasibility and safety of the combined outcome of CAS and CABG in neurologically symptomatic patients is evaluated. The CAS-CABG outcome for symptomatic patients remains underreported, notwithstanding randomized data supporting CAS for high-risk patients. The procedural success rate of CAS was 98%. The combined death, stroke and MI rate was 12.3%. The death and major stroke rate from time of CAS to 30 days after cardiac surgery was 3.5%. The MI rate from time of CAS to 30 days after cardiac surgery was 1.5%. In conclusion, this is the first single-center study reporting the combined outcome of CAS-CABG in symptomatic patients. The periprocedural complication rate and long-term results of the CAS-CABG strategy in this high-risk population support the reliability of this approach. In such a high-risk population, this strategy might offer a valuable alternative to the combined surgical approach; however, a large randomized trial is clearly warranted.

Part IV concerns the effect of CAS on cerebral CT perfusion (CTP).

In **chapter 5** we describe a prospective, non-randomised study (n= 16 neurologically asymptomatic patients) which was designed to analyse cerebral perfusion using CTP before and after CAS. Mean transit time (MTT) was significant lower and cerebral blood flow (CBF) was significantly higher in the non-target hemisphere compared to the target hemisphere before treatment (4.64±1.08 s vs. 5.67±1.29 and 57.37±24.90 s vs. 48.19±13.02, respectively). Mean dMTT decreased from 0.92±1.08 s before to 0.04±0.30 s after carotid revascularisation ($p<0.05$) and mean relative CBF (ratios

of the treated to the untreated hemisphere) increased from 0.92±0.12 to 1.04±0.12 after revascularisation ($p<0.05$). Subgroup analysis based on pre- treatment dMTT showed significant changes in 50% of the patients with larger dMTT. There was one transient ischaemic attack reported 30 days after combined procedure. In conclusion, a significant improvement of cerebral perfusion after carotid stenting is shown in about 50% of the asymptomatic patients. This suggests the potential presence of a compromised cerebral circulation in asymptomatic patients with severe carotid artery disease scheduled for cardiac surgery.

In **chapter 6** a comparison is given of the effect of stent placement on cerebral perfusion in symptomatic and asymptomatic patients using CT perfusion. Forty-five patients with carotid artery stenosis of ≥70% who underwent CAS were included. Thirty-one patients were treated because of symptoms; 14 asymptomatic patients were treated before coronary artery bypass grafting. Patients underwent CTP before and after stent placement. All perfusion parameters changed significantly after treatment in symptomatic patients: rCBF increased from 0.81 to 0.93 ($P < 0.001$), rCBV decreased from 1.02 to 0.95 ($P <0.05$), and dMTT decreased from 1.29 to 0.14 ($P <0.001$). In asymptomatic patients, only rCBF changed significantly with an increase from 0.92 to 1.03 ($P <0.05$). When we compared symptomatic and asymptomatic patients before treatment, rCBF in symptomatic patients was significantly lower. The decrease of rCBV after treatment in symptomatic patients resulted in a significantly lower value than in asymptomatic patients. In conclusion, CAS improves blood flow in the affected hemisphere in symptomatic and asymptomatic patients. CBF before treatment is more strongly impaired in patients with symptomatic carotid stenosis. Compensatory hyperemia on the symptomatic side before treatment turns into hypoxemia after treatment, suggesting impaired autoregulation in these patients.

Part V includes a report describing the use of embolic protection devices (EPD) during CAS and a randomized trial comparing different loading doses of clopidogrel measuring platelet reactivity and the number of microemboli.

In **chapter 7** the analyze of the debris captured in the distal protection filters used during CAS is shown. From May 2005 to June 2007, filters from 59 asymptomatic patients who underwent CAS were collected and sent to a specialized laboratory for light-microscope and histological analysis. On the basis of biomedical imaging

of the filter debris, the captured material could not be identified as embolized particles from the carotid plaque. On histological analysis the debris consisted mainly of red blood cell aggregates and/ or platelets, occasionally accompanied by granulocytes. No consistent histological evidence of embolized particles originating from atherosclerotic plaques were found. Post-procedure, three neurological events were reported: two (3.4%) transient ischemic attacks and one (1.7%) ipsilateral minor stroke. In conclusion, the filters used during CAS in asymptomatic patients planned for cardiac surgery often remained empty. These findings may be explained by assuming that asymptomatic patients feature a different atherosclerotic plaque composition or stabilization through antiplatelet medication. Larger, randomized trials are clearly warranted, especially in the asymptomatic population.

In **chapter 8** we describe the comparison of the effects of 300mg or 600mg clopidogrel loading dose, prior to CAS on the number of transcranial Doppler (TCD)-detected microembolic signals (MES) and we investigate the relationship between the magnitude of platelet reactivity and MES. In a prospective randomized, double-blind study, 35 consecutive asymptomatic patients (17.1% females), scheduled for CAS and cardiac surgery were included. No statistically significant difference in the number of TCD-detected MES, in the sum of all the single emboli or showers and platelet aggregation measurements between the two groups was observed. (aggregometry: 21.7 ± 18.3 versus 23.0 ± 18%, p=0.8499 and 45.8 ± 17.5 versus 46.5 ± 14.5%, p=0.9003) (verifyNow P2Y12 assay: 231 ± 93 PRU versus 222 ± 86 PRU, p=0.7704). In conclusion, it is shown that a loading dose of 300 mg of clopidogrel in combination with aspirin is as effective as 600 mg of clopidogrel in achieving adequate platelet inhibition and preventing periprocedural events in asymptomatic patients undergoing CAS prior to cardiac surgery.

In **chapter 9** a case of carotid stent fracture during carotid angioplasty is described.

Part VI of the thesis contains **chapter 10**, which offers the general discussion. First, present recommendations for asymptomatic and symptomatic patients are described. Second, the reduction of MI using CAS in stead of CEA prior to CABG in patients with concomitant carotid artery disease is evaluated. Third, cerebral perfusion and the importance of hemodynamic factors in the pathogenesis and treatment of ischemic cerebrovascular disease in patients undergoing cardiac surgery is debated. Fourth,

the use of distal protection devices is examined. Fifth, a selective preoperative screening for carotid artery disease is suggested.
Finally, the timing and medical management for the combined treatment has been studied, followed by the conclusions of this thesis.

Samenvatting

Dit proefschrift behandelt de resultaten van verschillende klinische aspecten tijdens de behandeling van patiënten met significant carotislijden die hartchirurgie (CABG) zullen ondergaan. In het bijzonder wordt stentplaatsing bij neurologisch asymptomatische en symptomatische patiënten beschreven. Ook de breinperfusie wordt bestudeerd, alsook het gebruik van een distaal protectie toestel en de bloedplaatjesremmers worden onderzocht.

In **deel I** van dit proefschrift, waarvan **hoofdstuk 1** onderdeel uitmaakt, wordt er een inleiding gegeven. Een overzicht van de richtlijnen, het mechanisme voor het optreden van een beroerte tijdens CABG, de verschillende technieken van revascularisatie, de screeningsmethode en tijdsintervallen worden bestudeerd.

In **deel II**, **hoofdstuk 2**, wordt de discussie geopend over dit controversieel onderwerp, waarbij zowel de pro-als anatgonisten de mogelijkheid geboden wordt hun bewijsvoering toe te lichten ter rechtvaardiging van hun stellingen. Verschillende aannames worden aan de tand gevoeld: 1. de incidentie van een significante carotisvernauwing (CV) is hoog en de meeste perioperatieve beroertes tijdens CABG komen voor in deze subgroep van patiënten met CV. 2. de perioperatieve beroerte bij patiënten die CABG ondergaan, treedt voornamelijk op in het stroomgebied van de carotis slagader. 3. indien CV een kleine bijdrage zou leveren bij het optreden van perioperatieve beroerte, dan zou preoperatieve carotis revascularisatie de kans op beroerte wegnemen bij deze patiënten en zou daarvoor moeten voorgesteld worden. 4. CV doet de doorstroming in de distale carotis interna afnemen en brengt daardoor de ipsilaterale hersenhemisfeer in gevaar voor ischemie tijdens extracorporele hart-long circulatie.5. preoperatieve carotis endarterectomie (CEA) is noodzakelijk om beroerte in het carotis stroomgebied te vermijden bij patiënten die CABG ondergaan. Concluderend blijkt er geen eenduidigheid te bestaan over de exacte invloed van de aangetaste autoregulatie van de hersenen bij patiënten die CABG ondergaan. Verder onderzoek over de primaire pathofysiologische oorzaak van beroerte tijdens CABG is aangewezen.

In **deel III** van dit proefschrift wordt de uitkomst vanuit één centrum van carotis stentplaatsing (CAS) en CABG in neurologisch asymptomatische en symptomatische

patiënten beschreven. Daarnaast, wordt er ook een redactionele commentaar door een expert over beide artikels in **hoofdstuk 3 en 4** gepubliceerd.

In **hoofdstuk 3** worden de resultaten beschreven van een onderzoek vanuit één centrum dat ontworpen werd om de toepasbaarhied en de veiligheid te beoordelen van CAS voorafgaand aan hartchirurgie bij neurologisch asymptomatische patiënten. De periprocedurele en de lange termijn resultaten van 356 opeenvolgende patiënten die CAS ondergingen voorafgaand aan CABG werden geanalyseerd. De procedurele kans van slagen voor CAS was 97.7%. Het sterfte- en beroerte cijfer was 4.8%. De verhouding voor het optreden van een myocard infarct (MI) tellend vanaf het moment van de CAS tot 30 dagen na CABG was 2.0%, en de gecombineerde verhouding van overlijden, beroerte en MI was 6.7%. Een distaal protectie toestel werd in 40% van de gevallen gebruikt.
Tot slot kunnen we stellen dat deze uitgebreide groep van asymptomatische patiënten die stapsgewijze CAS en hartchirurgie ondergingen, een laag cijfer van periprocedurele complicaties laat zien. Het hoge cijfer voor het niet optreden van overlijden en beroerte gedurende 5 jaar opvolging, ondersteunt de langdurige werking van deze benadering. Deze bevindingen suggereren dat deze nieuwe strategie een waardig alternatief zouden kunnen vormen voor patiënten met gecombineerd carotislijden en hartaandoeningen.

In **hoofdstuk 4** wordt de toepasbaarheid en de veiligheid van de gecombineerde uitkomst van CAS en CABG bij neurologisch symptomatische patiënten geëvalueerd. Een dergelijke uitkomst bij symptomatische patiënten wordt zeldzaam gerapporteerd, ondanks het feit dat gerandomiseerde gegevens CAS bij hoog risico patiënten ondersteunen. De procedurele kans van slagen voor CAS was 98%. De gecombineerde verhouding van overlijden, beroerte en MI was 12.3%. Het sterfte- en (major) beroerte cijfer tellend vanaf CAS tot 30 dagen na CABG bedroeg 3.5%. De verhouding voor het optreden van een MI tellend vanaf het moment van de CAS tot 30 dagen na CABG was 1.5%. Concluderend kunnen we stellen dat dit het eerste onderzoek is vanuit één centrum waarvan de gecombineerde uitkomst van CAS-CABG bij symptomatische patiënten wordt gerapporteerd. De periprocedurele complicatie cijfers en de lange termijn resultaten van de CAS-CABG strategie bij deze hoog risico populatie onderbouwen de betrouwbaarheid van deze benadering. Bij een dergelijke hoog risico populatie zou deze strategie een waardig alternatief vormen

voor de gecombineerde chirurgisch benadering; echter, gerandomiseerde onderzoek is vereist.

In **deel IV** worden de effecten van CAS op de CT breinperfusie (CTP) uit de doeken gedaan.

In **hoofdstuk 5** beschrijven we een prospectieve, niet gerandomiseerde studie (n= 16 neurologisch asymptomatische patiënten) die ontworpen was om de breinperfusie te analyseren gebruik makend van CTP voor en na CAS. De gemiddelde doorstroom tijd (MTT) was significant lager en de bloedstroom in het brein (CBF) was significant hoger in de niet te behandelen hemisfeer vergeleken met de te behandelen hemisfeer voorafgaand aan de ingreep (4.64±1.08 s vs. 5.67±1.29 en 57.37±24.90 s vs. 48.19±13.02, respectievelijk). De gemiddelde dMTT daalde van 0.92±1.08 s voordien, tot 0.04±0.30 s na carotis revascularisatie ($p<0.05$) en de gemiddelde relatieve CBF (verhouding van de behandelde tot de niet behandelde hemisfeer) nam toe van 0.92±0.12 tot 1.04±0.12 na revascularisatie ($p<0.05$). Subgroep analyse, gebaseerd op dMTT van voor de behandeling toonde een significante verandering bij 50% van de patiënten met langere dMTT. Er trad 1 TIA op 30 dagen na de gecombineerde procedure. Tot slot, een significante verbetering van de breinperfusie na CAS is aangetoond bij ongeveer 50% van de asymptomatische patiënten. Dit suggereert de mogelijke aanwezigheid van een gecompromitteerde brein circulatie bij asymptomatische patiënten met ernstig carotislijden die gepland staan voor hartchirurgie.

In **hoofdstuk 6** wordt een vergelijking gegeven van het effect van stentplaatsing op de breinperfusie, gebruik makend van CTP, bij symptomatische en asymptomatische patiënten. Vijfenveertig patiënten met een CV van ≥70% die een CAS ondergingen, werden geïncludeerd. Eenendertig patiënten werden behandeld omwille van symptomen; 14 asymptomatische patiënten werden behandeld voorafgaand aan CABG. De patiënten ondergingen een CTP voor en na CAS. Alle perfusie parameters veranderden op significante wijze na de behandeling in de symptomatische groep: rCBF nam toe van 0.81 tot 0.93 ($P < 0.001$), rCBV nam af van 1.02 tot 0.95 ($P <0.05$), en dMTT nam af van1.29 tot 0.14 ($P <0.001$). Bij de asymptomatische patiënten veranderde alleen de rCBF op significante wijze van 0.92 tot 1.03 ($P <0.05$). Als we de symptomatische en de asymptomatische patiënten vergelijken voor de behandeling, dan is de rCBF significant lager bij de symptomaten. De afname van

rCBF na de behandeling bij de symptomaten resulteerde in een significante lagere waarde dan bij de asymptomaten. Concluderend, CAS verbetert de bloedstroom in de aangedane hemisfeer bij symptomatische en bij asymptomatische patiënten. CBF voor de behandeling is meer aangetast bij patiënten met een symptomatische CV. De compensatoire hyperemie aan de symptomatische zijde voor de behandeling wordt omgezet in hypoxie na de behandeling, wat een aangetaste autoregulatie suggereert. Deel V bevat een artikel wat het gebruik van embolische protectie toestellen (EPD) tijdens CAS beschrijft en tevens een gerandomiseerde onderzoek wat de verschillende ladingsdosissen van clopidogrel vergelijkt door de bloedplaatjes reactiviteit en het aantal micro-embolieën te meten.

In **hoofdstuk 7** wordt de analyse beschreven van de opgevangen restanten uit de distale protectie filters gebruikt tijdens CAS. Van mei 2005 tot juni 2007, werden de filters van 59 asymptomatische patiënten die CAS ondergingen, verzameld en opgestuurd naar een laboratorium gespecialiseerd in lichtmicroscopie en histologische analyse. Op basis van biomedische afbeelding van de restanten uit de filter, kon het opgevangen materiaal niet geïdentificeerd worden als geëmboliseerde partikels afkomstig van een carotis plaque. Bij histologische analyse bleken de restanten voornamelijk te bestaan uit rode bloedcel aggregaten en/of bloedplaatjes, af en toe vergezeld van enkele granulocyten. Er werd geen consistent bewijs gevonden dat de geëmboliseerde partiële afkomstig waren vanuit atherosclerotische plaques. Er werden drie neurologische gebeurtenissen gerapporteerd post procedureel: twee (3.4%) TIA's en één (1.7%) ipsilaterale (minor) beroerte. Tot slot, de filters die gebruikt werden tijdens CAS bij asymptomatische patiënten gepland voor hartchirurgie bleven vaak leeg. Deze bevindingen zouden kunnen verklaard worden als men aanneemt dat asymptomatische patiënten een verschillende atherosclerotische plaque compositie vertonen of dat er plaque stabilisatie is opgetreden door de bloedplaatjes remmende medicatie. Grotere, gerandomiseerde onderzoeken zijn vereist, zeker bij de asymptomatische populatie.

In **hoofdstuk 8** beschrijven we de vergelijking van de effecten van 300 of 600 mg ladingsdosis van clopidogrel, voorafgaand aan CAS op het aantal met transcranial Doppler (TCD) gedetecteerde microembolische signalen (MES) en we onderzoeken de relatie tussen de maat van plaatjes reactiviteit en MES. In een prospectief gerandomiseerd, dubbel blind onderzoek, werden 35 consecutive asymptomatische

patiënten (17.1 % vrouwen) die gepland stonden voor CAS en CABG, geïncludeerd. Er werd geen statistisch significant verschil aangetoond tussen het aantal TCD gedetecteerde MES, noch tussen de som van alle enkelvoudige embolieen of 'showers', evenmin tussen de bloedplaatjes metingen in de beide groepen (aggregometrie: 21.7 ± 18.3 versus 23.0 ± 18%, p=0.8499 en 45.8 ± 17.5 versus 46.5 ± 14.5%, p=0.9003) (verifyNow P2Y12 test: 231 ± 93 PRU versus 222 ± 86 PRU, p=0.7704). Tot slot is het aangetoond dat een ladingsdosis van 300 mg clopidogrel in combinatie met aspirine even effectief is als 600mg clopidogrel voor het bereiken van adequate bloedplaatjes remming en in het voorkomen van periprocedurele complicaties bij asymptomatische patiënten die CAS dienen te ondergaan voorafgaand aan hartchirurgie.

In **hoofdstuk 9** wordt een casus beschreven waarbij er een breuk ontstaat van een carotis stent tijdens CAS.

In **deel VI** van dit proefschrift is **hoofdstuk 10** te lezen, waarin de algemene discussie staat beschreven. Ten eerste worden de huidige aanbevelingen voor asymptomatische en symptomatische patiënten beschreven. Ten tweede wordt de afname van het optreden van een MI, door gebruik te maken van CAS in de plaats van CEA voorafgaand aan CABG bij patiënten met gecombineerd carotis lijden, geëvalueerd. Ten derde wordt de breinperfusie en het belang van hemodynamische factoren in de pathogenese en de behandeling van ischemisch cerebrovasculair lijden bij patiënten die hartchirurgie ondergaan, besproken. Ten vierde wordt het gebruik van distale protectie toestellen onderzocht. Vervolgens wordt er een preoperatieve screenings methode voorgesteld. Ten laatste worden het tijdsinterval en de medicamenteuze behandeling rondom de gecombineerde ingreep bestudeerd, eindigend met de conclusies van het proefschrift.

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Dr. W. De Wilde, woeste Willem, dat ge mijn paranimf zijt, is bijna een evidentie, wetende dat we soul-mates zijn geworden de voorbij jaren. Ge zijt een echte dokter, ge zijt gedreven in alles wat ge onderneemt. Ge hebt u volledig gegeven om een gedegen interventiecardioloog te worden, de Woest trial is ondertussen een begrip geworden, wat zeer zeker ook zal resulteren in mooi proefschrift en binnenkort wordt ge misschien nog de jongste maatschapsvoorzitter ooit, respect. Wat we ondertussen al allemaal beleefd hebben buiten de werkuren kan al niet meer opgeschreven worden in één boek en het is misschien ook wijzer

om het niet op te schrijven. Dat we nog veel mogen mogen en kunnen kunnen.

Patje en matje, eerst zagen jullie uw dochter nachten en weekenden artikels schrijven en nu ik (iets minder nachtelijk). Ook al is het ver van jullie bed, toch hebben jullie ons altijd in alles ondersteund en leven jullie heel erg met ons mee. Bij jullie thuis voel ik me altijd thuis. Betere schoonouders zou ik me niet kunnen in beelden!

Papa en mama, jullie hebben me alles gegeven, meer dan dat ik ooit zou kunnen dromen. Jullie hebben altijd in me geloofd, wat ik ook ondernam (behalve dan misschien de bokslessen). Ik ben heel erg fier dat ik jullie zoon mag zijn en ik besef elke dag meer van welk een onschatbare waarde het is om door jullie opgevoed te zijn. Ik hoop dat ik mijn zoons op dezelfde manier kan grootbrengen. Ik zie jullie graag.

Broers, alle drie, ik voel me heel erg nauw met jullie verbonden, nu en voor altijd, wat er ook gebeurt. Ik zou me geen leven zonder jullie kunnen indenken maar heb het toch moeten leren. Ik wil jullie dicht bij mij ook al woon ik verder weg. Ik zie jullie graag.

Baptiste en Achilles, jullie zijn de essentie van mijn leven. Ik zie jullie graag, het liefst van al.

Lieve schat, er zouden bladzijden, hoofdstukken of zelfs terabytes nodig zijn om ook maar een beetje te beschrijven hoe graag ik u zie. Ik kan niet zonder u; knipperen met mijn ogen en u een fractie van een seconde niet zien, is verspilde tijd. Zelfs als ik slaap en droom over vrouwelijk schoon dan zijt gij het die ik zie. Ge zijt mijn vrouw, de moeder van mijn bloedjes en mijne beste vriend. Uw onvoorwaardelijke liefde voor onze kinderen maakt me sprakeloos en incorporeert alles wat het simpel woordje mama ooit zal kunnen betekenen. Mij geeft ge altijd het gevoel alsof ik heel bijzonder en speciaal ben; het is fantastisch om dat als man dag in dag uit te mogen voelen. Er zijn zoveel dingen die u een bijzondere vrouw maken, maar het meest van al is het uw allesdoordringende fijngevoeligheid voor alles en voor iedereen; wie kan er u niet graag zien? Ge zijt een uniek exemplaar, onvervangbaar en van onschatbare waarde, met geen geld ter wereld te kopen, want ge zijt een geschenk dat alleen één keer kan gegeven worden; ik heb het gekregen. Na meer

dan 20 jaar, heb ik leren beseffen dat er geen gij en ik meer is, en dat is een indrukwekkende gewaarwording die echter even eigen aanvoelt als mijn ademhaling. Ik zie u graag. Moi pour toi.

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